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Hot Topic Commentary

Defining the Value of Extracorporeal Liver Support in Acute and Acute-on-chronic Liver Failure

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Next to acute liver failure (ALF) without previous liver disease, the concept of acute-on-chronic liver failure (ACLF) has been developed.[1,2] In most cases patients developing ACLF first have acute decompensation (AD) of cirrhosis, often with ascites, hepatic encephalopathy, variceal bleeding, or hepatorenal syndrome. AD can be induced by infection or other factors, like hepatitis exacerbation. Both ALF and ACLF develop rapidly, ALF within 26 weeks of onset, ACLF in 2–4 weeks, and both conditions share the symptoms of a failing liver. Decreased detoxification with jaundice and hepatic encephalopathy, and impaired synthetic capacity of the liver with changes in coagulation parameters are part of these syndromes. In both ALF and ACLF multi-organ failure can develop, including hemodynamic instability, respiratory failure and acute kidney injury, and patients become susceptible to infections. Although standard medical treatment (SMT) in the intensive care unit has improved over the years,[2,3] both conditions often lead toward death, unless a timely liver transplantation (LT) is possible.[4,5]

In both ALF and ACLF there is accumulation of toxins, like ammonia and benzodiazepines, leading to encephalopathy. Inflammatory cytokines and damage-associated molecular patterns are among the factors worsening cellular injury, endothelial damage and increased vascular permeability, impairing regeneration, leading toward cell necrosis and regulated cell death, including ferroptosis.[6] Nitric oxide and its metabolites induce splanchnic and systemic vasodilatation with hemodynamic instability and acute kidney injury. Although much is still unknown about pathophysiology of ACLF, systemic inflammation seems the overarching mechanism.[2]

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALF, acute liver failure; B-ECLS, biological ECLS; DPMAS, double plasma molecular molecular absorption system; ECAD, extracorporeal albumin dialysis; ECLS, extracorporeal liver support systems; HE, hepatic encephalopathy; HVPE, high-volume plasma exchange; LT, liver transplantation; MARS, molecular absorbent recirculating system; NB-ECLS, nonbiological ECLS; RCT, randomized controlled trial; SMT, standard medical treatment; SPAD, single-pass albumin dialysis.

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The use of extracorporeal liver support systems (ECLS) to bridge the patient to LT or recovery has been investigated. ECLS aim to improve detoxification, biosynthesis, regulation, and regeneration, for improving neurological status, hemodynamics, reducing inflammation and enhancing regeneration.[7,8] Most publications on ECLS pertain to nonbiological systems (NB-ECLS). More recently biological ECLS (B-ECLS) are being developed and tested further; these include a bioartificial liver with hepatocytes, aiming at improved detoxification and adding biosynthesis. Different systems of NB-ECLS have been developed. As shown in Figure 1, most are based on filtration and absorption. They remove toxins by using membranes with different pore sizes, and include a dialysis circuit with albumin or plasma with absorbent columns to remove albumin-bound toxins. Various systems have been developed, with differences in type of renal replacement therapy, dialysate, membranes, absorption columns, extracorporeal volume and combination with other extracorporeal therapies like high-volume plasma exchange (HVPE). Apart from the rarely used single-pass albumin dialysis (SPAD) the Molecular Absorbent Recirculating System (MARS) is the best studied type of extracorporeal albumin dialysis (ECAD). It uses a small-pore high-flux dialysis with albumin in the dialysate and two absorption columns with activated charcoal and an anion exchange resin. This removes most water-soluble and albumin-bound toxins, but molecules larger than 50 kD, such as growth factors, do not pass the membrane. Plasma-absorption techniques like fractionated plasma separation and absorption (PROMETHEUS) and selective plasma filtration technology (SEPET) use more nonselective membranes with larger pores and the latter does not use a parallel dialysis circuit. In PROMETHEUS, plasma is fractionated through an albumin-permeable filter allowing passage of molecules <300 kD, allowing albumin and other proteins to pass; then an ion exchange column and a neutral column follow, and the cleansed albumin and plasma are returned to the standard blood-pool circuit where it is treated by conventional high-flux dialysis. In SEPET, because of the limited membrane pore size, mediators of inflammation are removed, but immunoglobulins, complement factors, blood clotting factors and stimulators of regeneration are largely retained.[7,8]

The clinical effects of ECLS are under investigation. The randomized clinical trials (RCTs) that have been conducted included different types of ECLS and separate studies of ALF and ACLF. Several NB-ECLS systems showed some detoxification capabilities and improvement of biochemistry, without a survival benefit. The FULMAR study suggested that ECLS

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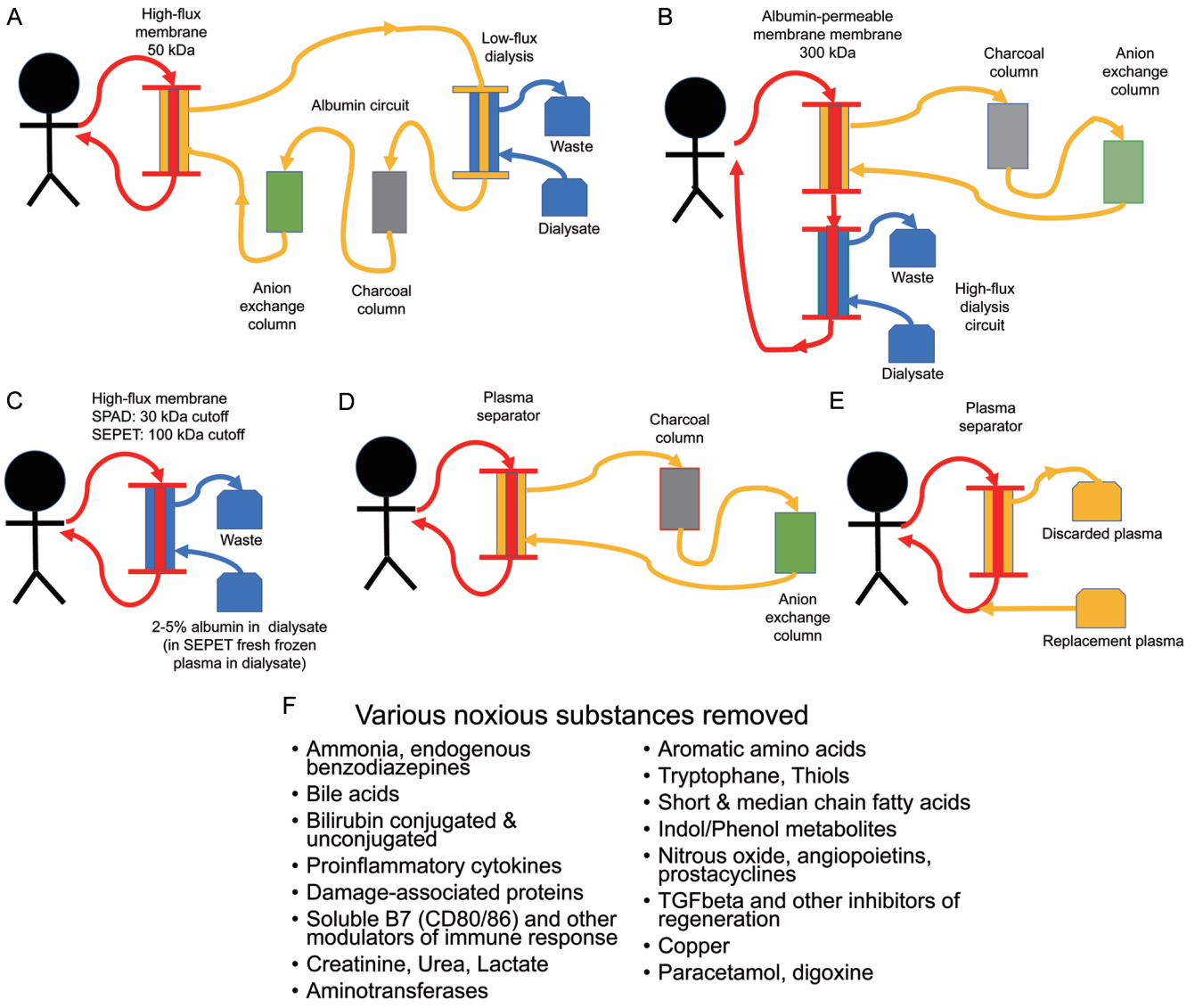

Fig. 1. Extra-corporeal liver assist systems. (A) MARS, molecular absorbent recirculating system; (B) PROMETHEUS, fractionated plasma separation and absorption; (C) SPAD, single-pass albumin dialysis or SEPET, selective plasma filtration technology; (D) DPMAS, double plasma molecular absorption system; (E) HVPE, high-volume plasma exchange; (F) The various noxious substances removed. Blood circuit, red; albumin or plasma circuit, yellow; dialysis circuit, blue.

with three or more MARS sessions may be considered for patients with ALF who are not candidates for LT. A multicenter study from the US Acute Liver Failure Study Group registry with propensity-score matched controls showed that MARS was significantly associated with increased 21-day transplant-free survival. In the largest RCT in ACLF so far, the RELIEF study, there was no survival benefit both in intention-to-treat and in per-protocol analysis, despite improved renal function in hepatic encephalopathy in the MARS group. Most studies in ALF and ACLF with different ECLS systems showed improved biochemistry, clearance of bilirubin, bile acids, toxins, and cytokines, most showed improved hemodynamic stability, and neurologic improvement. As ACLF is characterized by systemic inflammation, it may be important that MARS decreased the oxidative burst of neutrophils. MARS improved portal and systemic hemodynamics, while PROMETHEUS did not. That may be due to removal of nitric oxide by MARS, but not by PROMETHEUS. In the HELIOS study with PROMETHEUS in ACLF no survival benefit could be demonstrated. A theoretical risk of these systems is the interaction with pro- and anticoagulation and fibrinolysis in these patients who often have a bleeding tendency. Systems with large pore filters, like PROMETHEUS, theoretically may have the disadvantage of losing clotting factors. However, the larger studies so far mentioned have not shown negative effects on pro- and anticoagulation and fibrinolysis compared with SMT of MARS, PROMETHEUS, and HVPE. Of the few B-ECLS studies, the ELAD study reported a trend toward improved survival in the group with lower MELD scores.[1,7,8]

HVPE is a safe, established therapy for several autoimmune disorders. Case series in ALF suggested that HVPE could improve hemodynamic stability and hepatic encephalopathy. A prospective study of HVPE in ALF demonstrated a survival benefit for those not receiving LT, and a trend to improved survival for all patients. Moreover it was demonstrated that ammonia, damage-associated molecular pat-

Table 1. Summary of findings and recommendations regarding artificial liver support from the modified DELPHI consensus of international experts[10]

ECAD using MARS is the most studied ECLS.
ECAD showed a beneficial effect on hepatic encephalopathy (HE), refractory pruritus, renal function, reduction of cholestasis, bilirubin and bile acids, and improvement of systemic and portal hemodynamics and vasoactive mediators.
ECLS was considered safe, but use should be restricted to centers experienced in management of patients with advanced liver disease or with a transplant project.
In ALF
ECAD is associated with significant improvement of 21-day survival in acetaminophen etiology, which improvement appears correlated to patient selection and intensity of treatment
ECAD is not associated with improvement in 6- or 12-month survival
ECAD is not beneficial at late stages of ALF with multi-organ failure
ECLS is contra-indicated in patients with uncontrolled severe sepsis
HVPE is associated with improved in-hospital survival and transplant-free survival
In ALF either HVPE or ECAD may be considered as bridging therapy to LT, ECAD especially with acetaminophen toxicity as the etiology
In AD or ACLF
ECAD is not associated with improved 28–90 day survival
ECAD should be considered in patients with HE refractory to 24–48 h SMT
ECAD may be considered in hepatorenal syndrome not responding to terlipressin and albumin as bridge to LT
ECAD should not be considered in patients with either severe infections, sepsis, septic shock, acute respiratory distress syndrome (ARDS) or ACLF grade 3
Further expert recommendations
ECAD is preferably administered at an early stage of HE (grades 2–3) and as sessions of 8 h, minimally 3× on the first consecutive days to induce a significant improvement of HE and hemodynamics, minimum 3× in ALF and minimum 5× in the first 7–10 days in ACLF
The decision to stop or continue ECLS after a minimum of three sessions of 8 h should be based on a careful individual clinical assessment of efficacy and safety
Antimicrobial medications choice and dosing need to be adapted (when the effect of ECLS on their clearance is known)
ECAD may be considered in liver cholestasis and severe refractory pruritus not responding to SMT
ECAD might be considered in some cases after LT with criteria similar to non-LT population and only in patients listed for re-LT
ECAD might be considered in drug overdose/poison with high degree of albumin binding
ECAD is not recommended in post-hepatectomy liver failure outside prospective trials
ECAD is not recommended if high risk of bleeding exists (platelet count <40,000/mm^3, INR >2.5, fibrinogen <1 g/L) because of fibrinolysis and DIC
Circuit anticoagulation with unfractioned heparin or citrate should be used

ACLF, acute-on-chronic liver failure; AD, acute decompensation of cirrhosis; ALF, acute liver failure; ARDS, acute respiratory distress syndrome; DIC, diffuse intravascular coagulation; ECAD, extracorporeal albumin dialysis; ECLS, extracorporeal liver support systems; HE, hepatic encephalopathy; HVPE, high-volume plasma exchange; LT, liver transplantation; MARS, molecular absorbent recirculating system; SMT, standard medical treatment; SPAD, single-pass albumin dialysis.

terns and inflammatory cytokines like sB7 (CD80/86) were removed by plasmapheresis, possibly improving hemodynamic stability and creating an environment allowing liver regeneration.[9]

There are several shortcomings in all of these studies, including being underpowered, lack of blinding, confounding by indication, and heterogeneity of the patient groups studied. There were different etiologies of ALF or ACLF and differences in severity and organs affected. Recently, based on these studies, a modified DELPHI consensus was reached by international experts. The findings and expert recommendations are summarized in Table 1. Several clinical trials with ECLS are ongoing, some with new devices, as summarized in a consensus paper.[10]

In the current issue of the Journal of Clinical and Translational Hepatology Wu *et al*.[11] present data on an RCT in a group of 186 patients with ACLF due to hepatitis B virus (HBV) infection. These patients were randomized to SMT or to the double plasma molecular molecular absorption system (DPMAS), or to DPMAS in combination with half-dose HVPE with a low-volume of 1–1.5 L. Combining DPMAS and half-dose HVPE theoretically reduces the disadvantages of both systems, namely the impact of DPMAS on coagulation and the large volume involved in HVPE and limited plasma supply in some countries. The patients with a moderate degree of liver failure (prothrombin time >40%) receiving the combined DPMAS and half-dose HVPE had improved 28-day survival and had a cost-effectiveness advantage compared with SMT and DPMAS alone, but there was no survival benefit in patients with more severe liver failure.

A strength of this study is that it concerns relatively larger and rather homogeneous patient groups with ACLF due to HBV. The finding that patients with the less advanced stage of ACLF seemed to benefit, while those in more advanced stages did not is compatible with the recent DELPHI consensus recommendations.[10] Moreover, the combined system with DPMAS and half-volume HVPE was more cost-effective than that of full-dose HVPE. Obviously this study has limitations. The classification of ACLF by prothrombin time is not ideal. Despite a shared etiology of HBV heterogeneity in the patient groups regarding number of organs involved, stage of ACLF, and comorbidity cannot be excluded. It is remarkable that none of the patient groups had a survival advantage with HVPE alone, in contrast to the study of Larsen *et al*.[9] in ALF. This may be due to the difference between ALF and ACLF, difference in etiologies, technology (higher versus lower volume HVPE), or other differences. The cost advantage may disappear if all additional costs are included, and it may be different in other countries. While the current study is another important piece in the puzzle, it certainly is not the final answer. However, it may help in finding the optimal system for ACLF, and in defining the target population for ECLS, avoiding futile therapy in patients who would not benefit. It is important to adhere to the recommendations from the recent DELPHI consensus, which are summarized in Table 1, as much as possible, both in individual patient care as well as in trials. Importantly, ECLS should not be used during uncontrolled sepsis, and probably regional anticoagulation is to be preferred. There has been a lack of studies comparing different ECLS modalities. Because of hemodynamic improvement with MARS but not PROMETHEUS, the first might be preferred over the second, but it cannot be excluded that other systems are better than MARS. In ALF, plasmapheresis has a survival benefit if rapid LT is not possible. The paper by Wu *et al*.[11] suggests that a combination of DPMAS with plasmapheresis in ACLF may be more beneficial than either alone. Treatment in earlier ACLF stages may have more impact and be more cost-effective than treatment at more advanced ACLF stages. Large randomized controlled studies with more homogeneous patient groups are needed, also comparing different ECLS modalities, with stratification of patients according to an established scoring system like the CLIF-SOFA score. In parallel, mechanistic studies on hemodynamics, immunology, and regeneration can be performed to better understand ALF, ACLF, and treatment effects.

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Conflict of interest

BvH has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2022.

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