Current Evidence for Extracorporeal Liver Support Systems in Acute Liver Failure and Acute-on-Chronic Liver Failure

Constantine J. Karvellas, MD, SM, FRCPC[a,b,*],
Ram M. Subramanian, MD[c,d]

KEYWORDS

- Extracorporeal liver support • Albumin dialysis • Acute liver failure
- Acute-on-chronic liver failure • Extracorporeal liver assist device
- Liver transplantation

KEY POINTS

- Supporting detoxification and synthetic functions of the failing liver is the rationale for the use of extracorporeal liver support (ECLS) systems.
- Bioartificial ECLS (B-ECLS) systems incorporate a bioreactor containing various forms of hepatocytes to provide synthetic functions.
- Artificial and bioartificial liver support devices have shown certain detoxification capabilities and biochemical improvement in patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF), but their effects have failed to correlate with survival benefit.
- High-volume plasmapheresis (HVP) is the only therapy that has demonstrated a statistically significant benefit in transplant-free survival in ALF patients.
- Further refinement of target populations and adequate endpoints, optimization of therapy delivery, and avoidance of futile therapy seem to be essential steps for future ECLS devices to become integrated in standard medical therapy (SMT) for specific subpopulations of ALF and ACLF patients.

Disclosure Statement: None.
[a] Division of Hepatology, University of Alberta, Edmonton, Alberta, Canada; [b] Division of Critical Care Medicine, University of Alberta, 1-40 Zeidler Ledcor Building, Edmonton, Alberta T6G-2X8, Canada; [c] Division of Hepatology, Emory University, Atlanta, GA, USA; [d] Division of Critical Care Medicine, Emory University, Atlanta, GA, USA
* Corresponding author. Liver Unit, Division of Gastroenterology, University of Alberta, 1-40 Zeidler Ledcor Building, Edmonton, Alberta T6G-2X8, Canada.
E-mail address: dean.karvellas@ualberta.ca

Crit Care Clin 32 (2016) 439–451
http://dx.doi.org/10.1016/j.ccc.2016.03.003 **criticalcare.theclinics.com**
0749-0704/16/$ – see front matter

INTRODUCTION: THE TWO SYNDROMES OF LIVER FAILURE

Acute Liver Failure

ALF is defined by hepatic encephalopathy (HE) and synthetic dysfunction within 26 weeks of the first symptoms of liver disease.[1] The most common cause of ALF in North America and Europe is acetaminophen (*N*-acetyl-p-aminophenol [APAP]).[2,3] Particularly in APAP-induced ALF, cerebral edema and intracranial hypertension continue to be major causes of morbidity and mortality along with multiorgan failure due to the systemic inflammatory response (SIRS).[4,5] Current management of ALF (in particular, hyperacute ALF) is directed at reducing intracranial hypertension, including osmotic agents (mannitol or hypertonic saline),[6] control of blood pressure, ammonia-lowering therapies (eg, hemofiltration[7]), and therapeutic hypothermia.[8]

Acute-on-Chronic Liver Failure

In contrast, ACLF is defined as patients with cirrhosis hospitalized for acute decompensation and organ failure who are at a high mortality risk.[9] ACLF usually presents as an acute deterioration in liver function over a 2-week to 4-week period in a patient with preexisting chronic liver disease. Similar to ALF, the lack of the metabolic and regulatory function of the liver results in life-threatening complications that may include variceal bleeding, acute kidney injury (AKI), HE, cardiovascular failure, and susceptibility to infections culminating in multiorgan failure.[10] Recently the chronic liver failure (CLIF)–sequential organ failure assessment (SOFA) score has demonstrated that accumulating organ failures in ACLF patients in the absence of transplant is associated with increased mortality.[9]

Rationale for Use of Extracorporeal Liver Support in Acute Liver Failure and Acute-on-Chronic Liver Failure

In both ALF and ACLF, toxins accumulate as a result of impaired hepatic function and clearance. Ammonia, inflammatory cytokines, aromatic amino acids, and endogenous benzodiazepines have been implicated in the development of HE and cerebral edema (ALF). Other systemic factors, such as nitric oxide and cytokines, have been linked with circulatory and renal dysfunction in liver failure. Proinflammatory cytokines and damage-associated molecular patterns (DAMPs) have broad effects, ranging from increased capillary permeability to modulating cell death and immune dysregulation.

Currently, the only definitive therapy for patients with ALF and ACLF when poor prognostic criteria are met is liver transplantation (LT). Many patients die, however, before a suitable graft is available and, for those who progress to multiorgan failure, LT is not an option. Particularly in APAP-ALF, however, the liver often maintains some regenerative capacity, so the rationale for supportive therapy and extracorporeal systems is to provide an environment facilitating recovery to create or prolong a window of opportunity for LT, or, in the best case scenario, until native liver recovery occurs in APAP-ALF without cerebral edema/multiorgan failure, or a period of stability for those with ACLF until an organ becomes available.[11]

From a theoretic perspective, an effective ECLS should assist 3 major hepatic functions: detoxification, biosynthesis, and regulation.

In both ALF and ACLF, aims of ECLS are to remove putative toxins, preventing further aggravation of liver failure; to stimulate liver regeneration; and to improve the pathophysiologic features of liver failure.[12] None of the devices currently available, however, fulfills these requirements completely.