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Acute-on-Chronic Liver Failure: What are the Implications?

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Abstract Acute-on-chronic liver failure (ACLF) is a clinical entity that is well recognized by those who care for patients with cirrhosis, however in spite of this widespread recognition, there remains little consensus with regard to definition and clinical features. While many similarities exist between ACLF and decompensated cirrhosis, there are also key differences, the implications of which are far reaching for both clinicians and patients alike. Among these differences are the possibility of a reversible component, the presence of a defined insult, prognosis, and outcomes associated with ACLF (see Fig. 1). However, for ACLF to have meaningful clinical implications, it first must be defined. If ACLF can be clearly defined and more easily recognized, then clinicians may be better able to prevent, treat, prognosticate, and counsel such patients.

Keywords Acute-on-chronic liver failure · Cirrhosis
End-stage liver disease

Introduction

In 1998, cirrhosis was the tenth leading cause of death in the United States, however this number may actually underestimate the number of deaths due to cirrhosis [1]. Additionally, there are greater than 300,000 hospital admissions related to complications of cirrhosis in the United States annually (data not published). As a direct result, nearly all providers of primary care, hospital medicine, and intensive care will encounter patients with cirrhosis. It is important for these providers to have guidance with regard to appropriate management when caring for this population

Cirrhosis is a progressive illness that may culminate in multiple system organ failure and death. For all practical purposes, cirrhosis itself is an irreversible phenomenon and the only curative option is liver transplantation. Unfortunately, for many patients transplant is not an option. Because of the complexities involved with determining transplant eligibility, clinicians who are not experienced in transplant medicine may make incorrect judgments regarding transplant eligibility, and therefore incorrect determination of the patients overall prognosis. Adding to the complexity of caring for patients with advanced liver disease is the presence of a potentially reversible condition known as acute-on-chronic liver failure (ACLF) which may be easily confused with advanced decompensated cirrhosis.

Often, patients who present with complications of cirrhosis are termed “end-stage” cirrhosis. In a number of cases the term “end-stage” is incorrectly applied, which may lead to under-resuscitation of patients who may have a reversible component to their illness. Conversely, many patients with true end-stage cirrhosis, an irreversible terminal illness (in the absence of a viable transplant option), will be subjected to excessive and non-beneficial medical intervention. The purpose of this manuscript is to provide a rationale for the concept of ACLF as opposed to end-stage cirrhosis, and to discuss potential clinical implications of an emerging clinical entity.

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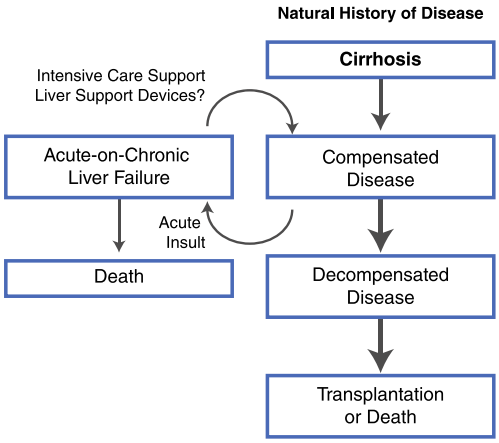

Fig. 1 A conceptual framework for differentiating ACLF from the natural history of cirrhosis. The right side of the diagram represents the pathway in which the majority of patients with cirrhosis will progress. The left side of the diagram represents patients who suffer an acute insult with associated deterioration (ACLF). With appropriate intensive care support, or perhaps with improvements in liver support devices, a percentage of these patients will go back to the previously compensated state. A similar percentage will not recover and ultimately succumb to their illness

Natural History of Cirrhosis

Cirrhosis is the end result of persistent hepatocellular insult, with the leading causes being chronic viral hepatitis, alcohol, and non-alcoholic fatty liver disease. Cirrhosis is characterized pathologically by a decrease in functional hepatocyte mass and architectural disruption of the liver by diffuse fibrosis. The clinical manifestations which result stem from a diminished functional capacity of the liver (i.e. impairment of synthetic function, and impaired metabolic functions) and those which result from portal hypertension and its associated complications. Cirrhosis may exist for many years in a compensated form with median survival of 10 years, however once decompensation ensues (as reflected by jaundice, ascites, variceal hemorrhage, or encephalopathy), mortality greatly increases with a dismal 5 year survival of 16% [2].

In select cases, the progression of cirrhosis may be slowed or halted if the underlying disease process is treated as in cases of viral hepatitis or alcohol related disease. With progression, patients will ultimately transition from compensated disease to decompensated disease. The time course over which this transition occurs is extremely variable and depends on a variety of factors which include, but are not limited to, underlying pathology of liver disease, age, presence of coexisting medical problems, sex, and genetics. Factors determining progression to decompensated disease are hepatic vein pressure gradient, MELD score, and serum albumin [3]. Once a transition to a persistently decompensated state occurs as reflected by refractory ascites, persistent encephalopathy, and renal failure, the disease should be regarded as a terminal end-stage illness if transplantation is not an option. Predictors of mortality in decompensated cirrhosis are the CTP and MELD scores [4, 5].

Defining ACLF as a Unique Clinical Entity

For a clinical entity to have meaningful significance, it must be unique, be recognizable, and have impact in patient management. For ACLF to be defined and recognized as a unique clinical entity, it must meet three major criteria: 1) It must be distinct from end-stage cirrhosis; 2) It should have at least one diagnostic sign or clinical test; 3) Other possible diagnoses should be able to be excluded.

At the present time, early studies are underway to identify a clinical pattern of disease that is distinct from end-stage cirrhosis, though large multi-center studies are lacking. A single diagnostic sign or clinical test has yet to be identified, however cerebral edema in the presence of chronic liver disease may serve this purpose. Finally, exclusion of other potential diagnoses will require careful evaluation of patients presenting with complications of cirrhosis.

In contrast to the natural disease progression of cirrhosis, a relatively new clinical entity of ACLF has been proposed [6•]. While on the surface there are many similarities between ACLF and end-stage cirrhosis, there are important differences. There are three key concepts which may serve to define ACLF as a unique clinical entity; a reversible component, a precipitating event, and a 3 month mortality, which is significantly higher than expected with decompensated cirrhosis (see Table 1).

The element of reversibility is perhaps the most important defining feature of ACLF. It is important to clarify that when discussing reversibility as it pertains to ACLF, we do not suggest that cirrhosis is reversible, rather that there is a component of the acute deterioration which is reversible. A study by Jalan and colleagues [7] identified and followed a large group of patients hospitalized with complications of cirrhosis. This study demonstrated that the mortality rate in this group was 53%, suggesting that reversibility occurred in nearly 50% of patients [7]. What is not clearly defined in this study is to what degree reversibility occurred. In other words, in order to be clinically meaningful, reversibility should reflect a return to a functional baseline, not simply the avoidance of death. Patients who suffered a repeat insult within a short time period had markedly higher mortality indicating that recovery is likely not to the pre-insult level.

An identifiable precipitating event is a second clue to the diagnosis of ACLF. The majority of cases have bacterial or fungal infections as a late event. Precipitating events leading to ACLF include superimposed acute viral hepatitis, drug induced hepatitis, or surgery. In end-stage cirrhosis, precipitating events leading to death are usually

Table 1 Comparison of ACLF and decompensated cirrhosis

Present in both conditions:	Unique to ACLF:
• Multi-system organ failure	• Reversibility
• Deranged systemic inflammatory response	• Precipitating Event
	• High Mortality (when compared to cirrhotic patients with similar MELD scores)
	• Cerebral Edema?

infections related to variceal bleeding or ascites, skin infections, pneumonia, or urinary tract infection.

Patients with ACLF have a larger functional cell mass at the time of insult and have previously well compensated disease. The insult in ACLF is likely that which would typically be associated with acute or fulminant liver failure, e.g. acetaminophen toxicity, acute viral infection, non-hepatic surgery, or to a lesser extent infection. The important difference between ACLF and acute liver failure in this setting is the existence of underlying cirrhosis in cases of ACLF. In the presence of cirrhosis, clinically significant cerebral edema is a rare finding but is known to exist [8•]. Cerebral edema with elevated intracranial pressure may in fact be a defining feature of ACLF. The mortality at 1 week, 6 weeks, and 3 months is estimated at 20%, 40% and 50%, respectively. The potential of spontaneous recovery is regarded as high and need for transplantation low.

Lastly, there are important short term differences in outcomes for patients presenting with ACLF as compared to patients with end stage cirrhosis. In one series, patients with presumed ACLF had significantly higher mortality at 30 days compared with patients with decompensated cirrhosis and the same MELD score. For ACLF the 30 day mortality at MELD scores of 20 and 30 was 23% and 35%, respectively. This is compared to decompensated cirrhosis with identical MELD scores whose 30 day mortality rates were 3% and 12% respectively (data not published).

Implications for the Patient and the Clinician

Management of patients with advanced liver disease remains a challenge. Perhaps one of the most difficult problems is determining which patients will benefit from ongoing aggressive management, which patients are transplant candidates, which patients require artificial or bioartificial liver support, and which patients will no longer benefit from intensive care support and therefore for whom all treatment is futile.

For patients and clinicians alike, a host of medical decisions are based on the best understanding of the prognosis of the disease. For example resuscitation status, palliative care decisions, and the utility and appropriateness of intensive care support are all influenced by this understanding. Unfortunately, many times there is significant confusion regarding prognosis in cirrhosis and patients receive mixed messages.

Patients with end-stage liver disease and no realistic transplant option should be counseled as to the ramifications of their precarious position. A reasoned discussion with regard to the prognosis will no doubt allow the patient and family to make informed decisions. In more advanced stages of disease, discussion of end-of-life care should be entertained and palliative care or hospice should be offered. This is also true for patients initially deemed transplant candidates but who suffer deterioration which does not respond to aggressive intensive care support and therefore become too ill to undergo transplantation.

Conclusions

Cirrhosis is a commonly encountered problem with high morbidity and mortality. Treatment options are limited and are mainly supportive; transplantation remains the only curative option. However, the number of patients with cirrhosis who will ultimately receive transplant is far out numbered by those who will not. This disparity results in a large number of hospitalizations related to cirrhosis, many of which culminate in a need for intensive care support. End-stage disease results when a persistent decompensated state exists. In contrast, ACLF carries the connotation of a potentially reversible process which, if aggressively treated, may allow the patient to return to a previous level of health and ideally, return to a functional status.

Current attempts to better define the natural history of ACLF and to better define the clinical features of this process are underway. At present no simple tool exists for differentiating end-stage cirrhosis from ACLF and no single diagnostic sign or test exists. For clinicians to accurately determine if a patient is suffering from ACLF or decompensated cirrhosis requires a sound knowledge of the natural history of both processes coupled with a review of patients' past medical history. Future research will better define ACLF. In the interim, when it is unclear, all patients should receive aggressive care to a level which is compatible with the patients' overall goals of care. All patients with end-stage liver disease may benefit from palliative care and being active on the transplant list does

not preclude this addition [9]. In fact, patients' overall quality of life may be improved by such consultation.

All patients should have evaluation in a liver transplant center to help establish the stage of illness and to define potential transplant options for the patient and to provide direction for primary care providers. Certainly, ongoing communication between all concerned parties will ensure that the patient remains well informed and that he or she receives the best possible care.

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