Liver replacement therapy with extracorporeal blood purification techniques current knowledge and future directions

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Abstract

Clinically, it is highly challenging to promote recovery in patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF). Despite recent advances in understanding the underlying mechanisms of ALF and ACLF, standard medical therapy remains the primary therapeutic approach. Liver transplantation (LT) is considered the last option, and in several cases, it is the only intervention that can be lifesaving. Unfortunately, this intervention is limited by organ donation shortage or exclusion criteria such that not all patients in need can receive a transplant. Another option is to restore impaired liver function with artificial extracorporeal blood purification systems. The first such systems were developed at the end of the 20th century, providing solutions as bridging therapy,

either for liver recovery or LT. They enhance the elimination of metabolites and substances that accumulate due to compromised liver function. In addition, they aid in clearance of molecules released during acute liver decompensation, which can initiate an excessive inflammatory response in these patients causing hepatic encephalopathy, multiple-organ failure, and other complications of liver failure. As compared to renal replacement therapies, we have been unsuccessful in using artificial extracorporeal blood purification systems to completely replace liver function despite the outstanding technological evolution of these systems. Extracting middle to high-molecular-weight and hydrophobic/protein-bound molecules remains extremely challenging. The majority of the currently available systems include a combination of methods that cleanse different ranges and types of molecules and toxins. Furthermore, conventional methods such as plasma exchange are being re-evaluated, and novel adsorption filters are increasingly being used for liver indications. These strategies are very promising for the treatment of liver failure. Nevertheless, the best method, system, or device has not been developed yet, and its probability of getting developed in the near future is also low. Furthermore, little is known about the effects of liver support systems on the overall and transplant-free survival of these patients, and further investigation using randomized controlled trials and meta-analyses is needed. This review presents the most popular extracorporeal blood purification techniques for liver replacement therapy. It focuses on general principles of their function, and on evidence regarding their effectiveness in detoxification and in supporting patients with ALF and ACLF. In addition, we have outlined the basic advantages and disadvantages of each system.

Core Tip: Elimination of liver toxins during liver failure is a highly difficult and complex process and demands a combination of multiple methods. Although the evolution of artificial extracorporeal systems is remarkable, it is still insufficient to meet the current therapeutic demands. Several methods and circuits are available, each one with different features, advantages, and disadvantages. There is an urgent need for more research, randomized controlled trials, and evidence. Implementation of protocols combining the available techniques in response to each patient's special needs is probably the key to personalized treatment, as bridging therapy either to recovery or to liver transplantation.

INTRODUCTION

Artificial extracorporeal blood purification techniques offer the possibility of liver replacement therapy (LRT) in patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF). Artificial liver support systems (LSSs) can efficiently remove cytokines and a wide variety of hepatotoxic metabolites, including ammonia, fatty acids, bilirubin, bile acids, and amino acids[1]. The removal of cytokines using LSSs has been shown to intervene in the immunologic processes occurring during ALF and ACLF. Thus, these system-based therapies are considered immunomodulatory interventions, with their widespread implementation in treating both septic patients and those with liver failure. An increasing number of studies are being conducted to evaluate the role of the immune system in the pathophysiology of liver failure, which presents certain features that differentiate ACLF from ALF. More specifically, ACLF is a clinical syndrome that is characterized by the acute decompensation of chronic, pre-existing liver disease, usually led by a precipitating event, such as an underlying infection and is often accompanied by multiorgan failure (MOF) and high mortality. The basis of the pathophysiological mechanisms in ACLF is the hyperinflammatory state, which is triggered by factors called pathogen- and damage-associated molecular patterns (PAMPs and DAMPs)[2]. On the other hand, ALF represents a life-threatening condition that is usually the result of an offending agent, such as medications or viral infections in patients without pre-existing liver disease. It is characterized by an overwhelming systemic

inflammatory response, hepatocyte necrosis and accumulation of bile acids and ammonia, which can lead to permanent liver damage, encephalopathy and cerebral edema[3,4].

The production of toxins and vasoactive agents by intestinal bacteria and the accumulation of these molecules due to the diminished liver detoxification capacity play a significant role in the pathophysiology of liver failure[5]. The accumulation of these toxins induces complications of liver failure, such as increased intracranial pressure (ammonia) and hepatic encephalopathy (HE) (ammonia and amino acids). Furthermore, it is associated with increased mortality, especially in patients with high levels of bilirubin[6]. Therefore, the removal of all these deleterious molecules can protect patients from a wide variety of complications and dangers, thereby exerting beneficial effects.

Although progress has made these modalities very effective in removing their target molecules, whether this improves overall survival (OS), transplant-free survival (TFS) or even short-term survival, as bridging to liver transplantation (LT) is a question that remains to be answered. Nevertheless, except for plasma exchange (PE) therapy, none of these systems has resulted in favorable outcomes such as those mentioned in randomized controlled studies (RCTs), and only a few studies have systematically investigated these issues. This is largely attributed to complex liver physiology. Because each method individually has a narrow spectrum of toxin removal, a combination of methods is used in the majority of cases. The clinical condition of patients with ALF and ACLF is highly complex and is constantly changing, demanding adaptation to the modality applied; thus, only a combination that fits the specific clinical condition can be used. In addition, concerns exist about the loss of antibiotics and functional molecules such as albumin during these therapies, whereas cytokine removal is non-selective for most of these systems, leading to an imbalance between the levels of pro- and anti-inflammatory mediators, with unpredictable clinical effects.

The present review outlines the principles of function and the applications of the most popular and widely available artificial extracorporeal systems for LRT (Figure 1). It describes their methods of detoxification, major advantages and disadvantages, their practice in patients with liver failure, and their effect on patients' survival.

RENAL REPLACEMENT MODALITIES (CONVECTION/DIFFUSION THERAPIES)

Continuous renal replacement therapy

Apart from liver dysfunction, patients with ALF and ACLF often present with decompensation of functions of other organs, including the kidneys, with relative rates reaching up to 70%[7]. Renal replacement therapy (RRT) is often necessary in these patients either due to concomitant renal failure or due to a liver indication, in most cases hyperammonemia. Hyperammonemia is a common metabolic disorder, which is associated with cerebral edema and elevated intracranial pressure, especially in patients with ALF and rarely in those with ACLF. In fact, due to the serious complications associated with hyperammonemia, mainly regarding HE and cerebral edema[8], prompt initiation of RRT is indicated even in the absence of renal failure, when this serious metabolic derangement is present at these patients[8,9]. Although no specific cut-off for the initiation of RRT exists based solely on this indication, the majority of the studies suggest it's initiation when the value of ammonia is thrice greater than the upper limit of normal, or greater than 200 μmoles/L or when the patient shows severe encephalopathy[9].

Nowadays, continuous RRT (CRRT) is preferred over intermittent hemofiltration or peritoneal dialysis in ALF and ACLF due to its well-documented advantages in critically ill patients, mostly related to hemodynamic stability[10,11]. In addition, it can be used in complicated cases of refractory to medical treatment hepatorenal syndrome (HRS)[12]. It presents a more favorable and safe profile regarding changes in osmolality and their effect on intracranial pressure/brain edema, contributing to the maintenance of cerebral homeostasis[10]. CRRT aids in maintaining a circulatory, acid-base, and electrolyte balance during the pro-, peri-, and post-LT periods[10,13]. It exerts beneficial effects on other complications of liver failure, such as HE[14]. Moreover, it facilitates the control of fluid balance, avoidance of volume overload, and deterioration of peripheral edemas-ascites due to third-space fluid loss[12,15]. In several cases, especially in pediatric patients, it is combined with PE therapy and has produced good results[16,17].

It can remove water-soluble, small- and medium-sized molecules (mostly urea, creatinine, phosphorus, and ammonia). Furthermore, it extracts cytokines non-selectively and, in the majority of cases, to a lower degree compared to hemoperfusion[18,19]. However, it is unable to remove albumin-bound molecules.

It is inexpensive and widely available almost in every intensive care unit (ICU) or high-dependency unit (HDU), whereas its side effects are few and primarily catheter-related.

Although the effect of CRRT therapy on survival has been randomly studied, there exist a few reports on its beneficial short-term effects[14,20] thus improving the possibility for LT.

High-volume hemofiltration

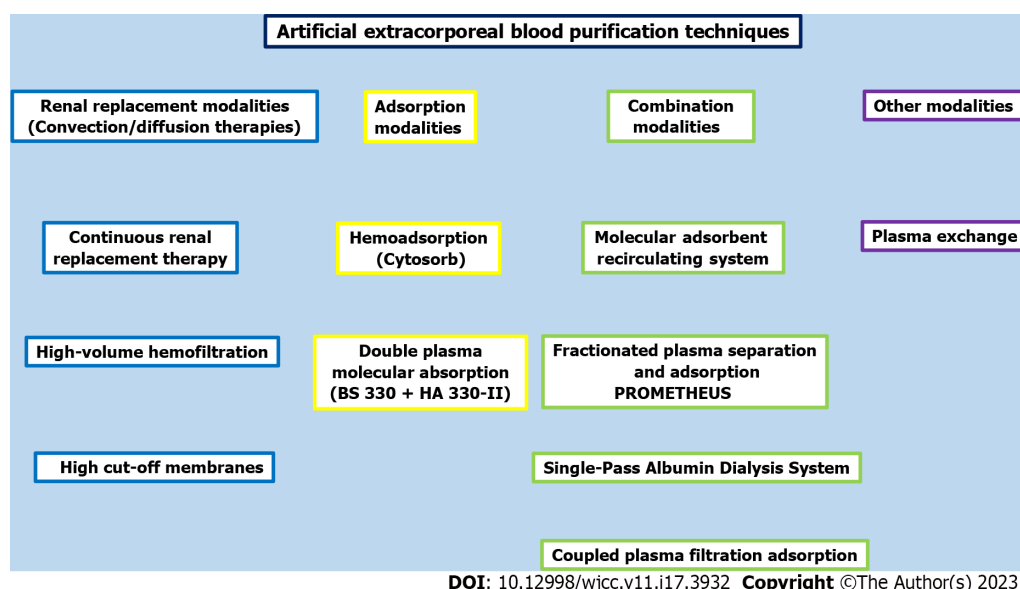High-volume hemofiltration (HVHF) therapy is characterized by high effluent rates and is performed

Figure 1 Most popular available blood purification methods with artificial extracorporeal systems for liver replacement therapy.

either continuously or intermittently. Although its limits differ significantly among studies, relative rates can be as high as 50 mL/kg/h to 70 mL/kg/h (continuous treatment) and 100 mL/kg/h to 120 mL/kg/h (intermittent treatment)[21,22]. It represents an interesting alternative to conventional RRT because it can more effectively remove medium-sized and water-soluble molecules and cytokines with a wide range of molecular weights, from 5 kDa to 60 kDa using convection for removing solutes. Increased ultrafiltration rates also enhance the elimination of ammonia[23,24], which is of utmost importance for patients with ALF and ACLF. Furthermore, high ultrafiltration rates allow the filters to perform some degree of adsorption, targeting molecules with molecular weight above the threshold of the filter membrane and thereby expanding the range of cytokines and substance removal[25].

This last feature has an associated disadvantage, which is the undesirable loss of molecules and substances with functional or beneficial properties, including albumin[26,27], nutrients, and antibiotics [25]. However, the technique can be used to remove a small degree of albumin-bound metabolites, primarily uremic toxins[28].

The method has been used primarily for inborn urea cycle disorders[29], in combination with PE, for children[30,31] and for adults with liver failure and hyperammonemia[23,24]. Further research is warranted to explore the possibility of more widespread applications, as it is inexpensive and effective, can be performed in every ICU or HDU, and requires no special equipment. Only prescription dosing and familiarization with the modality are sufficient to allow the proper use of HVHF in patients with ALF and ACLF[30].

High cut-off membranes

High cut-off (HCO) membranes represent an evolution in RRT in clearing middle molecular weight substances and cytokines. Their median pore radius is approximately 0.01 μm, providing a cut-off of 60 KDa, which is close to that of normally functioning glomeruli[32]. This property enhances the removal of uremic toxins that are either protein-bound or of middle molecular weight but also results in loss of albumin when these membranes are used. Cytokine removal is also augmented with HCO membranes. Examples of cytokines removed by these membranes include interleukin (IL)-8, IL-6, and tumor necrosis factor-alpha (TNF-α)[33].

These membranes present interesting prospects for treating patients with ALF and ACLF due to the extent and quality of cytokines and toxin removal that they offer[34,35]; however, this hypothesis must be further tested and evaluated.

ADSORPION MODALITIES

Adsorption therapies are administered either by direct hemoperfusion or by plasma separation and subsequent plasma perfusion[19]. In addition, these therapies can be applied either as stand-alone or in combination with other extracorporeal modalities such as a CRRT circuit[36] or an extracorporeal membrane oxygenation (ECMO) device[37], which further improve their utility. They can successfully eliminate albumin-bound toxins and cytokines[19,37] with less complexity and more cost-effectiveness as compared to the Molecular adsorbent recirculating system (MARS) and the Fractionated plasma

separation and Adsorption (FPSA)-Prometheus. These characteristics enhance their attractiveness for further research as promising options for patients with liver failure.

Hemadsorption

Direct hemoperfusion (Cytosorb): Small-scale studies have been conducted on Cytosorb hemoperfusion. It consists of a synthetic membrane with biocompatible polystyrene beads that have a large surface area and can remove molecules up to 55 kDa[38-40]. It was initially used for cytokine adsorption in sepsis and other hyperinflammatory conditions such as burns, pancreatitis, and hemophagocytic lymphohistiocytosis, where it is known to produce a beneficial effect by alleviating the excessive inflammatory response. IL-6 has been identified as a potential target of Cytosorb treatment[19,39,40].

Acute liver dysfunction presents with similar immunologic disorders, which forms the basis for the introduction of hemoadsorption in liver diseases. In cases of liver failure, drug-induced cholestasis, and acute alcoholic hepatitis, Cytosorb has been reported to be effective in reducing the levels of plasma bilirubin, ammonia, bile acids, and C-reactive protein (CRP) by altering the immune response in patients with high levels of proinflammatory cytokines[3,19,39,40].

Cytosorb is often paired with other extracorporeal therapies, such as continuous venovenous hemofiltration or ECMO, particularly in the ICU setting[39]. The literature reports several case series on patients with coronavirus disease-19 on ECMO, where encouraging results were obtained following the use of Cytosorb. In contrast, other trials have not reported any benefits in terms of mortality, vasopressor requirement, and organ dysfunction[1,19].

The advantages of Cytosorb include its high safety profile and ease of use. Cytosorb is mostly effective at around 12 h of use, with a blood flow rate of 150 mL/min to 500 mL/min, with the effect continuing up to 24 h[19]. Its adverse effects include the removal of beneficial substances, such as anti-inflammatory cytokines or medications, and thrombocytopenia[3,41].

Although Cytosorb appears to be a promising therapeutic method and serves as a bridge to transplantation in patients with ALF or ACLF, the literature reports limited evidence; large prospective data or results of RCTs are still missing[39-41]. In addition, conflicting results have been reported in several existing trials. For instance, a study by Scharf *et al*[42] demonstrated that the reduction in IL-6 in seriously ill patients was insignificantly different in patients treated with and without Cytosorb. The indications and endpoints of Cytosorb treatment, the effect on mortality, and risk stratification in terms of which patients would benefit from its use remain to be elucidated in large controlled, and adequately powered studies[19,42].

Plasma-perfusion after plasma separation

Double plasma molecular absorption system (DPMAS)-(BS 330 + HA 330-II): Another artificial LSS is double plasma molecular absorption system (DPMAS), which uses a neutral macroporous resin (HA 330-II) and an anion-exchange resin (BS 330). Toxic plasma is separated and cleansed by perfusion over the two hemoperfusion columns and subsequently recirculated to the body[43]. This combination efficiently removes macromolecules, medium-sized molecules, and toxins bound to plasma proteins, bilirubin, bile acids, ammonia, phenol, mercaptan, and inflammatory molecules. Thus, it potentially improves prognosis in patients with liver failure. In addition, the system requires no plasma or fluid replacement during treatment. It has been reported that DPMAS can reduce the levels of total bilirubin to more than 40%[43-45].

The advantages of this method include reduced risk for anaphylactic reactions, which are common in PE therapy, as it is a well-tolerated treatment. A major disadvantage of DPMAS is its inability to supplement for albumin and coagulation factors, correlating with the non-selective adsorption of the columns. This results in a significant loss of these molecules, coagulation disorders, and bleeding complications. To overcome these issues, DPMAS has been used in combination with PE; studies have reported that combined techniques substantially improved survival rates[43,44]. Because DPMAS is a new achievement, there are limited data on the effectiveness of DPMAS, derived from studies with small sample size. Larger, prospective trials are required to assess the exact efficacy, risk benefits, and outcomes[43,45,46].

COMPINATION MODALITIES

MARS

Another artificial liver replacement system for albumin dialysis is MARS. It can remove albumin-bound molecules and decrease the plasma concentrations of bilirubin, ammonia, creatinine, urea, and cytokines in patients with liver failure[47-49].

The system comprises a blood compartment, an albumin compartment, and a "renal" compartment. Its circuit allows the passage of molecules < 50 kDa and the extraction of albumin-bound toxins. Blood is passed through an albumin-high-flux dialysis membrane with adsorbent columns, and the albumin-bound molecules are released[47,49] and are then removed through the diffusion process[5]. The requirement for continuous albumin infusion is mitigated by the recirculation of albumin dialysate[47,

49]. Afterward, traditional dialysis is performed to remove the toxins from the dialysate.

Moreover, MARS can modify the inflammatory response related to liver failure and its consequences, such as the development of systemic inflammatory response syndrome and MOF. It can efficiently remove certain proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β, as well as certain anti-inflammatory cytokines, such as IL-10. In addition, treatment with MARS is associated with hemodynamic and clinical improvement in cases of portal hypertension, HE, refractory pruritus, Wilson's disease, and drug-induced liver injury[47-49].

The majority of patients with liver failure develop bleeding disorders and have impaired hemostasis, leading to hemorrhagic complications. Therefore, anticoagulation regimens in MARS are highly significant. The most widely used anticoagulant is unfractionated heparin. In addition, no anticoagulation *vs* regional anticoagulation with citrate has been studied. Another significant aspect of MARS is that it eliminates certain antibiotics, particularly the low protein-bound antibiotics, such as quinolones and meropenem. Such cases require careful dose adjustments and therapeutic drug monitoring[47,49].

Limited data exist on the clinical outcomes of MARS in retrospective, uncontrolled trials with conflicting results. The benefits mostly include the treatment of HE and improved hemodynamics[47, 49]. In addition, it has been reported to be beneficial in ALF in severely ill patients[49]. Although direct cost from its use is high, and it is performed exclusively in special reference centers, when combined with standard medical therapy it was found even more cost-effective than standard medical therapy alone, highlighting the need for more precise and holistic estimation of total cost and benefit drawn by these therapies[50]. Further RCTs are required to elucidate the potential effects on mortality and any added benefits of MARS on disease outcomes and define the clinical and laboratory profiles of patients who would benefit from such intervention. Currently, MARS remains another appealing option for bridging to transplantation in patients with liver failure.

FPSA-Prometheus

Prometheus is a kind of LSS introduced at the end of the 20th century[51]. Its functioning is based on an integration of plasma separation, albumin dialysis, adsorption, and high-flux hemodialysis. The system consists of a 250-kDa albumin-permeable filter, a neutral resin adsorber, an anion-exchange column, and a high-flux hemofilter. Patient's albumin passes through the 250-kDa filter, thus leading to reduction of the plasma concentration of albumin. The blood subsequently is detoxified as it passes through the adsorber, the column, and the hemofilter, following which the purified blood is returned to the patient.

This combination allows the elimination of both water-soluble and albumin-bound toxins and drugs. Prometheus significantly reduces the levels of bilirubin, with studies reporting a better performance than MARS in removing highly albumin-bound substances such as unconjugated bilirubin[52-55]. Although a recent, well-designed meta-analysis reported lack of efficient clearance of ammonia and creatinine by the Prometheus system[2], other studies support reverse findings[52,53,55,56]. Moreover, Prometheus effectively eliminates bile acids[52,55], even better than MARS[53,54]. Urea[2,56] and amino acids[57], implicated in the pathogenesis of HE, have been found to be adequately removed. This has been shown to result in significant improvement in HE[57] in these patients, and several case reports have found the same[58].

The results regarding the clearance of cytokines have been conflicting, with certain studies reporting reduced levels of cytokines[59], whereas others do not[2,60].

Other indications, including refractory pruritus and HRS, have been studied with encouraging results for Prometheus[61,62].

Prometheus has a good safety profile and good hemodynamic tolerance, although no improvement in the hemodynamic parameters was observed as compared to MARS[54]. Moreover, it has been used to treat severely ill patients. No major adverse effects have been recorded after decades of use, apart from a few reports regarding catheter-related, primarily septic complications[63], technical issues such as clotting of the circuit[64], and others such as thrombocytopenia[65].

The impact of Prometheus on OS and TFS is unclear because of lack of available data, whereas results regarding the survival rate of patients with HRS as a whole are conflicting[12,66]. However, these therapies can simultaneously improve patient's compromised renal and liver function by removing cytokines implicated in the worsening of renal function and HRS[12,62].

Although several research groups have been unable to demonstrate the OS benefits of using Prometheus[2,67], subgroup analyses have revealed a favorable effect on patients with more severe liver disease [Model for End-Stage Liver Disease (MELD) score > 30] and in patients with type 1 HRS[67]. Novel, well-designed, preferably RCTs are required to reach reliable conclusions regarding the use of these systems.

Single-pass albumin dialysis system

Single-pass albumin dialysis (SPAD) is an alternative to MARS and Prometheus modality of LRT for albumin dialysis. It is an inexpensive, widely available, simple technique that requires only a simple CRRT machine and exogenous albumin. Although an HCO filter has been reported to be used[68]; in most cases, a high-flux hemofilter is used as a dialyzer. The albumin-containing dialysate flows opposite to the blood in the filter, extracting the hydrophobic substances from the saturated albumin of the blood to the dialysate, which is subsequently disposed. Although this technique efficiently eliminates

albumin-bound toxins, it causes a significant loss of albumin, which is a major disadvantage of the method.

Another important issue that needs attention is that dialysate's ideal albumin concentration and flow rate are not standardized. Different values have been proposed by various studies, whereas commercial albumin-containing CRRT fluids are not provided by companies and should be prepared before use, thereby increasing the workload on nurses. Recent suggestions to improve these issues include using a 3% albumin solution at the dialysate, 700 mL/h to 1000 mL/h dialysate flow rate, and constructing instructions for easy preparation of bags containing 3% albumin[24].

SPAD can effectively remove bilirubin, bile acids, and other albumin-bound toxins, and the hemofilter simultaneously removes small-sized, water-soluble toxins.

Metabolic disarrangements (elevated lactate/low calcium levels) and loss of antibiotics have been reported. Therefore, close monitoring of patients is highly essential for early detection and treatment[24, 69].

The SPAD method has been reported to effectively remove bilirubin[69-71], bile acids (although less effectively than MARS)[69], urea, and creatinine (although less effectively than MARS)[69-71]. It has been used in ALF patients with Wilson's disease[72], for elevated bilirubin levels following acute hepatitis A[73], liver failure, and HE in pediatric patients[74], and HRS[75]. Because the majority of these studies are either case reports or case series, more research, preferably RCTs, is warranted to describe the effect of SPAD on OS and TFS and other liver-related outcomes.

Coupled plasma filtration adsorption

Coupled plasma filtration adsorption (CPFA) was developed during the 1990s. It uses a combination of adsorption (resin cartridge) and convection (CRRT) in the same circuit. Thus, it is different from other adsorption therapies (Cytosorb and DPMAS), where CRRT is an alternative option and not a prerequisite. Another characteristic of the method is plasma separation, performed by a plasma filter. It is the first step of the procedure before adsorption. Plasma is subsequently cleared from albumin-bound substances and mediators through the cartridge. Finally, the passage through a hemofilter removes water-soluble substances. Thus, the method has several advantages. Slow plasma passage from the resin allows better interaction and adsorption of substances, whereas the absence of blood cells, especially platelets, prevents clotting during the passage of the separated plasma through the cartridge[76]. Moreover, it incurs minimal or no loss of significant molecules such as albumin and coagulation factors and does not require the replacement of the patient's plasma. Compared to other methods of removal of albumin-bound toxins (MARS, Prometheus, Cytosorb, PE), CPFA is less expensive. However, CPFA cannot be performed in patients with septic shock due to associated potential harm[19,77].

The available literature reports that CPFA can effectively remove bilirubin, tryptophan, phenols[78, 79], bile acids[79], and cytokines[80]. It has been used for liver indications such as ALF and ACLF[81, 82], after LT[83], in hypoxic hepatitis[84], and combined with PE therapy for ALF due to Wilson's disease[85]. Future studies are required to elucidate its role as an LRT.

OTHER MODALITIES

Plasma exchange

Plasma exchange (PE) is the LRT with the highest proven beneficial effects on patient outcomes. Recent meta-analyses[2], guidelines and RCTs[11,86] have reported beneficial outcomes for 3-mo OS and TFS, respectively, especially for patients with early initiation of the treatment and not undergoing LT and same results come from well-designed reviews, regarding 1- and 3-mo survival in nontransplanted patients[87]. The effect is more pronounced when high-volume PE (the replacement of thrice the patient's estimated plasma volume) is performed[86-88], whereas standard-volume PE has demonstrated good results in certain sub-groups of patients with liver failure[89,90].

The circuit consists of a plasma filter, with pore sizes approximately 0.2 µm (far larger than those of hemofilter[32], thus allowing the extraction of larger molecular weight proteins, including antibodies, immune complexes, paraproteins, and lipoproteins[91,92]). In addition, it consists of a replacement solution containing plasma and/or albumin. The process separates plasma substances from whole blood and replacement with plasma and/or albumin follows, thereby exchanging the patient's plasma with that of healthy donors. The method allows the removal of cytokines, albumin-bound and water-soluble toxins, and the replacement of plasma proteins, including clotting factors that are severely diminished in patients with liver failure[93]. However, it cannot effectively eliminate small and medium molecular weight water-soluble molecules. Simultaneous CRRT could be necessary for patients with concomitant renal failure[31,94]. The immunomodulatory effects of PE therapy have been outstanding, as evident from its benefits reported for other indications such as chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, multiple myeloma, Guillain-Barre syndrome, and thrombotic thrombocytopenic purpura. These advantages make PE treatment of choice for suppressing the inflammatory cascade of liver failure, whereas substitution of clotting factors offers the advantage of correcting coagulation disorders often observed in these patients. In addition, it has been shown that PE

reduces vasopressor requirements and ammonia levels and improves HE. It exerts no effect on intracranial pressure elevation[93]. However, it is an expensive method, primarily due to the use of significant quantities of fresh frozen plasma (the circuit for PE does not have a significant cost). Furthermore, it could induce the side effects associated with the use of blood products, such as allergic reactions, transfusion-related acute lung injury, the transmission of infectious diseases and hypocalcemia. Apart from CRRT, it is frequently combined with other modalities, such as DPMAS[43-45].

NEW SYSTEMS AND METHODS UNDER RESEARCH

Carbalive and Dialive

Bacterial translocation remains one of the major causes for disease-related morbidity and mortality in patients with ACLF. An established method of prevention is the use of oral antibiotics, which are poorly absorbed by the gastrointestinal tract, however this approach comes with increased resistance and cost. CARBALIVE is a novel, non-antibiotic related intervention, which is under investigation. It consists of a microporous carbon absorbent, which is orally administered and removes bacterial endotoxins from the bowel, thus preventing the harmful consequences of inflammation, which usually accompanies bacterial translocation. Recent trials revealed positive preliminary results in patients with decompensated cirrhosis, while CARBALIVE seems to be safe and well tolerated. Another novel option for endotoxin removal and bridging to transplant in patients with ACLF is DIALIVE. It represents a dual filtration system. One filter removes toxin products from bloodstream and the other one removes and replaces albumin. Preliminary results are promising in terms of safety and tolerability. Data for both of these two modalities still need to be validated in larger randomized clinical trials[95].

DISCUSSION

Pathophysiologically, liver failure is regulated by immune-mediated reactions, mainly consisting of overproduction of proinflammatory cytokines, that results in a cascade of excessive inflammatory response[2]. As most of LRT systems were found to perform cytokine clearance, their application has been studied as to how it affects the dysregulation of the immune system by reducing cytokine levels and alleviating the catastrophic consequences of immune system over-activation. There are two main issues that must be further elucidated: (1) Studies regarding the effectiveness of the LRT systems to reduce cytokine levels have given conflicting results[42,60]. This can be attributed to the heterogeneity of the amount and type of pro- and anti-inflammatory cytokines produced in patients with liver failure. In several cases, the overproduction of cytokines has been reported to overcome the elimination capacity of the LSS[60]; and (2) LRT systems eliminate both pro- and anti-inflammatory cytokines[42], resulting in non-predictable and simultaneous suppression and activation of the immune system respectively. The clinical impact of the effect of LRT systems on the imbalance between pro- and anti-inflammatory mediators in liver failure remains unclear, and further studies are warranted in this field.

Table 1 lists the different characteristics of all modalities discussed in this review, including costs, complexity, applicability, and methods of toxin clearance. The attempted comparison of costs and complexity of these modalities is preliminary and arbitrary and could differ between different centers and countries. Their extent of applicability is based on whether these methods can be performed in any ICU or HDU (broad), or in ICUs and HDUs with particular experience, knowledge, and equipment (medium), or, finally, in special reference centers for LRT (limited).

Costs included in Table 1 mainly regard direct costs from the use of each method, not including the expenses that emerge from the rest of the support that these patients require. However, indirect costs from ICU/HDU hospitalization that represent a significant burden worldwide[96], including albumin supplementation, antibiotic administration for hospital-acquired infections (a very frequent complication for these patients) and maintenance of the above-mentioned expensive health-care facilities, are not included. On the other hand, keeping these patients alive until LT is available while reducing their morbidity and mortality is another parameter that must be taken into consideration. Of note, there are studies that find these therapies cost-effectively superior to standard medical therapy alone[50]. Thus, the exact balance between cost and effectiveness of application of these methods remains to be elucidated.

A key point to this approach is to detect patients that may benefit at a significant degree from LRT and apply these methods accordingly. Use of appropriate biomarkers, in the context of compatible clinical picture, could serve as a tool for distinguishing those patients and identify the most appropriate method for them, offering a personalized approach to the treatment of ALF and ACLF. Such biomarkers are under intense study in sepsis and COVID-19. The measurement of endotoxin levels with an endotoxin activity assay for initiation of polymyxin B hemoperfusion and measurements of CRP, IL-6 or ferritin for initiation of Cytosorb therapy are relative examples[97,98]. However, such biomarkers have not been identified for ALF and ACLF yet, and their identification presents a challenging target for

Table 1 Comparison of basic characteristics of artificial liver support systems

System	Detoxification methods	Cost	Complexity	Applicability	Detoxification capacity/range	Impaction OS/TFS	Main characteristics
Continuous renal replacement therapy	Diffusion, convection	Low	Low	Broad (all ICUs, HDUs)	Restricted (water-soluble, low and medium molecular weight substances, mainly ammonia, cytokines)	Few data, no RCTs	Simple, no removal of albumin-bound toxins
High-volume hemofiltration	Convection	Low	Low	Broad (all ICUs, HDUs)	Restricted (water-soluble, low and medium molecular weight substances, mainly ammonia, cytokines), but more effectively than CRRT	Few data, no RCTs	Simple, better removal of low and medium sized molecules and cytokines than low-volume. No significant removal of albumin-bound toxins, loss of albumin, nutrients
High cut-off membranes	Diffusion, convection	Low	Low	Broad (all ICUs, HDUs)	Middle molecules up to 60 kDa, protein-bound uremic toxins, cytokines (IL-8, IL-6, and TNF-α)	Few data, no RCTs	Simple, removal of protein-bound-medium sized uremic toxins cytokines. No removal of other albumin bound toxins, loss of albumin
Direct hemoper-fusion (Cytosorb)	Adsorption	Medium to high	Medium	Medium (ICUs, HDUs with experience)	Molecules up to 55 kDa, bilirubin, ammonia, bile acids, IL-6, CRP	Few data, no RCTs	Simple, removal of albumin bound toxins, bilirubin, bile acids, cytokines. Needs more literature
Double plasma molecular absorption system	Plasma separation, adsorption	Medium	Medium	Medium (ICUs, HDUs with experience)	Macromolecules, medium-sized plasma protein bound molecules and toxins, bilirubin, inflammatory molecules	Few data, no RCTs	Simple, removal of albumin bound toxins, bilirubin, bile acids, cytokines; needs more literature
Molecular adsorbent recircu-lating system	Albumin dialysis-diffusion, adsorption, convection	High	High	Limited (special centers)	Albumin-bound molecules < 50 kDa, water-soluble substances, Cytokines (TNF-α, IL-6, IL-1β, and IL-10)	Not found/not found	With available literature, removal of albumin-bound toxins; complex, expensive, limited access, uses exogenous albumin
Fractionated plasma separation and Adsorption-PROMETHE-US	Plasma separation, albumin dialysis-diffusion, adsorption, convection	High	High	Limited (special centres)	Broad (albumin-bound toxins, water-soluble substances of a wide range of molecular weight, cytokines)	Not found/not found	With available literature, removal of albumin-bound toxin; complex, expensive, limited access
Single-pass albumin dialysis	Albumin dialysis-diffusion, convection	Medium	Low	Broad (all ICUs, HDUs)	Albumin-bound substances (bilirubin, bile acids), small-sized (< 500 Da) water-soluble toxins	Few data, no RCTs	Simple, removal of albumin-bound substances, water soluble toxins; high cost of exogenous albumin, metabolic disarrangements
Coupled plasma filtration adsorption	Plasma separation, adsorption, convection	Medium	Medium	Medium (ICUs, HDUs with experience)	Albumin-bound molecules and toxins (bilirubin, tryptophan, phenols, bile acids), cytokines, water soluble toxins	Few data, no RCTs	Simple, removal of albumin-bound toxins, bilirubin, bile acids, cytokines; needs more literature
Plasma exchange	Separation of plasma substances, replacement with FFP	Medium to high, mainly due to the FFP	Medium	Medium (ICUs, HDUs with experience)	Broad (removal of cytokines, albumin-bound and water-soluble toxins, antibodies, immune complexes, lipoproteins)	Beneficial (RCTs and guidelines)	Effective with available literature from RCTs, replaces plasma proteins, clotting factors; expensive, need, cost and complic-ations of blood products

OS: Overall survival; TFS: Transplant-free survival; ICUs: Intensive care units; HDUs: High dependency units; RCTs: Randomized controlled trials; FFP: Fresh frozen plasma; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; kDa: Kilodalton; CRP: C-reactive protein.

future research. Alternatively, certain sub-groups of patients, such as those that are more severely ill [49], those with more severe liver disease (MELD score > 30) or with type 1 HRS[67], and those with early initiation of treatment, that will not undergo LT[11] have been found to receive more favorable effect from LRT, and treating these sub-groups preferably is a reasonable approach for achieving cost-effective use of the LRT systems. Nevertheless, proper validation of indications and application of suitable tools for identifying these patients represent fields for thorough future research.

Table 2 summarizes in tabular form data from a selection of the studies that were included in this review, with the main key points that were drawn by each study, while Table 3 (adapted with modifications from a recent study regarding expert consensus recommendations for the majority of currently available LSSs[99]) highlights advantages, disadvantages, side effects, complications and contraindications of LSSs.

It is worth noting that the impact from the application of LSSs on OS and TFS remains unclear because of the lack of data, especially from RCTs. The majority of the studies have limited sample sizes and present methodological issues, especially the risk of bias. Properly designed, double-blind, RCTs with efficient statistical analysis and adequate sample size to achieve statistical power must be performed by experienced researchers. In order to draw reliable conclusions, enrollment should be done on the basis of discrete inclusion criteria, comparing groups of equal severity and comparable comorbidities, with separate study of patients with ALF and those with ACLF, as these entities have differences in pathophysiology, clinical presentation and prognosis.

Choice of study outcomes is also challenging. The most commonly used include OS, TFS, all-cause mortality, liver-related mortality, improvement of HE, HRS or other complications of liver failure[2, 100]. Nevertheless, the majority of patients with ALF and ACLF are severely ill and present MOF, with high rates of mortality, making it difficult to prove the beneficial effects of any of these interventions. In order to overcome this obstacle, other endpoints, such as short-term survival as bridging to LT, have been proposed[66], however LT is not offered as an immediate or future option to most of these patients. Thus, proper identification of other suitable endpoints is demanded. Simple to use and interesting endpoints to consider could be the reduction of ACLF-grades, the reduction of MELD score and estimators of patients' quality of life; the latter is increasingly being used in other circumstances, such as at patients after LT and could present an interesting alternative for assessing the impact of LRT on patients' health status.

At this point of time artificial LRT systems mostly serve as bridging therapies towards LT. Factors including cost, lack of available evidence and complexity restrict their applicability. However, the introduction of new systems like DIALIVE, CARBALIVE, and new methods like adsorption therapies (their cost is lower compared to previous systems and gets lower over time, they are simple in use and can be widely available, they have a wide range of clearance of molecules and toxins) and the evolution of technology along with the evidence acquired regarding already available systems and techniques (MARS, prometheus, and PE therapy) give the perspective for more widespread use of LRT. The goal for LRT should be its application at every patient with ALF or ACLF that will benefit from it, regardless of the presence or absence of exclusion criteria for LT, and regardless of any anticipated delay for LT. Ideally, the experience from RRT should be adapted, where technological progress and cost deterioration from widespread use have made RRT widely available, practically for every patient that needs it.

CONCLUSION

LRT is a constantly evolving and widely offered therapeutic approach for patients with ALF and ACLF. Different systems and methods described in this review can efficiently detoxify all toxins and molecules implicated in the pathophysiology of ALF and ACLF and responsible for the associated complications. Amongst the available LRT systems, certain modalities are neither expensive nor highly sophisticated and can be applied almost in every ICU or HDU supporting this category of extremely complicated patients. Although these systems have not yet gained a strong position among treatment guidelines regarding patients with liver failure, this is probably due to the poor quality of available evidence. Recent meta-analyses have reported promising results[100,101], indicating the need for further research and more RCTs. Another challenge for clinicians treating these patients is to decide the appropriate method, correct initiation time, and parameters of the prescribed therapy for these patients. In addition, the majority of them are critically ill, with coagulation disorders and liver complications (HE, HRS, ascites, hyperammonemia, and elevated intracranial pressure). Considering the restricted available literature on these systems, these decisions need to be made prudently and more research is warranted in this field. Nevertheless, standard medical therapy for liver failure has probably reached its peak; LT is lifesaving but not easily accessible and demands lifelong immunosuppression. Thus, LRT represents a highly promising alternative offering new potentials for treating ALF and ACLF in the future, improving the survival of these patients either toward recovery of liver function or as support for impaired liver function until LT becomes available. Options, including the use of combinations of different methods, application of multiple methods in a patient according to the phase of the disease

Table 2 Selected data from available guidelines, systematic reviews, meta-analyses or clinical studies included in this review

Ref.	Type of study	Modality-ies studied	Summary of key points of each study
[2]	Systematic review/meta-analysis	LRT systems	Liver failure pathophysiology involves immune system over-activation and overproduction of proinflammatory cytokines, resulting in multiple-organ failure; reducing cytokine levels and thus correcting the dysregulation of the immune system is the pathophysiologic base of the application of LRT systems
		Plasma exchange	The best currently available LRT system in ACLF regarding 3-mo OS
[9]	Review	Continuous renal replacement therapy	It has indication for initiation of when ammonia is more than × 3 the uln, or more than 200 μmoles/L or when severe encephalopathy occurs
[10]	Review	Continuous renal replacement therapy	It has a role in the maintenance of circulatory, acid-base, and electrolyte balance during the pro-, peri-, and post-LT periods. It facilitates control of fluid balance and avoidance of volume overload/of peripheral edemas-ascites in patients with ALF and ACLF
[11]	Guidelines	Plasma exchange	It improves transplant-free survival in ALF, and modulates immune dysregulation; patients with early treatment initiation that will not undergo LT may benefit most
[19]	Review	Adsorption therapies	They are delivered either by direct hemoperfusion or by plasma separation and subsequent plasma perfusion
		Direct hemoperfusion (Cytosorb)	It reduces levels of plasma bilirubin, ammonia, bile acids, and C-reactive protein and alters the immune response by absorbing proinflammatory cytokines; IL-6 has been identified as one of its main therapeutic targets; it presents high safety profile and easy application; indications, endpoints, effect on mortality and detection of which patients receive benefit from its use remain to be elucidated
[24]	Review	Single-pass albumin dialysis	Dialysate's ideal albumin concentration and flow rate are not standardized while there are no commercially available albumin-containing Continuous renal replacement therapy fluids. Metabolic disarrangements and loss of antibiotics have been observed
[30]	Clinical study	High-volume hemofiltration	An inexpensive and effective method that can be performed in every ICU or HDU, requiring no special equipment. Increased ultrafiltration rates enhance the elimination of ammonia
[35]	Clinical study	High Cut-off membranes	Cytokine and toxin removal by these membranes may represent a promising intervention in ALF and ACLF
[36]	Review	Adsorption therapies	They are delivered either as stand-alone or in combination with other extracorporeal modalities; the evidence to support their routine use is still conflicting and insufficient. May be of utmost benefit when applied early in the course, for an adequate duration, and frequently repeated until hemodynamic stability is achieved; they require carefully monitoring of drug levels, supplemented with additional doses as needed
[38]	Review	Adsorption therapies	They have been used with positive effects in chronic dialysis and chronic liver disease
		Direct hemoperfusion (Cytosorb)	It removes molecules up to 55 kDa
[43]	Systematic review/meta-analysis	Double plasma molecular absorption system	It combines two resins that remove macromolecules, medium-sized molecules, and toxins bound to plasma proteins, bilirubin, bile acids, ammonia, phenol, mercaptan, and inflammatory molecules
[44]	Clinical study	Double plasma molecular absorption system	It is frequently combined with Plasma exchange therapy, to overcome loss of for albumin and coagulation factors, with promising results on survival rates
[48]	Randomized controlled study	Molecular adsorbent recirculating system	It removes albumin-bound molecules and decreases the plasma concentrations of bilirubin, ammonia, creatinine, urea, and cytokines. It has good safety profile
[49]	Review	Molecular adsorbent recirculating system	Recirculation of albumin dialysate restricts albumin loss; under certain circumstances and indications, it has been associated with hemodynamic and clinical improvement at patients with liver disease; dose adjustments and therapeutic drug monitoring, especially for low protein-bound antibiotics, is required
[50]	Clinical study	Molecular adsorbent recirculating system	Expensive method, application in selected centers, but when compared to standard medical therapy alone it was found more cost-effective
[52, 57]	Review, Clinical study	PROMETHEUS	It performs albumin dialysis. It removes bilirubin, ammonia, creatinine, bile acids, amino acids, cytokines and is associated with a small reduction in plasma concentration of albumin; it was associated with improvement in HE
[54]	Randomized controlled study	PROMETHEUS	It presents good safety profile and good hemodynamic tolerance
[67]	Randomized controlled study	PROMETHEUS	Favorable effect on patients' subgroups such as those with more severe liver disease (MELD score > 30) and with type 1 HRS
[69]	Randomized controlled study	Single-pass albumin dialysis	It is inexpensive, apart from the cost of albumin, and requires no special center for its application; it performs albumin dialysis and removes bilirubin, bile acids, urea and creatinine
[76]	Review	Coupled plasma	It combines plasma separation, adsorption and convection, with no loss of albumin or coagulation

		filtration adsorption	factors; it can effectively remove bilirubin, tryptophan, phenols, bile acids, cytokines
[77]	Randomized controlled study	Coupled plasma filtration adsorption	It cannot be performed in patients with septic shock
[87]	Review	Plasma exchange	It improves 1- and 3-mo survival in nontransplanted patients. More pronounced effect and high level of evidence for high volume plasma exchange
[93]	Review	Plasma exchange	It removes cytokines and albumin-bound toxins, and replaces plasma proteins; it effectively suppresses the inflammatory cascade of liver failure, while substituting clotting factors and correcting coagulation disorders; relatively expensive, it presents transfusion related side effects and cost

LRT: Liver replacement therapy; OS: Overall survival; ALF: Acute liver failure; ACLF: Acute-on-chronic liver failure; uln: Upper limit of normal; LT: Liver transplantation; IL: interleukin; ICU: Intensive care unit; HDU: High Dependency Unit; kDa: Kilodalton; MELD: Model for end-stage liver disease; HRS: Hepatorenal syndrome; HE: Hepatic encephalopathy.

Table 3 Advantages, disadvantages, side effects, complications and contraindications, with intended population to treat, for each liver support system (adapted with modifications from[99])

Method	Advantages	Disadvantages-side effects-complications-contraindications	Intended population
Plasma exchange	Easy operation, broad-spectrum rapid, and efficient removal of various toxins, supplementation of fresh frozen plasma, shorter treatment time, acceptable patient tolerance	Higher treatment cost, poor clearance of water-soluble toxins, aggravation of hepatic encephalopathy, plasma allergy, risk of infection associated with blood products, water and sodium retention after treatment	Patients with hepatic failure, hyperbilirubinemia, cryoglobulinemia, Guillain-Barré syndrome, thrombotic thrombocytopenic purpura, myasthenia gravis
Continuous renal replacement therapy	Hemodynamic stability in critically ill patients, maintenance of cerebral homeostasis, inexpensive and widely available	Unable to remove albumin-bound molecules	Critically ill patients, patients with refractory hepatorenal syndrome
High-volume hemofiltration	More effective removal of medium-sized and water-soluble molecules and cytokines; enhances the elimination of ammonia	Undesirable loss of molecules and substances with functional or beneficial properties, including albumin, nutrients, and antibiotics	Patients with ALF and ACLF, inborn urea cycle disorders, in children and adults with liver failure and hyperammonemia
High cut-off membranes	Removal of uremic toxins	Loss of albumin	Patients with ALF and ACLF
Direct hemoperfusion (Cytosorb)	Reduces the levels of plasma bilirubin, ammonia, bile acids, and C-reactive protein, high safety profile and ease of use	Higher treatment cost Removal of beneficial substances, such as anti-inflammatory cytokines or medications, and thrombocytopenia	Patients with liver failure, drug-induced cholestasis, and acute alcoholic hepatitis; bridge to transplantation in patients with ALF or ACLF
Double plasma molecular absorption system	Rapid removal of bilirubin, inflammatory mediators without requiring exogenous plasma	Inability to replenish coagulation factors; hypotension is likely to occur during the initial treatment period	Patients with liver failure, hyperbilirubinemia, hepatic encephalopathy, perioperative treatment of liver transplantation
Molecular adsorbent recirculating system	Effective removal of protein-bound and water-soluble toxins, excellent biocompatibility, relatively safe	Markedly expensive and complex, cannot supplement coagulation factors	Patients with acute severe liver injury or liver failure
Fractionated plasma separation and Adsorption-PROMETHEUS	Elimination of both water-soluble and albumin-bound toxins and drugs, good safety profile and good hemodynamic tolerance	Markedly expensive and complex, lack of efficient clearance of ammonia and creatinine	Patients with hepatic encephalopathy, hepatorenal syndrome
Single-pass albumin dialysis	Inexpensive, widely available, simple technique, effectively removes bilirubin, bile acids, and other albumin-bound toxins	Significant loss of albumin, metabolic disarrangements and loss of antibiotics	Patients with ALF, Wilson's disease, acute hepatitis A, liver failure, hepatic encephalopathy, hepatorenal syndrome
Coupled plasma filtration adsorption	Removes medium and small molecular weight water-soluble toxins and is capable of volume regulation and renal support	Higher equipment requirements, higher treatment cost	Patients with liver failure, renal insufficiency, hyperammonemia, rhabdomyolysis, burns, severe autoimmune diseases, poisoning

LSS: Liver support system; ALF: Acute liver failure; ACLF: Acute-on-chronic liver failure.

and the toxins to be removed, and adoption by centers of LRT protocols have already been described[24, 102]. Such options could probably be ideal for treating these highly complicated patients. We believe that as technology and knowledge evolve, the future of these systems will witness major advancements.

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