Toward an Improved Definition of Acute-on-Chronic Liver Failure

Acute clinical deterioration in patients with chronic liver disease may result in multisystem organ failure and is associated with significant morbidity and mortality, with per-patient costs associated with intensive care ranging between $116,000 and $180,000 in the United States.[1] Mortality in these patients, however, has remained unchanged over the past 20 years at >50%. As a means of identifying patients with cirrhosis at high risk for acute deterioration, both the Asia-Pacific Association for the Study of the Liver (APASL) and a joint conference of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) proposed definitions of this condition termed acute-on-chronic liver failure (ACLF).[2,3] The differences between the 2 definitions have resulted in confusion rather than clarification of the problem. For example, APASL includes noncirrhotic chronic liver disease but not decompensated cirrhosis as representing "chronic," whereas EASL-AASLD include only cirrhosis, either compensated or decompensated to define chronic liver disease. This perspective serves to resolve some of these issues and outline an approach to better define ACLF.

Definition of ACLF

In the simplest terms, ACLF is abrupt hepatic decompensation in patients with chronic liver disease. Therefore, any definition of ACLF has to encompass the duration over which the deterioration occurs (to define "acute"), characterize "chronic," and identify the degree of hepatic dysfunction to define "failure."[2] The APASL definition of ACLF is "acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease."[3] EASL/AASLD describes ACLF as "an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure."[2] Differences between the APASL and AASLD/EASL definitions relate to duration of illness, what qualifies as "chronic," and the type of precipitating events.[4] The precipitating events in the APASL statement are primarily hepatic in origin, whereas the EASL-AASLD definition includes sepsis. Further hampering the proposal for a standard definition is the variability in observer experience and the lack of standard management for these patients.

To appropriately define ACLF as a separate entity, the following requirements should be met: (1) The condition should be distinct from acute liver failure (ALF) and (2) distinguishable from "decompensated cirrhosis"; (3) pathophysiology should be defined; (4) specific clinical signs and laboratory or other tests that confirm the diagnosis and exclude other diseases should be stated; and (5) a validated clinical scoring system to assess severity of ACLF should be available. Therefore, the proposed definition of ACLF should characterize the condition as being distinct from ALF or decompensated cirrhosis without extrahepatic organ failure using clinical, biochemical, radiologic, and/or histologic criteria. Such a definition would be possible only with extensive, prospectively collected and validated data and should be applicable in all parts of the world. As an initial step, patients with all chronic liver disease (with or without cirrhosis) should be included for data collection to ultimately arrive at a definition of ACLF. There are limited prospectively collected data from the East on acute deterioration of chronic liver disease related to hepatitis B virus and hepatitis E virus infections. Recently, 2 prospective studies using large cohorts of patients in Europe (CANONIC study)[5] and in North America (NACSELD study)[6] attempted to define a group of patients with cirrhosis at risk for multiple organ failure. Both the CANONIC and NACSELD studies included only patients with cirrhosis. In the CANONIC study, hospitalized patients with acute decompensation defined by the "acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infection, or any combination of these" were included. ACLF was then diagnosed based on predefined criteria for organ failure and a 28-day mortality rate of 15%. Renal failure as defined was associated with a greater risk of mortality than other organ failures. The importance of extrahepatic organ failure was highlighted by the fact that even among patients with elevated serum bilirubin levels, the mortality was only 4% if they did not have extrahepatic organ failure. The NACSELD study demonstrated that the presence of ≥2 extrahepatic organ failures was associated with increased mortality in infected cirrhotic patients; the increase in mortality with only a single organ failure was low, but this study included only patients with bacterial infections and not all cirrhotic patients requiring hospital admission.[7] If ACLF is to be defined as a condition wherein patients are at significantly increased risk for mortality, the definition of ACLF should include extrahepatic organ failure. It may seem counterintuitive to define "liver failure" by "extrahepatic organ failure"; nonetheless, the precedence already exists of ALF being defined by the presence of encephalopathy occurring within a period of 1–8 weeks after the onset of jaundice in patients without preexisting liver disease.[8] Similarly, subfulminant hepatic failure, subacute hepatic failure, or late-onset hepatic failure have been defined by different authors as the onset of hepatic encephalopathy within a period ranging between 2–24 weeks after the onset of

jaundice.[9,10] It should be recognized in all patients with liver disease that multiple organ failure may not be a consequence of liver failure alone, but may be a result of sepsis. Because of limited, well-designed studies in the field, any definition of ACLF proposed can only be an interim one and requires validation in geographically diverse populations, both in the East as well as in the West. Chronic liver diseases included may be cirrhotic or noncirrhotic. Because there is "acute deterioration," the duration between the precipitating event and onset of organ failure defining ACLF cannot be >6 months, the currently accepted interval of time to define "chronic." The interval to define "acute" is probably weeks between the insult and extrahepatic organ failure, but needs to be defined. The duration of increased mortality risk in the CANONIC study was very evident at 28 days and 3 months after enrollment. The AASLD/EASL consensus proposed a period of increased mortality risk of 3 months based on data on ACLF that develops in patients with compensated cirrhosis undergoing major surgery.[11] Cirrhotic patients may develop rapid hepatic decompensation and then multiple organ failure after surgery; most patients develop infections before death. Postoperative mortality is increased for ≤3 months compared with controls with cirrhosis not undergoing surgery. In these patients, multiple organ failure as reflected by an American Society for Anesthesia score of V was the only variable associated with 7 day postoperative mortality.[11]

Because of limited prospective data from the East, a consensus working definition of "ACLF" that serves at this time only to identify patients from whom data are to be collected to ultimately arrive at a validated definition is as follows: "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 one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset." Such a definition identifies patients with well-compensated or decompensated cirrhosis or underlying undiagnosed chronic hepatitis with reactivation of hepatitis B; superimposed alcoholic, viral, or drug-induced liver injury; or major surgery. Figure 1 summarizes the current understanding of the pathogenesis of ACLF.

Prognostic Features and Clinical Scoring System for ACLF

Thus far, generic scoring systems have been used for determining prognosis in what is thought to be ACLF. There are liver specific scoring systems such as the Child-Turcotte-Pugh score[12] and the Model for End-stage Liver Disease score.[13] Generic organ failure scores such as the Sequential Organ Failure Assessment score (SOFA)[14] are also used. At this time, there are no scores specific for ACLF, but the proposed CLIF-SOFA score[5] is an important step in this direction. Similarly, data from NACSELD also suggest that extrahepatic organ failure assessment has important prognostic value.[7] Whether scores developed thus far are "prognostic" and not reflective of the dying process will need to be validated. Scores that can be updated regularly may be particularly useful in determining when treatments such as intensive care alone, artificial liver support, or liver transplantation are most appropriate.

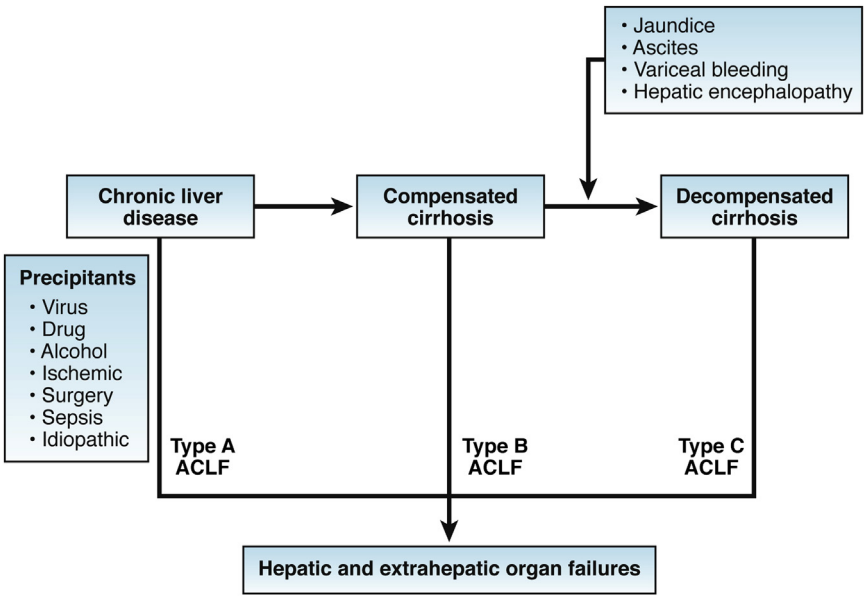

Figure 1. Proposed unifying pathogenesis for different types of acute-on-chronic liver failure (ACLF).

A Multimodal Classification That May Identify Clinical, Prognostic, and Pathophysiologic Subtypes

It is very likely that ACLF is not 1 disease, but rather a syndrome. The defining point of this condition is multisystem organ failure, which can occur irrespective of the inciting event or underlying etiology of chronic liver disease. The initial clinical presentations may be variable and the prognosis may differ depending on the specific precipitating factor. The CANONIC study does provide the basis for differentiation of ACLF from decompensated cirrhosis.[5] In that

prospective study of hospitalized cirrhotics, 303 patients had ACLF as per the predetermined criteria at admission, and 112 developed ACLF within 28 days with, a mortality rate of 34% at 28 days and 51% at 90 days. Mortality among those who did not develop ACLF was only 1.9% at 28 days and 9.7% at 90 days. The presence of extrahepatic organ failure in differentiating ACLF from decompensated cirrhosis was critical because presenting symptoms alone were not different between patients with ACLF and decompensated cirrhosis. Patients with ACLF were younger, more frequently alcoholic and infected, and with higher white blood cell counts and plasma C-reactive protein than patients with decompensated cirrhosis. An intriguing and important finding was that patients without prior hepatic decompensation had higher short-term mortality than patients with prior hepatic decompensation that supports the position that ACLF can be distinguished from decompensated cirrhosis.

ACLF may be divided into 3 categories depending on whether or not there is underlying cirrhosis, and in patients with cirrhosis, whether or not there is a history of previous hepatic decompensation. Extrahepatic organ failure is common to all types of ACLF. Decompensated cirrhosis without extrahepatic organ failure does not fit into this spectrum and such patients should not be included among the ACLF group. When patients with decompensated cirrhosis do develop multiple organ failure, often as a terminal event, such patients would be deemed to have ACLF.

Type A ACLF

Noncirrhotic ACLF is a type of liver failure that may be seen in patients with noncirrhotic chronic liver disease with an acute flare resulting in liver failure, including hepatic encephalopathy, and is often indistinguishable on clinical presentation from acute or subacute liver failure. Such patients include: Reactivation of hepatitis B, hepatitis A or hepatitis E infection superimposed upon chronic hepatitis B,[15] autoimmune hepatitis, hepatitis E virus infection in patients at risk for nonalcoholic steatohepatitis,[16,17] and those with or at risk for chronic liver disease such as fatty liver with superimposed drug-induced liver injury.[18–20]

Analysis of the database from the Department of Veterans Affairs in the United States also confirms that patients with either underlying chronic liver disease or with diabetes are at higher risk for liver failure with superimposed viral hepatitis.[21] Current data suggest that type A ACLF may occur more commonly in the East (hepatitis B virus and hepatitis E virus infection) and may be distinguishable from ALF only by the presence of significant hepatic fibrosis (chronicity) on liver biopsy (Table 1).

Type B ACLF

Type B ACLF or cirrhotic ACLF is seen in patients with well-compensated cirrhosis who rapidly deteriorate after a major hepatic insult such as acute viral, drug, or alcoholic hepatitis, infection, or surgery; however, a precipitating event may not always be identified. Clinical features of cirrhosis may be more obvious in such patients. Extrahepatic organ failure develops usually within 4 weeks of the precipitating event. Alcoholic hepatitis superimposed on cirrhosis may be the most common cause of ACLF in some areas of the world.

Type C ACLF

Cirrhotic ACLF with previous hepatic decompensation (type C ACLF) occurs in patients with a previous history of jaundice and/or complications of portal hypertension such as variceal bleeding, ascites, or hepatic encephalopathy and possible hospitalization. Short-term mortality in the CANONIC study in patients with previous decompensation (type C ACLF) was significantly lower than in patients without previous hepatic decompensation (type B ACLF).

Definition of Principles of Management Including Role of Liver Support Devices

Management

The "PIRO" concept (predisposition, insult, response, organ failure)[22] can be considered a useful framework to determine optimal management (Table 2); a detailed discussion of individual interventions is beyond the scope of this perspective.

Role of Liver Transplantation

Liver transplantation has been undertaken in carefully selected patients with alcoholic hepatitis with excellent results.[23,24] Patients with ACLF unrelated to alcoholic hepatitis from the CANONIC study in the United States and the East have also been demonstrated to benefit from liver transplantation. The US data suggest that Model for End-stage Liver Disease score is the appropriate scoring system to prioritize organ allocation for transplantation in these patients.[25] Further studies, however, are needed to determine optimal selection of patients and timing of liver transplantation and whether ACLF patients should be prioritized on par with patients with ALF.

Clarification of Important Research Questions

Although the definition of ACLF at this time is only a proposal, it is clear that the syndrome is distinct from decompensated cirrhosis without extrahepatic organ failure. Future endeavors should be targeted at prospective collection of data for further refinement of the existing proposals (Table 3). Specifically, data from Asia on patients with reactivation of hepatitis B and hepatitis E superimposed on chronic liver disease are necessary to clearly define the natural history and prognosis of type A ACLF. Biobanks and sample collections are required to outline the pathophysiology of the disease for the specific subtypes of

Table 1. Spectrum of Liver Failure

	Accepted types of liver failure		Proposed types of ACLF		
Variable	Acute liver failure	Subacute liver failure	Type A: noncirrhotic ACLF	Type B: cirrhotic ACLF	Type C: cirrhotic ACLF with previous hepatic decompensation
Interval between symptoms (jaundice) and organ failure	<8 weeks[8]; <2 weeks[9]; <4 weeks[10]	2–12 weeks[9]; 5–12 weeks[10]; 8–24 weeks[21]	Variable (wks) and to be defined by data	Variable (wks) and to be defined by data	Variable (mo) interval between hepatic decompensation and organ failure
Etiology	Several, including viral and drug	Several, including viral and drug	Flare of hepatitis B; HEV or HAV infections superimposed on HBV or NASH; autoimmune hepatitis	Any etiology for cirrhosis	Any etiology of cirrhosis
Precipitating event	Unknown	Unknown	Spontaneous or discontinuation of therapy in HBV, viral infection such as HEV or HAV	Viral, drug, surgery, alcoholic hepatitis, and infection in patients with cirrhosis; Wilson disease	Variable, including all events listed under type B
Cerebral edema	Present	Uncommon	May be present	Uncommon[22]	Uncommon[22]
Multisystem organ failure	Early	Late	Early	Early and required for diagnosis	Required for diagnosis
Liver histology	Massive necrosis; no chronicity	Submassive necrosis; evidence of early fibrosis	Submassive necrosis and fibrosis; no cirrhosis	Cirrhosis: Specific histology awaits further studies, but cholestasis often present on the background of alcoholic etiology	Cirrhosis: Specific histology awaits further studies, but cholestasis often present on the background of alcoholic etiology
Prognosis	Spontaneous recovery possible depending on etiology, but liver transplant often required; mortality 45%–90% without liver transplant depending on etiology	Spontaneous recovery unusual; mortality almost invariable in absence of liver transplant	Variable and to be studied; treatment of underlying condition such as HBV may result in recovery to baseline	Variable and to be studied. CLIF-C score to be validated; recovery to baseline might be possible with intensive care; artificial liver support remains unproven	Prognosis correlates with MELD and CLIF-C score; lower 28-day mortality than patients without previous hepatic decompensation
Improvement in survival with liver transplantation	Yes	Yes	Yes	Yes	Yes

ACLF, acute-on-chronic liver failure; CLIF-C, CLIF consortium; HAV, hepatitis A virus; HBV, hepatitis B virus; HEV, hepatitis E virus; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis.

Table 2. The Predisposition, Insult, Response, Organ Failure (PIRO) Concept Principles of Management of Acute-on-Chronic Liver Failure

Assessment	Intervention
Predisposition	
Severity of cirrhosis	
Etiology,	Early identification,
CTP score,	Risk stratification,
MELD score	Preventative strategies
Injury	
Precipitating event	
Hepatic: virus, drugs, alcohol, etc	Rapid intervention example: tenofovir for hepatitis B
Extrahepatic: infection	Rapid treatment of infection Albumin for SBP
Variceal bleeding	Early TIPS for high-risk patients
Response	
Inflammation	
Inflammation	Goal-directed approaches
Immune failure	[Novel interventions such as caspase inhibition, GCSF] ? Plasmapheresis
Organ	
Organ failure	
Scores such as SOFA, APACHE, CLIF-C score	Intensive care, organ support, artificial/bioartificial liver support systems, liver transplantation

ACLF, acute-on-chronic liver failure; APACHE, Acute Physiology And Chronic Health Evaluation; CLIF-C, CLIF consortium; CTP, Child-Turcotte-Pugh; GCSF, granulocyte colony-stimulating factor; HAV, hepatitis A virus; HBV, hepatitis B virus; HEV, hepatitis E virus; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis; SBP, spontaneous bacterial peritonitis; SOFA, Sequential Organ Failure Assessment score; TIPS, transjugular intrahepatic portosystemic shunt.

Table 3. Acute-on-Chronic Liver Failure: Research Needs

Immediate priorities
Pool prospective data from the East and West to allow definition of ACLF and characterize clinical course
Standardize management protocols for treatment of precipitating events and organ failure
Develop and characterize animal models of ACLF to help define pathophysiology and allow development of novel therapies
Intermediate and long-term priorities
To understand ACLF better
Clinical- and biomarkers to understand pathophysiology and outline subtypes of ACLF
Noninvasive markers to diagnose chronic liver disease
Prognostic scores to guide management decisions and stratify groups in treatment trials
Define systemic, immunologic, and organ dysfunction in ACLF
Role of inflammation and tolerance in the pathogenesis of ACLF to improve outcome in patients with ACLF
Investigational protocols addressing
Optimal intensive care
Extracorporeal liver support systems
Stimulation of hepatic regeneration
Drugs targeting systemic inflammation or apoptosis
Role of liver transplantation

ACLF, acute-on-chronic liver failure.

ACLF. Survival data are required to develop scoring systems to determine which patient would benefit from intensive care, which patients would resolve with treatment directed at the specific insult (eg, hepatitis B[26]), which patients would benefit from novel therapies such as granulocyte colony-stimulating factor,[27] or artificial liver support, which patients require early liver transplantation, and in whom treatment would be futile. Determining prognosis is possible only if there is a uniform management strategy in all patients studied, including standardization of intensive care.[1] The role of noninvasive markers of hepatic fibrosis in detecting "chronic liver disease" at the time of diagnosis of ACLF needs to be evaluated in this population. Biomarkers are needed to optimize diagnosis and understand the pathophysiology of complications,[28] especially for patients who have no apparent precipitating factors for ACLF development, and for prognostication. The role of extracorporeal liver support systems, stimulation of hepatic regeneration, and drugs that inhibit apoptosis and systemic inflammation need to be explored further. The time frame to reach a validated definition of ACLF, develop prognostic scores, and reach a better understanding of the pathogenesis of multiple organ failure in this situation is likely to be 3–5 years.

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