Defining ‘acute on chronic liver failure’: an identity crisis!

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‘We should be careful to get out of an experience only the wisdom that is in it and stop there; lest we be like the cat that sits down on a hot stove lid. She will never sit down on a hot stove lid again—and that is well; but also she will never sit down on a cold one anymore.’

Mark Twain
1835–1910

What’s in the name?

A clinical syndrome represents a typical constellation of physical and laboratory findings that may be seen as a part of one or more primary disease processes. Clinical syndromes have often been born out of astute observations by experienced clinicians with sharp observation and pattern recognition skills. Defining clinical syndromes is helpful since familiarity with a particular clinical pattern leads clinicians along the ‘problem-solving’ pathway to arrive at a specific diagnosis and plan an appropriate management in future patients. Description of a new clinical syndrome naturally attracts attention and ‘case definition’ is an essential first step in any focused investigations related to the new clinical entity. Historically, many of the clinical syndromes were described with the presumption of a common underlying pathophysiological mechanisms. Although, seldom have these stood the tests of time and scientific rigor: most syndromes continue to have multiple causes, often with disparate treatment modalities and outcomes.

Clinicians have for long recognized that patients with cirrhosis could decompensate acutely due to precipitating events such as variceal bleeding, ischemic hepatitis, or sepsis. A perception that common pathophysiological mechanisms underlie these presentations (in contrast with progressive decompensation that occurs in end-stage cirrhosis) has led to the christening of this syndrome, ‘acute on chronic liver failure’ (ACLF).

Alcoholic hepatitis as a paradigm for ACLF

Alcoholic hepatitis is one of the most recognized ‘acute on chronic’ liver conditions. This is a common clinical syndrome with rapid onset of jaundice and liver failure that generally occurs after years of heavy drinking. Other common clinical features include fever, tender hepatomegaly, coagulopathy and encephalopathy in its severe form. Liver biopsy in patients with alcoholic hepatitis reveals ballooning of hepatocytes and Mallory-Denk bodies, which are often surrounded by neutrophils. The condition is associated with binding of gut-derived lipopolysaccharide (LPS)-endotoxin to CD14 (monocyte differentiating antigen), which in turn combines with toll-like receptor 4 (TLR4), leading ultimately to activation of several cytokine genes. Cytokines such as tumor necrosis factor-alpha (TNF-α) have both a paracrine effect on hepatocytes, leading to induction of cytotoxicity, and systemic effects such as fever, anorexia and weight loss that are characteristics of alcoholic hepatitis [1]. Alcoholic hepatitis is considered to be the most severe manifestation...
of alcoholic liver disease with 30-day mortality rates of 35–50% [2]. Although majority of subjects with histological evidence of alcoholic hepatitis also have co-existent cirrhosis [3, 4], short-term outcome of alcoholic hepatitis is clearly worse than that of decompensated cirrhosis. Consistent with this, glucocorticosteroids, which dampen the inflammatory process and reduce circulating TNF-α, or pentoxifylline, a phosphodiesterase inhibitor that modulates TNF-α transcription, may improve short-term survival in patients with alcoholic hepatitis [5, 6] without any significant influence on the long-term outcome.

However, one needs to acknowledge that despite a large number of studies over the past three decades, the debate as to whether the clinical manifestations or histological features define alcoholic hepatitis remains unresolved. There is no consensus on which of the plethora of available prognostic models (Maddrey discriminant function [7], Glasgow alcoholic hepatitis score [8], Lille model [9] and Model of end stage liver disease [MELD] [10] including its modifications) should be used to assess severity of alcoholic hepatitis and identify candidates suitable for specific therapy. Also, there is no universal acceptance that steroid therapy is beneficial in alcoholic hepatitis [2, 11].

Sepsis and ‘sepsis-like’ state

Beyond alcoholic hepatitis, the observation that conditions classified as ACLF are often associated with multiple organ failure similar to that in patients with ‘septic shock’ has led to the hypothesis that a form of ‘immune paralysis’ may underlie both conditions. Monocytes are important mediators of the immune response to sepsis with their ability to secrete cytokines such as interleukin 1 (IL-1) and TNF-α which lead to recruitment of inflammatory effector cells such as polymorphonuclear cells and lymphocytes. The monocytes also present antigens with MHC class II molecules to T cells leading to the latter’s activation and proliferation. The monocytes from patients with septic shock demonstrate a reduced ability to produce TNF-α in response to LPS and reduced HLA-DR expression, a phenomenon called as ‘endotoxin tolerance’. In a recent study, patients with ACLF (cirrhosis with a recent development of jaundice, ascites, hemodynamic instability and or encephalopathy requiring admission to intensive care unit) were found to have immunological defects that are strikingly similar to those seen in association with ‘sepsis’ [12]. In contrast, patients with stable cirrhosis did not manifest such ‘immune paralysis’. However, in 13 of 27 subjects in the ACLF group, acute decompensation had been triggered by infections (spontaneous bacterial peritonitis, pneumonia and erysipelas) [12], and hence, it can be argued that ‘functional monocyte deactivation’ seen in ACLF group was indeed secondary to ‘sepsis’ rather than a phenomenon that typifies ACLF.

Circulatory changes and oxidative stress

Patients with cirrhosis have characteristic circulatory changes with the development of systemic vasodilation, a hyperdynamic circulation which is associated with decrease in effective arterial blood volume [13]. These circulatory changes become exaggerated during the run up to ACLF. Endothelial nitric oxide synthase (eNOS) may be responsible for this splanchnic vasodilatation. In addition, cytokine or endotoxin challenge leads to a widespread expression of inducible NOS (iNOS) which is associated with microvascular damage in cardiac, pulmonary, renal and hepatic tissue [14]. Albumin infusion has been used to counter these circulatory changes and it has been shown to be effective in the management of spontaneous bacterial peritonitis [15] and hepatorenal syndrome [16]. However, a recent study has investigated the functional capacity of albumin to undertake various functions such as fatty acid transport, metal chelation, drug binding and antioxidant activity using electron paramagnetic resonance spectroscopy in patients with acute deterioration of cirrhosis and controls [17]. These investigations showed that the loss of metal chelation function, as evidenced by increasing ischemia-modified albumin (IMA), expressed as IMA to total albumin ratio (IMAR) was significantly higher in patients with ACLF (defined as cirrhosis with organ dysfunction) compared with those with cirrhosis but no organ dysfunction. Raised IMAR also correlated closely with disease severity (MELD score) and survival. The authors speculated that IMA reflects exposure of albumin to hydroxyl radicals; increasing IMA and associated loss of metal chelation function would contribute to release of metal ions into the system, where they become redox active contributing to further radical formation [17]. Thus, the effect of albumin in patients with ACLF may be mediated by mechanisms other than its value as a plasma expander.

While a journey through the concept of ACLF has improved our understanding of pathophysiological mechanisms underlying many common events that modify the natural history of cirrhosis, admittedly the distinction between ACLF and decompensated cirrhosis is increasingly blurred with rapidity of decompensation being the key difference.

What’s inside the name?

Experts from the Asian Pacific Association for the Study of the Liver (APASL) have arrived at the definition and diagnostic criteria for ACLF and their consensus recom-
mendations have been published recently [18]. APASL should be commended for the enthusiasm and perseverance (the process started in 2004) that took to develop these recommendations which include lists of conditions that are classified as acute events, chronic liver diseases and the criteria that define liver failure. The key to the distinction of ACLF is the acuity of events (<4 weeks) that precipitates liver failure in contrast with more prolonged period of deterioration seen with decompensated end-stage cirrhosis. The recommendations have also included chronic liver diseases such as non-alcoholic steatohepatitis (NASH) and chronic hepatitis in addition to cirrhosis as the underlying chronic liver damage on which acute liver injury supervenes. This may allow some important research questions to be asked especially in relation to hepatotoxicity.

Determined to establish an identity to ACLF, recommendations list conditions that qualify as ‘acute events’; an attempt to distinguish events that cause hepatic insult and ‘is of hepatic origin’ (infections with hepatotropic viruses included within the definition) from those which aren’t (other systemic infections and sepsis are excluded) has led to some arbitrary distinctions. For example, the presumption that reactivation of hepatitis B leading to ACLF is distinct from acute liver failure, but shares a common pathophysiology with other acute events included in the definition defies any evidence that is presented. On the other hand, description of pathophysiology of ACLF includes largely the role of sepsis and ‘sepsis-like’ state in contradiction to its exclusion from the definition. Alcoholic hepatitis which is the most eligible member for ACLF group has been included. Acute variceal bleeding that often complicates liver cirrhosis precipitating decompensation has also been included despite the acknowledgement that no consensus was reached regarding this being an acute event. While surgical intervention has made the list of ‘acute event’ in spite of the debate as to whether or not it causes direct hepatic insult; ischemic hepatitis and portal vein thrombosis have been left out. As the stated objective of the consensus was to identify patients with ‘a homogenous presentation and similar outcome’, neither was it necessary to list conditions that qualify as acute events (as the definition of acuity, liver failure and chronic conditions would have sufficed), nor adequately justified as the outcome should be what matters. Unsurprisingly, the strength of support to individual recommendations has been variable especially those for which experts failed to achieve unanimity.

Hope is that the ‘consensus’ will stimulate epidemiological studies that estimate the burden of some of these problems in countries where these definitions become adopted. Although recognising ACLF in those with known chronic liver disease may remind the clinician of the potential reversibility of the acute insult, in those subjects where underlying chronic liver disease is unknown at the time of acute presentation, classification of ACLF will be retrospective. Beyond this, it would be hasty to conclude that these definitions ‘identify patients who have a homogenous presentation with similar outcome’ and unreasonable to expect a common underlying pathophysiology or similar response to interventions in these circumstances.

Sir Peter Medawar, winner of the Nobel Prize in Physiology or Medicine 1960, said once—‘I believe that a reasonable case can be made for saying, not that we believe in God because He exists, but rather that He exists because we believe in Him...’. On a similar note, one has to accept that the consensus recommends that ‘acute on chronic liver failure’ be recognized as a clinical syndrome. One should remain open minded as to whether proposed investigations unravel a novel pathophysiology, unique natural history or lead to a critical intervention that improves the outcome and link these otherwise apparently heterogeneous conditions. Only time will tell.

References