Acute-on-Chronic Liver Failure

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Over the past 2 decades, the concept of acute-on-chronic liver failure (ACLF) has been proposed as an alternate path in the natural history of decompensated cirrhosis. ACLF thus is characterized by the presence of a precipitating event (identified or unidentified) in subjects with underlying chronic liver disease leading to rapid progression of liver injury and ending in multi-organ dysfunction characterized by high short-term mortality. Multiple organ failure and an increased risk for mortality are key to the diagnosis of ACLF. The prevalence of ACLF ranges from 24% to 40% in hospitalized patients. The pathophysiological basis of ACLF can be explained using the following 4-part model: predisposing event, injury caused by a precipitating event, response to injury, and organ failure. Although several mathematical scores have been proposed for identifying outcomes with ACLF, it is as yet unclear whether these organ failure scores are truly prognostic or only reflective of the dying process. Treatment paradigms continue to evolve but consist of early recognition, supportive intensive care, and consideration of liver transplantation before onset of irreversible multiple organ failure.

**Keywords:** Cirrhosis; Portal Hypertension; MELD; Survival Scores; Sepsis.

For years, a dichotomous fate had been assigned to persons with chronic liver disease or cirrhosis: a period of stable compensated liver disease followed by progression to decompensated liver disease toward eventual death in the absence of liver transplantation (LT). Decompensation was heralded by the onset of ascites, jaundice, variceal bleeding, or hepatic encephalopathy, with a median survival of 2 years. There was no term to describe the events between decompensated cirrhosis and multiple organ failure, from which these patients eventually died. Over the past 2 decades, the concept of acute-on-chronic liver failure (ACLF) has been proposed as an alternate path in the natural history of decompensated cirrhosis. Multiple organ failure and increased risk for mortality are key to the diagnosis of ACLF. It now is recognized that patients with compensated cirrhosis and patients with chronic liver disease without cirrhosis also may develop multiple organ failure and are included in the ACLF definition. This review updates our current understanding of ACLF (definitions and pathophysiology), characterizes associated extrahepatic organ dysfunction, identifies current prognostic markers and predictive models, and describes potential therapies.

**Definition**

As compared with the general population, persons with compensated cirrhosis have a 5-fold (hazard ratio, 4.7; 95% confidence interval, 4.4–5.0) and persons with decompensated cirrhosis have a 10-fold (hazard ratio, 9.7; 95% confidence interval, 8.9–10.6) increased risk of death.¹ In a recent population-based study of Danish alcoholic cirrhotic patients, the median 1-year survival rate was 83% in persons with compensated cirrhosis and between 36% and 80% for persons with decompensated cirrhosis.² The underlying premise of defining ACLF is to identify a subset of patients with either chronic liver disease or cirrhosis who have an unexpected rapid and abrupt decompensation of hepatic function with extrahepatic organ failure. There is an increased risk of short-term mortality similar to persons with acute liver failure (ALF), and substantially higher than expected with the natural progression of cirrhosis with chronic decompensation.³ In a recent study, cirrhotic patients with ACLF had 90-day mortality rates of 34% vs 1.9% for chronic decompensation. ACLF is characterized by a paralysis of immune response akin to changes seen among persons with severe sepsis.⁴ This is in contrast to ALF, which is characterized by onset of coagulopathy and encephalopathy within 8 weeks in subjects without underlying chronic liver disease.⁵ Cerebral edema may be encountered in ACLF, but rarely is seen in decompensated cirrhosis without ACLF.

Three separate definitions have been derived from multicenter efforts from the Asia–Pacific region, European groups, and North American groups³,⁶–⁹ (Table 1). It must be recognized that the characterization of each organ

**Abbreviations used in this paper:** ACLF, acute-on-chronic liver failure; AKIN, Acute Kidney Injury Network; ALF, acute liver failure; CLIF, Chronic Liver Failure; CLIF-C OF, Chronic Liver Failure–Consortium Organ Failure; DAMP, damage-associated molecular pattern; HBV, hepatitis B virus; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; IL, interleukin; LPS, lipopolysaccharide; LT, liver transplantation; MELD, model for end-stage liver disease; SOFA, Sequential Organ Failure Assessment.

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### Table 1. Definitions of Acute on Chronic Liver Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>ACLF</th>
<th>Components</th>
<th>Survival</th>
<th>Common regional precipitants and underlying disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCELD infection-related ACLF</td>
<td>≥2 extrahepatic organ failures</td>
<td>Shock, grade 3 or 4 hepatic encephalopathy, need for dialysis, or need for mechanical ventilation</td>
<td>30-day mortality: 27% (1), 49% (2), 64% (3), and 77% (4) extrahepatic organ failures</td>
<td>Bacterial infection, 57% with nosocomial infection Varied etiology of underlying liver disease</td>
</tr>
<tr>
<td>European Association for the Study of the Liver–CLIF Consortium</td>
<td>Hepatic or extrahepatic organ failure with &gt;15% 28-day mortality</td>
<td>Grade 1 (1) patients with single kidney failure; (2) patients with kidney dysfunction (1.5–1.9 mg/dL) and/or mild to moderate hepatic encephalopathy along with single failure of liver, coagulation, circulation, or respiration; (3) patients with hepatic encephalopathy along with kidney dysfunction (1.5–1.9 mg/dL) Grade 2: ≥2 failures Grade 3: ≥3 organ failures</td>
<td>28-day mortality 22%, 32%, and 77%</td>
<td>Bacterial infection Underlying liver disease: alcoholic liver disease and HCV</td>
</tr>
<tr>
<td>Asia Pacific Association for the Study of the Liver</td>
<td>Acute hepatic insult manifesting as jaundice (bilirubin &gt;5 mg/dL) and coagulopathy (INR &gt;1.5) complicated within 4 weeks of onset by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease</td>
<td>Liver failure</td>
<td></td>
<td>Reactivation of hepatitis B, superinfection with hepatitis E Underlying liver disease: hepatitis B, alcoholic cirrhosis, hepatotoxic drugs</td>
</tr>
</tbody>
</table>

INR, international normalized ratio; NASCELD, North American Consortium for the Study of End-Stage Liver Disease.
failure was different between the separate consortium definitions. In addition, the timing of precipitating injury, importance placed on extrahepatic organ failure, especially infection, and definition of chronic liver disease and cirrhosis were different across the 3 iterations. To consolidate the complementary definitions, a framework was proposed by a working group on behalf of the World Gastroenterology Organization. According to this consensus, ACLF is a “syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR [International Normalized Ratio]) and 1 or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from it.” Furthermore, ACLF is classified based on whether it occurs in patients without cirrhosis (type A; eg, reactivation of hepatitis B), in persons with compensated cirrhosis (type B; eg, acute alcoholic hepatitis in patients with cirrhosis), or in patients with a history of prior hepatic decompensation (type C; eg, infection in patients with a history of ascites) (Figure 1). Because organ failure is required for defining ACLF, the diagnosis of ACLF currently may be made at a point in time when the process largely is irreversible. Therefore, a definition that takes into consideration prognostic factors other than organ failure is required to allow early diagnosis and treatment of ACLF.

Prevalence and Natural History

The prevalence of ACLF is hard to assess given variations in definitions of ACLF. In the European multicenter study, the prevalence among hospitalized cirrhotic patients was 31%. In the North American experience, the prevalence of infection-associated ACLF (>2 associated organ failures) was approximately 24.3%. Similarly, in a European population-based cirrhotic cohort (2001–2010), the prevalence of infection-related ACLF was 24%. In a single-center prospective nationwide inception cohort study in Italy, ACLF was observed in 12% of hospitalized cirrhotic patients. In another study, ACLF developed in 40% at 5 years for persons with cirrhosis.

Limited data exist on the natural history of ACLF. By using follow-up data from the Chronic Liver Failure (CLIF) consortium, of 388 patients, approximately 50% had resolution or improvement in their ACLF, 20% worsened, and 30% had a steady or fluctuating course. The prognosis was best in patients with grade 1 ACLF (discussed later) with the highest resolution in grade 1 ACLF (resolution 54.5%) as compared with ACLF grade 3 (16%). The time course assessing improvement, resolution, or worsening could be determined within 48 hours in 40%, within 3 to 7 days in 15%, and within 8 to 28 days in another 15% of the population. Long-term outcomes also may be different based on the precipitating factor. In a single-center study of 405 patients with ACLF from China, subjects with hepatic insults (eg, viral hepatitis, hepatotoxic drugs) as compared with extrahepatic insults (eg, bacterial infection or surgery) had similar short-term mortality rates (48.3% vs 50.7% 28-day transplant-free mortality), but lower 1-year mortality rates (63.9% vs 74.6%; P < .02). There were also differences in predictors of poor prognosis such as the presence of multi-organ failure being more predictive of death in subjects with extrahepatic precipitants rather than hepatic-related insults.
Etiology

There also were differences in etiologies of ACLF based on the region of the world. Reactivation of hepatitis B and superimposition of acute hepatitis A or hepatitis E on chronic liver disease are important causes of ALF as well as ACLF in Asia. Alcoholic hepatitis and infections are reportedly more common in Western centers, but do also contribute to a significant proportion of patients with ACLF in the East. Given that approximately half of subjects with cirrhosis who are admitted to the hospital have evidence of infection or sepsis and a further 25% develop nosocomial infections with high inpatient hospital mortality, infection plays an overwhelming role in the natural history of ACLF.

Costs

Unfortunately, there are sparse data on the cost of hospitalization because it often is hard to parse out hospital-level data and accurately identify subjects with ACLF vs non–ACLF-related decompensated liver disease. In one estimate of the nationwide inpatient sample in the United States, the mean cost per ACLF hospitalization was twice as high as that for patients with cirrhosis without ACLF (approximately $32,000 for ACLF, compared with $16,000 for cirrhosis without ACLF).16

Pathophysiology

Borrowing from the sepsis literature, Jalan and we described the pathophysiological basis of ACLF using a 4-part model of predisposing event, injury resulting from precipitating event, response to injury, and organ failure10–12,17,18 (Figure 2). In their model, predisposition refers to underlying cirrhosis and concomitant illnesses. Injury may be caused by one of many insults such as alcoholic hepatitis, superimposed viral hepatitis, reactivation of hepatitis B, gastrointestinal bleeding (variceal or nonvariceal), drug-induced liver injury, ischemia, and surgery. The prevalence of identified bacterial infection is higher among persons with ACLF as compared with those without ACLF.6 A precipitating injury may be unknown in approximately half of the cases. The inflammatory response is important, with a robust response as judged by the presence of increased C reactive protein level or an increased leukocyte count associated with worse outcomes. It is unclear whether the inflammation is a response to the inciting event or a part of the inciting event. It also is likely that the compensatory anti-inflammatory response is important in determining the risk for nosocomial infection and the higher risk of mortality.19 Organ failure is the last component, with increasing numbers of organ failures (ie, hemodynamic collapse, renal failure, pulmonary compromise, liver failure) portending poor outcomes, especially in the setting of chronic liver disease.
In normal conditions, the liver exerts an important defensive role against pathogens and related antigens. The liver resident macrophages (ie, Kupffer cells) and sinusoidal endothelial cells act as the first-line defense mechanisms against gut-derived toxins and bacteria. Kupffer cells are present within the lumen of the hepatic sinusoids and exert potent phagocytic activity. Upon activation of Kupffer cells, there is significant release of proinflammatory cytokines (interleukin [IL]1, IL6, IL17, IL18, tumor necrosis factor-α), which induces leukocyte recruitment and oxidative stress, as well as complement activation. Both Kupffer cells and sinusoidal endothelial cells also have antigen-presenting capabilities through expression of major histocompatibility complex classes I and II.

In cirrhosis, there is loss or damage of Kupffer cells resulting from sinusoidal fibrosis and capillarization, portosystemic shunt formation, and impaired hepatic synthesis of complement proteins and soluble pattern-recognition receptors. In addition, compromise of circulating immune cell function has been shown in cirrhosis. Patients with ACLF show significant cellular immune depression, as measured by reduced ex vivo tumor necrosis factor-α production and monocyte HLA-DR expression after lipopolysaccharide (LPS) stimulation. This effect is significantly more pronounced in ACLF patients compared with patients with compensated cirrhosis. A large gene-expression profiling study of cirrhotic peripheral blood mononuclear cells showed induction of immune paralysis after ex vivo exposure to LPS. In comparison with healthy controls, LPS-stimulated cirrhotic peripheral blood mononuclear cells showed a higher expression of certain proinflammatory cytokines and chemokines. Patients with hepatitis B virus (HBV)-related ACLF showed an increase in the regulator T cells and a functional decrease of myeloid dendritic cells, which are associated with poor outcome. ACLF patients also show increased numbers of monocytes and macrophages expressing MER-receptor tyrosine kinase, which displays a potent suppressive effect on the innate immune response. Recent studies on the beneficial use of granulocyte colony–stimulating factor for patients with ACLF showed an increase in circulating and intrahepatic myeloid and plasmacytoid dendritic and T cells.

These findings show some similarities between the pathophysiology of ACLF and severe sepsis. Septic patients show both a pro-inflammatory response and an anti-inflammatory response characterized by suppression of the immune system leading to multiorgan failure. Unfortunately, there are no current studies on the immune system response at the different stages of ACLF. These studies would be helpful in further understanding the sequence of events leading to organ failure and death.

In addition to bacterial translocation and infection contributed to by impaired immune response in cirrhosis, sterile mechanisms associated with hepatocellular damage also may elicit a prominent inflammatory response. Sterile inflammation, as induced by alcohol, surgery, or ischemic/reperfusion, is driven mostly by damage-associated molecular patterns (DAMPs), as opposed to pathogen-associated molecular patterns. DAMPs derive from necrotic hepatocytes and have been shown to activate host pattern-recognition receptors, such as Toll-like receptors and nucleotide-binding oligomerization domain-like receptors. These in turn promote expression of adhesion proteins and release of proinflammatory cytokines (eg, IL1B, IL18) and growth factors, which further attract and activate additional inflammatory cells. Several DAMPs have been described in the literature, but their role in ACLF needs to be elucidated further. Recently, a small study found increased serum levels of high-mobility group box chromosomal protein 1, an important hepatocyte-derived DAMP, in patients with ACLF (Figure 2).

Extrahepatic Organ Failure

The presence of multisystem organ failure is a requirement for the diagnosis of ACLF and critical in differentiating this condition from decompensated cirrhosis. In addition, the number of systems affected has important prognostic value.

Renal System

Kidney dysfunction is common and associated with high mortality in cirrhotic patients. Overall, isolated renal failure carries a 28-day mortality rate of up to 18.6% in patients with ACLF. The diagnosis of renal failure has been defined as serum creatinine level greater than 1.5 mg/dL or need for renal replacement therapy in patients with cirrhosis. A newer definition of acute renal failure was proposed by the Acute Kidney Injury Network (AKIN), which considers the absolute change in serum creatinine level or change in urine output over a 48-hour period. The AKIN criteria have been validated recently as a prognostic tool in hospitalized cirrhotic patients in a stage-dependent fashion. The AKIN criteria, however, have yet to be incorporated into a prognostic score for ACLF.

The most common causes of acute kidney injury in cirrhosis include volume-responsive prerenal azotemia, acute tubular necrosis, and hepatorenal syndrome (HRS). HRS is a unique form of prerenal azotemia that is not responsive to volume expansion alone but usually is reversible with liver transplantation. HRS results from a hyperdynamic circulatory state, leading to significant renal vasoconstriction. Management of HRS includes the use of splanchnic vasoconstrictors that promote an increase in the effective renal arterial blood volume. Vasoconstrictor drugs such as terlipressin significantly improve renal function and overall short-term survival.
less likely to respond to terlipressin, suggesting alternative mechanisms of renal impairment in this population. In addition, response to terlipressin in ACLF may not be related simply to the degree of renal impairment, other factors may play a role. In addition to circulatory changes, AKI in ACLF also likely is modulated by systemic inflammation. This is supported by the beneficial role of pentoxifylline in decreasing the risk of renal failure in patients with severe alcoholic hepatitis and the renal protective effect of intravenous albumin in spontaneous bacterial peritonitis. Bacterial infection is the precipitating event of AKI in approximately 30% to 40% of patients with cirrhosis and is an important driver of inflammation in this group. Renal failure associated with infections carries a poor prognosis, with a 3-month survival rate of 31% in one study. Intestinal decontamination with daily oral norfloxacin in the prevention of spontaneous bacterial peritonitis leads to a significant decrease in the incidence of AKI and improves survival.

In addition to renal failure, hyponatremia is known to have an important prognostic value in cirrhosis. Indeed, the presence of hyponatremia in patients with ACLF was associated with lower 3-month survival rates compared with patients with ACLF without hyponatremia (35.8% vs 58.7%, respectively).

**Hepatic Encephalopathy**

Hepatic encephalopathy is a common complication of cirrhosis and is associated with higher in-hospital mortality. Hepatic encephalopathy can present in 3 different settings: acute liver failure, decompensated cirrhosis, and ACLF. Isolated hepatic encephalopathy seems to occur in older cirrhotic patients, without evidence of extrahepatic organ dysfunction. The prognosis typically is good in this older group of patients with hepatic encephalopathy (HE), even in those requiring intensive care unit admission and mechanical ventilation. HE associated with ACLF, on the other hand, occurs in the setting of extrahepatic organ failure(s) and carries a poor prognosis. This prognostic gap likely is related to superimposed systemic inflammation, characteristic of ACLF, in addition to circulating neurotoxins such as hyperammonemia, which is observed in both groups.

Another important difference between isolated HE and HE associated with ACLF is that the latter may lead to cerebral edema and increased intracranial pressure, whereas the former typically will not. Animal studies have suggested the development of acute brain edema to be a result of hyperammonemia plus systemic/neuroinflammation. Hyponatremia also has been identified as an important risk factor for cerebral edema, likely owing to differences in osmolality between the intracellular and extracellular spaces.

**Cardiovascular System**

Similar to decompensated cirrhosis, ACLF patients also show important hemodynamic changes, including a decrease in mean arterial pressure, systemic vascular resistance, and cardiac index, and a significant increase in hepatic venous pressure gradient. These portal and systemic circulatory changes improve significantly after resolution of the acute episode and correlate well with clinical recovery.

Systemic inflammation likely accounts for the acute vascular changes observed in ACLF, similar to septic shock. An increase in circulating proinflammatory cytokines, such as tumor necrosis factor, promotes peripheral vasodilation and aggravates intrahepatic resistance. In addition, patients with ACLF may show relative adrenal insufficiency and, consequently, low serum cortisol levels. This, in turn, results in decreased peripheral response to vasoconstrictors.

**Respiratory System**

Respiratory failure in patients with ACLF usually is related to pulmonary infections, although patients may require mechanical ventilation for other indications, including airway protection during variceal bleeding and/or advanced grades of hepatic encephalopathy. Pulmonary infections account for 14% to 48% of all infections in cirrhotic patients. Both acute lung injury and acute respiratory distress syndrome occur. The need for mechanical ventilation is a poor prognostic indicator in ACLF, with 1-year mortality rates of 89%. Ventilation for longer than 9 days and increased total bilirubin level at intensive care unit discharge were identified as independent risk factors associated with high mortality.

**Coagulation System**

Prolonged prothrombin time and low platelet count are common features of cirrhosis and are used as surrogate markers of coagulation dysfunction in this condition. Unfortunately, the abnormalities in the coagulation and fibrinolytic systems are extensive and are not recognized by routine testing. In stable cirrhosis, both the procoagulant and anticoagulant factors are decreased equally, resulting in either normal thrombin generation or a tendency for hypercoagulability. Bacterial infections in cirrhotic patients are thought to impair coagulation by increasing endogenous heparinoids. This seems to be a temporary effect that resolves after the infection has cleared. Platelet dysfunction also has been observed in infected patients, especially in patients with renal failure, and likely contributes to hemostatic impairment. These detrimental vascular effects are countered further by the protective role of antibiotics in reducing early variceal rebleeding rates.
Potential Biomarkers

As our understanding and recognition of ACLF increases, so does our need to diagnose and risk-stratify patients accurately for better outcome prediction and therapy guidance. Currently, only a few studies have investigated potential biomarkers for the diagnosis of ACLF. A recent study evaluating the metabolomic profile of patients with alcoholic cirrhosis admitted to the hospital with ACLF identified signals related to ACLF, compared with compensated or decompensated cirrhosis, including lactate, pyruvate, ketone bodies, glutamine, phenylalanine, tyrosine, and creatinine. Metabolic profiling has been applied in patients with HBV-related ACLF and 38 characteristic serum metabolites were identified, 17 of which also showed a potential prognostic role. Systemic inflammatory response is an important pathophysiologic feature of ACLF and, therefore, inflammatory or immune markers also have been investigated in this condition. A significant up-regulation of tumor necrosis factor-α and interferon-γ was observed in HBV-related ACLF, compared with chronic hepatitis and normal controls.

However, more data are required before these biomarkers can be applied widely as diagnostic or prognostic tools.

Predictive Models

Multiple scoring systems have been used or developed to help predict outcomes in patients with ACLF. The Model for End-Stage Liver Disease (MELD) score, the Maddrey discriminant function, and the Lille model have been shown to predict early mortality in acute alcoholic hepatitis. A recent study in patients with alcoholic hepatitis showed that the combination of MELD score at admission and Lille score after 1 week of steroids has the best discriminant as well as calibration value of all models or combinations of models. This combined model may help in making treatment decisions including selecting patients for specific treatments as well as determining futility of care. A combination of the MELD score, age, and American Society of Anesthesiologists classification has been validated for predicting survival in cirrhotic patients undergoing surgery, another common precipitant of ACLF.

The commonly used scoring systems in cirrhosis (ie, Child–Turcotte–Pugh score and MELD score), assess the kidney, brain, and coagulation systems in addition to the liver. Therefore, an improved scoring system for ACLF is required that takes into consideration inflammation and other organ dysfunction. Recently, the EASL–CLIF Consortium proposed a modified Sequential Organ Failure Assessment (SOFA) score to include factors associated with chronic liver disease (CLIF-SOFA scale).

The CLIF–SOFA scale assessed the function of 6 organ systems (liver, kidneys, brain, coagulation, circulation, and lungs) (Table 2). A recent retrospective study, including 971 patients, validated the use of the CLIF–SOFA score in cirrhosis. The SOFA and CLIF–SOFA scores had similar abilities to predict patient survival, with greater area under the receiver operating curve values than those obtained from MELD and Acute Physiology and Chronic Health Evaluation II scores.

A simplification of the CLIF–SOFA score has been proposed. Two new cut-off points for each organ system have been added to distinguish 3 severity categories that were correlated with 28-day mortality Chronic Liver Failure Consortium Organ Failure score (CLIF-C OFs). The CLIF-C OFs performed similar to the original

<table>
<thead>
<tr>
<th>Organ</th>
<th>Measurement</th>
<th>Score</th>
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<td>Liver</td>
<td>Bilirubin, mg/dL</td>
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<tr>
<td></td>
<td>&lt;1.2</td>
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</table>

E, Epinephrine; Fio2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; NE, Norepinephrine; RRT, Renal Replacement Therapy; Spo2, oxygen saturation.
CLIF–SOFA score in predicting 28-day mortality. Those authors then developed a mathematic model, including age and white blood cell count, to improve the CLIF-C OF performance. This new score, CLIF-C ACLF, was proven to be superior to MELD and MELD-sodium in predicting mortality in ACLF in the study population and in an externally validated cohort.89

In contrast to these elaborate models, Bajaj et al,9 using data from the North American Consortium for the Study of End-Stage Liver Disease group, proposed that increasing number of organ failures may be sufficient to accurately predict short-term mortality, at least among persons with ACLF who develop an infection. Hence, the overarching theme is that regardless of the underlying liver disease, it is the presence of multiorgan failure that predominantly drives the outcomes.

Gustot et al90 assessed ACLF grades at different time points to evaluate the clinical course in this group of patients. Interestingly, they found that the ACLF grade at 3 to 7 days was a better predictor of severity independent of initial assessment. Patients with a nonsevere early course had a 28-day, transplant-free mortality rate of 6% to 18%, compared with 42% to 92% mortality in patients with a severe early course. It is not yet clear whether these organ failure scores are truly prognostic (ie, allow early recognition and can improve the outcome) or are only reflective (ie, they are describing the dying process).

Therapies

There is no specific ACLF treatment; rather, treatment follows the paradigm of addressing the predisposing event, preventing injury, attenuating the inflammatory response, and providing supporting care for ensuing organ failures (Table 3). Appropriate intensive care management of subjects with ACLF is the mainstay of treatment.10 Early recognition of subjects at the highest propensity to either present with or develop ACLF is important so that urgent evaluation for liver transplantation can take place. The role of alcohol as a common precipitant is a confounding factor given the variability of center-specific criteria for abstinence.

Management of any decompensation is contingent on first addressing the precipitating event. For example, in the setting of acute alcoholic hepatitis, administration of prednisolone early in the course may play a role if warranted by the severity of disease. However, the interplay between the high prevalence of infection among persons with ACLF and administration of prednisolone is unknown. Furthermore, the absolute reduction in mortality with steroid-based therapy is apparent only at 28 days; long-term reduction in mortality is related to abstaining from alcohol. A reduction in the risk of infection with early use of antibiotics in persons with gastrointestinal bleeding may improve outcomes. The administration of antiviral therapy for ACLF owing to reactivation of hepatitis B may lead to improved survival.91 In a single-center study from India, subjects with spontaneous reactivation of chronic hepatitis B with ACLF and no access to LT were randomized to receive either tenofovir or placebo. Three-month survival was higher among persons receiving tenofovir compared with the placebo group (57% vs 15%, respectively). In a recent meta-analysis, subjects with ACLF who received nucleos(t)ide analogues had significantly lower 3-month mortality rates (45% vs 73%, respectively; $P < .01$) as well as incidence of reactivation (1.8% vs 18%, respectively; $P < .01$) compared with those who did not.92

The role of granulocyte colony–stimulating factor as a promoter of hepatic regeneration was reported in a small group of patients with ACLF and in a larger group of subjects with decompensated cirrhosis.27 In this latter single-center, placebo-controlled, randomized trial, receipt of a combination of granulocyte colony–stimulating factor and darbopoietin $\alpha$ was associated

<table>
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<tr>
<th>Assessment</th>
<th>Intervention</th>
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<td>Predisposition</td>
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<td>Injury</td>
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<tr>
<td>Severity, etiology</td>
<td>MELD score, CTP score</td>
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<td>Precipitating event</td>
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<td>Infection</td>
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<td>Injury</td>
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<td>Early antivirals for hepatitis B</td>
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<td>Prednisone?</td>
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<td>Response</td>
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<td>Early antibiotics</td>
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<tr>
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<td>G-CSF?</td>
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<tr>
<td>Cardiopulmonary</td>
<td>Role of albumin?</td>
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<td>Prognostic score</td>
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<td>?Goal-directed therapy</td>
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<td>Artificial/bio-artificial liver in selected patients?</td>
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<td>SOFA, APACHE, CLIF</td>
<td>Liver transplantation</td>
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APACHE, Acute Physiology and Chronic Health Evaluation; CTP, Child-Turcotte-Pugh; G-CSF, granulocyte colony–stimulating factor; PIRO, Predisposition Injury Response Organ failure; RRT, Renal Replacement Therapy.
Adapted from Jalan et al.3
with improved survival at 1 year (68.6% vs 26.9%, respectively; \( P < .01 \)), with a lower rate of septic shock in follow-up evaluation (6.9% vs 38.5%, respectively; \( P < .01 \)).

The role of liver assist devices remains unclear.\(^9^3\) MARS (Gambro Lundia, Lund, Sweden), a nonbiologic molecular adsorbent recirculating system, was examined among persons with ACLF. In the Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial, which included 180 patients with ACLF, there was no survival difference between patients randomized to MARS or standard therapy (28-day mortality rate was 41% vs 40% in subjects with MARS vs standard of care alone, respectively).\(^9^4\) In a study of another nonbiological device, Prometheus (Prometheus, Fresenius, Germany), using fractional plasma separation absorption and dialysis, a survival benefit was not observed in persons with ACLF (mortality rate was 34% vs 37% in subjects assigned to the device vs standard of care, respectively). There was a survival benefit seen only among persons with type I hepatorenal syndrome and MELD scores higher than 30.\(^9^3\) Bio-artificial liver assist devices also are being studied (http://clinicaltrials.gov/show/NCT01471028).

**Liver Transplantation**

Currently, there is no urgent status assigned to persons with ACLF and it is unclear whether ALF criteria should be applied to subjects with ACLF. Given that timing of LT is important, it also is unclear whether King’s College hospital ALF criteria also should be applied for ACLF or whether MELD-based organ allocation is appropriately applicable. Driven by the presence of multi-organ failure, subjects with ACLF often have high MELD scores. Candidates with MELD scores greater than 35 have higher wait list mortality than status 1 patients and receive priority for liver transplantation second only to patients with ALF.\(^9^5\) However, the presence of severe cerebral edema, intracranial bleeding, active infection in a majority, need for ventilator support, and hemodynamic instability that may be present in persons with ACLF are obvious contraindications to transplantation.\(^7\) Furthermore, recent data suggest that certain diagnoses previously not considered for LT globally such as acute alcoholic hepatitis may have acceptable outcomes after liver transplantation. In a single-center European cohort inclusive of ACLF with acute alcoholic hepatitis (2002–2010; mean MELD score, 28; 144 subjects),\(^9^6\) only 10 persons survived without LT over a median follow-up period of 1.5 years. Among the highly selected 33 patients who underwent liver transplantation, the 1- and 5-year survival rates of 87% and 82%, respectively were comparable with the rates for non-ACLF patients. Subjects with better renal function and lower C-reactive protein level were more likely to receive LT as compared with those patients with sepsis or needing mechanical ventilation. Bahirwani et al examined subjects with ACLF between 2002 and 2006 (50% hepatitis C) at a large American transplant center. ACLF was defined as an increase in MELD score of 5 points within 4 weeks before LT. There was no significant difference in deaths after transplant or renal failure after LT. ACLF was not a predictor of death after LT but was a significant predictor when simultaneous liver–kidney transplant was included. In another recent single-center study from China (100 patients; 2004–2012; mean MELD score, 32), the 1 and 5-year cumulative survival rates were 76.8% and 74.1%, respectively, after transplant. In all studies, no comparison was performed between patients with ACLF and those with chronic decompensation matched for disease severity by MELD score.

The role of living donor LT also was evaluated for subjects with ACLF owing to reactivation of hepatitis B virus infection.\(^9^7–9^9\) In a single-center study the 5-year survival rate was 93% for persons with ACLF resulting from chronic hepatitis B, 90% for other causes of ACLF, 79% for persons with other causes of cirrhosis, and 91% for persons with acute liver failure. Overall, hepatitis B was represented disproportionately across all the etiologies.\(^9^8\) The role of simultaneous liver–kidney transplant for ACLF patients with renal dysfunction recently was examined among persons undergoing deceased donor transplantation (China; 133 subjects; 2001–2009).\(^1^0^0\) The survival rate for patients without renal dysfunction was 72% at 5 years, which was comparable with 82% for patients who underwent simultaneous liver and kidney transplantation. Subjects with ACLF resulting from hepatitis B and hepatorenal syndrome who only underwent LT alone had a 5-year survival rate of 56%.

**Conclusions**

ACLF is an increasingly recognized entity associated with high mortality. The pathogenesis of inflammation and organ failure and optimal management are the subject of intensive investigation across continents. More data are required before ACLF can be defined and treated accurately. Future strategies include defining the group of patients who need urgent liver transplantation, those who would benefit from intensive care alone, those who will benefit from liver-supportive devices or hepatic regenerative therapies, and those patients in whom all intervention is futile.

**References**

41. de Carvalho JR, Villela-Nogueira CA, Luiz RR, et al. Acute kidney injury network criteria as a predictor of hospital mortality in...


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Conflicts of interest
The authors disclose no conflicts.
GASTROENTEROLOGY ARTICLE OF THE WEEK
January 7, 2016


1. Features that define ACLF include
   a) liver failure developing in a patient with no pre-existing liver disease
   b) acute hepatic decompensation + >1 extrahepatic organ failure in patients with chronic liver disease
   c) development of jaundice and coagulopathy in a previously stable cirrhotic patient
   d) cirrhosis must be present to be classified as ACLF

2. A 58 year old with a history of alcoholic cirrhosis and ascites presents with abdominal pain, peritoneal fluid findings consistent with SBP, bilirubin of 13, INR 2.0, and serum creatinine of 2.2. This would be classified as ACLF type:
   a) A
   b) B
   c) C
   d) D

True or False

3. The difference between decompensated cirrhosis and ACLF is the presence of extrahepatic organ failure in the latter syndrome.

4. The precipitating factor of ACLF is identified in over 80% of cases

5. Cerebral edema is a very common contributing cause of HE in ACLF

6. A non-cirrhotic patient with known chronic HBV infection presents with recent onset jaundice (bilirubin 8.9), INR 2.0, mild confusion. He would be considered as a case of ACLF type A

7. Immune paralysis or a significant compromise of circulating immune cell function is an important part of the pathogenesis of ACLF

8. Steroid therapy for alcohol related ACLF is associated with improved long term (>30d) survival
TOOLS TO INCORPORATE ACLF GRADING INTO PRACTICE

1. Decide if the patient meets criteria for ACLF:

   - NO ACLF:
     - no organ failure, **OR**
     - single "non-kidney" organ failure **OR**
     - single cerebral failure who have serum creatinine <1.5
       - 28 day mortality = 4.7%; 90-day mortality =14%

2. Go to website to calculate CLIF-C score, only if the patient meets criteria for ACLF.
   Website:  [Http://www.clifconsortium.com](http://www.clifconsortium.com)

   - ACLF Grade 1:
     - single kidney failure **OR**
     - Single failure of liver, coagulation, circulation, or respiration, with serum creat 1.5-1.9 and/or mild to moderate encephalopathy **OR**
     - Single cerebral failure with serum creatinine 1.5-1.9.
       - 28d mortality =22%; 90d mortality =41%

   - ACLF Grade 2:
     - 2 organ failures
       - 28d mortality = 32%; 90d mortality =52%

   - ACLF Grade 3:
     - 3 or more organ failures
       - 28d mortality =77%; 90d mortality =79%

Defining organ failure:

- **Liver**: bilirubin >12.0
- **Kidney**: creatinine > 2.0
- **Cerebral**: Grade 3 or 4 encephalopathy
- **Coagulation**: INR >2.5 or platelet count <20,000
- **Circulation**: Need for vasopressors to keep SBP at 90 or higher
- **Lungs**: PaO/FiO2 <200  **or**  SpO2/FiO2 ≤ 214
Acute decompensation without ACLF:

If acute on chronic liver failure, Calculate CLIF-C score to predict mortality:

http://www.clifconsortium.com

High risk - ≥60, 3 month mortality >30%
Low risk - ≤45, 3 month mortality <2%

References:
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J Hepatology 2015;62:831-840