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# Liver dialysis in acute-on-chronic liver failure: current and future perspectives

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**Abstract** Patients with acute-on-chronic liver failure (ACLF) are known to have a very high mortality rate as the majority of these patients succumb to multiorgan failure. Liver transplant remains the only option for these patients; however, there are problems with its availability, cost and also the complications and side effects associated with immunosuppression. Unlike advanced decompensated liver disease, there is a potential for hepatic regeneration and recovery in patients with ACLF. A liver support system, cell or non-cell based, logically is likely to provide temporary functional support until the donor liver becomes available or the failing liver survives the onslaught of the acute insult and spontaneously regenerates. Understanding the pathogenesis of liver failure and regeneration is essential to define the needs for a support system. Removal of hepatotoxic metabolites and inhibitors of hepatic regeneration by liver dialysis, a non-cell-based hepatic support, could help to provide a suitable microenvironment and support the failing liver. The current systems, i.e., MARS and Prometheus, have failed to show survival benefits in patients with ACLF based on which newer devices with improved functionality are currently under development. However, larger randomized trials are needed to prove whether these devices can enable restoration of the complex dysregulated immune system and impact organ failure and mortality in these patients.

**Keywords** Liver dialysis · ACLF · Extracorporeal liver support · Plasma dialysis

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## Introduction

Extracorporeal liver support therapies are used to bridge the liver until recovery or liver transplantation in patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF). ACLF has been recognized as a distinct clinical entity, even though there are some differences in how it is defined in the East and the West [1, 2]. Irrespective of the definitions, the high mortality in this subset of patients and limited transplant options make a strong case for assessing the utility of liver dialysis and support as an attractive option.

### Pathogenesis of liver failure in ACLF and role of liver dialysis

The pathophysiology, natural course and evolution of liver failure in ACLF are still a conundrum, as in a subset of cases, the condition is potentially reversible, and hence management is focused with the hope that the liver will recover if the patient can be supported through this acute deterioration (Fig. 1). The hepatocellular injury in ACLF is driven to a large extent by a "cytokine burst," with elevated levels of a multitude of cytokines [3], low-molecular-weight toxins and vasoactive substances that are known to accumulate secondary to the failing liver. There is an additional challenge of the injury due to endotoxins and

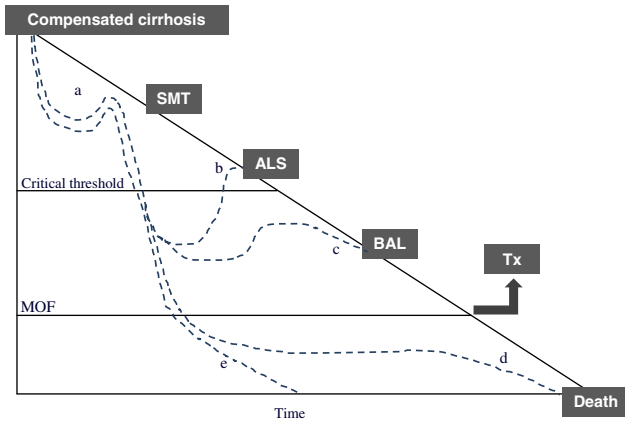


**Fig. 1** Variation in the course of patients with ACLF depending upon the severity ofacute insult. (a) Mild decompensation that is reversed with standard therapy seen in a subset of cases (e) Severe insults which lead to rapid deterioration and death (b) and (c) Other insults which lead to a degree of liver failure that requires artificial liver support as a bridging therapy until spontaneous regeneration or liver transplantation. (d) Delay in supporting the failing liver resulting in prolongation of the course of liver failure eliminating the possibility of liver transplantation and causing death from multiorgan failure (MOF) [4]

metabolites released from the gut bacteria. These toxins not only potentiate the hepatic injury, but also deprive the liver of an environment conducive to regeneration. The released toxins are responsible for the systemic inflammation and loss of adaptive and innate immunity, and they cause vital organ dysfunction, which affects all the major organs [3].

## Extracorporeal liver-assist devices

Several extracorporeal liver support systems such as hemodialysis, hemofiltration, plasma exchange and charcoal perfusion have been used in the past. However, in all these, protein-bound toxins were only removed to a minor extent. Later on came the concept of removal of protein-bound toxins via albumin as a substrate for adsorption in the molecular adsorbent and recirculation system (MARS) and fractional plasma separation and adsorption (FPSA-Prometheus). MARS was introduced in 1993 [5]. It requires a MARS monitor device and hemodialysis/hemofiltration. The patient's blood is passed through a hemofilter (Marsflux filter) with a size selection threshold of less than 60 kDa; it is thus impermeable to albumin and albumin-bound toxins, such as unconjugated bilirubin, which are retained on the blood side of the membrane. In the secondary circuit, 20 % albumin solution is circulated, which passes the filter in a counterdirectional flow and acts as the dialysate. Toxins in the patient's blood dissociated from albumin binding cross the MARS membrane in view of the concentration gradient and bind to the albumin, which is there in the secondary circuit. Subsequently, in the secondary circuit, the toxin-bound albumin solution first undergoes dialysis using a low-flux filter to remove water-soluble toxins and is then regenerated by passing through two adsorbers: an anion exchanger resin and an uncoated charcoal adsorber. Finally, the cleansed albumin re-enters the hemofilter of the primary circuit (Fig. 2). The duration of a single MARS session is approximately 6–8 h. After that time, the binding capacity of the adsorbers decreases significantly, and adsorbers need to be replaced in case the session needs to be prolonged. Single-pass albumin dialysis (SPAD), which is similar to MARS, is also a simple procedure. The only difference is that after each passage of the dialyzer/hemofilter, the dialysate is discarded, and the albumin dialysate in SPAD consists of 4 % albumin as compared to 20 % albumin in MARS. The continuous albumin purification system (CAPS) is based on the same principle as albumin dialysis. In this cellulose triacetate membrane, 5 % albumin dialysate, bilirubin adsorber columns, and charcoal adsorber columns are used. CAPS is safe and has shown improvement in both renal and liver function [6]. Selective plasma filtration therapy (SEPET) was developed by Cedars Sinai Medical Center, Los Angeles, CA, in which a membrane with a 100-kDa pore size was included in a standard hemodialysis system that allowed albumin to pass across the membrane while the larger molecules could not. The filtered plasma is discarded and replaced by fresh frozen plasma [7]. However, the problems of combining plasma exchange (PE) with hemodialysis versus hemodialysis alone were highlighted by Abe et al. [8], who showed that HD is required with PE for correction of calcium and citrate values. PE is a non-selective modality that removes not only cytokines, but also the beneficial growth factors for hepatic regeneration, i.e., HGF. Prometheus (FPSA) was introduced in 1999 by Falkenhagen et al. [9]. In this system, an albumin-permeable filter with a size selection threshold of approximately 250,000 Da (250 kDa) is used, thus enabling removal of both albumin and protein-bound toxins, which can pass through the membrane and are then directly removed from the blood by a special adsorber within the secondary circuit. The Prometheus system combines the FPSA method with high-flux hemodialysis (of the blood) in an extracorporeal detoxification system. Using a standard dialysis catheter, the patient's blood with all the toxins enters the primary extracorporeal circuit where the albumin fraction of the blood is selectively filtered through a specific membrane, i.e., Albuflow, which is a polysulfone, albumin-permeable filter, and subsequently enters a secondary circuit where the toxins are adsorbed by two adsorber columns, i.e., a neutral resin adsorber (Prometh® 01) and an anion exchanger (Prometh 02). After passing through the two adsorber columns, the purified blood enters the primary circuit wherein a conventional dialysis of the patients' blood using a high-flux

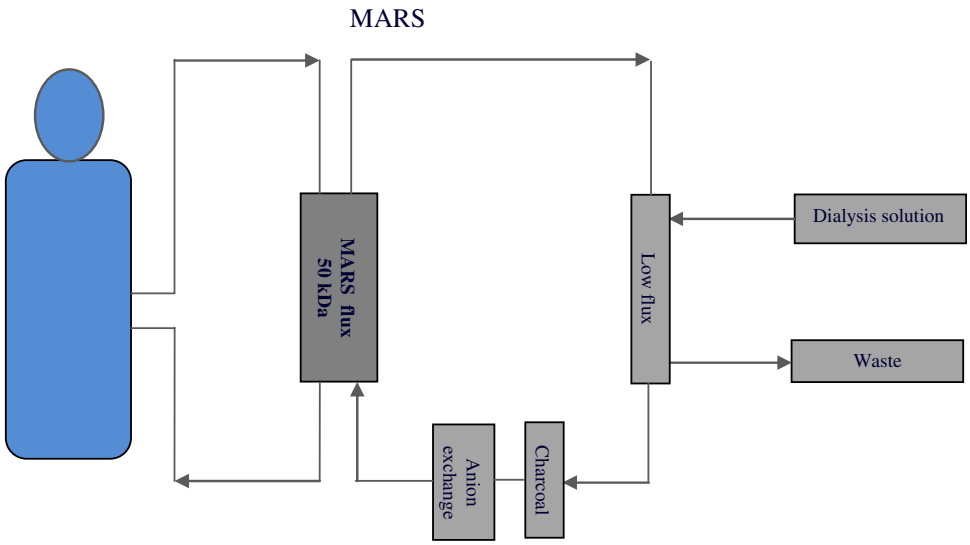


**Fig. 2** Schematic diagram of Molecular Adsorbent and Recirculation System [MARS]. In MARS the patient's blood is dialysed against a dialysate containing 20% albumin. The MARSflux membrane allows molecules up to 50 kDa to pass to the dialysate. Dialysate then undergoes standard dialysis and passes over charcoal and anion resin to reactivate albuminbinding receptors [4, 5]

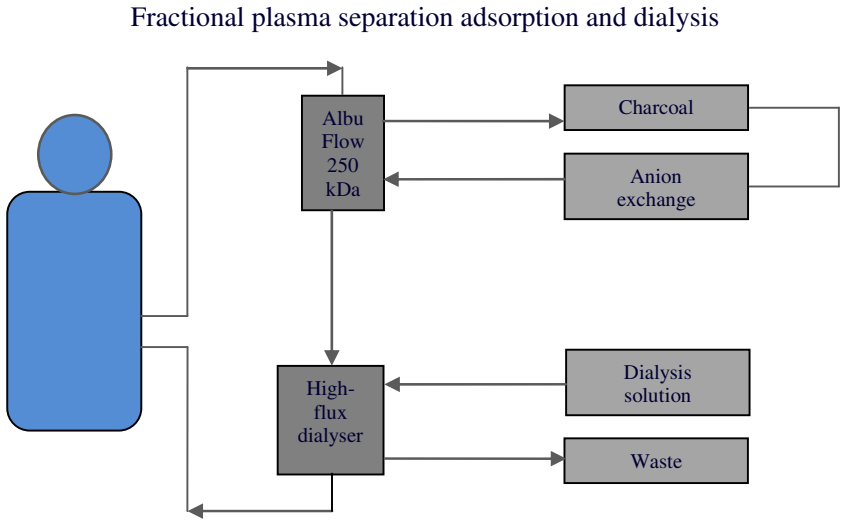


**Fig. 3** Schematic diagram of Prometheus or Fractional Plasma Separation Adsorption [FPSA]. This allows filtration of plasma and albumin through a membrane (Albuflow), which allows molecules up to 250 kDa to filter through and the filtrate is then passed over neutral resin and anion exchange resin, and returns back to the blood circuit. The blood is then dialysed and returns back to the patient [4, 9]

dialyzer is performed, which enables effective removal of water-soluble compounds. The systemic hemodynamics improve with MARS, and hypotension is rarely reported as compared to Prometheus. This is because the albumin that fills in the secondary circuit is exogenous albumin as compared to the Prometheus system in which it is the patient's albumin, which fills in the secondary circuit causing more hemodynamic alterations. The frequency of bleeding episodes is also reported less frequently with MARS than Prometheus as the coagulation factors and large proteins are unable to cross the MARS membrane. For the same reason, the toxin removal efficacy of Prometheus has been proven to be better than that of MARS [10, 11] (Fig. 3). A list of the toxins removed and toxin removal efficiency comparing MARS and Prometheus are shown in Table 1.

## Hepatic encephalopathy in ACLF

The proposed mechanisms in the pathogenesis of HE in liver failure are hyperammonemia altered blood brain-barrier permeability and a consequent change in the amino-acid transport that in turn leads to reduced cerebral blood flow and glucose and oxygen consumption [12, 13]. Animal studies have demonstrated a decrease in intracranial pressure after treatment with FPSA [14]. A favorable shift in the amino acid profile toward branched chain amino acids, reduction in plasma ammonia levels and oxygen saturation of jugular venous bulb blood ($SjVO_2$) have also been reported [15, 16].

Heemann et al. [17] looked at 24 patients with acute decompensation of cirrhosis with hyperbilirubinemia (serum bilirubin >20 mg/dl). These patients were

**Table 1** Liver dialysis systems

| S. no | Circulating toxins | SPAD | MARS | Prometheus |
|---|---|---|---|---|
| 1 | Ammonia | ++ | + | +++ |
| 2 | Bilirubin | +++ | ++ | +++ |
| 3 | Bile Acids | ++ | ++ | +++ |
| 4 | Creatinin | ++ | ++ | +++ |
| 5 | Urea | +++ | + | +++ |
| 6 | Blood pH | +++ | ++ | +++ |
| 7 | Heavy metals | +++ | +++ | +++ |
| 8 | Albumin-bound toxins | +++ | ++ | +++ |
| 9 | Water-soluble toxins | +++ | +++ | +++ |
| 10 | Platelet count reduction | ++ | ++ | +++ |
| 11 | Platelets function | −− | −−− | −−− |
| 12 | PT/INR | ++ | + | +++ |
| 13 | Mean arterial pressure | ++ | +++ | ++ |
| 14 | SVRI | ++ | +++ | ++ |
| 15 | Endogenous vasoactive compounds | ++ | +++ | ++ |
| 16 | Circulating inflammatory cytokines | ++ | ++ | +++ |

'+' minimum reduction, '++' moderate reduction, '+++' significant reduction [19]

randomized to standard medical treatment, SMT (controls, $n = 12$) or SMT+ MARS ($n = 12$). Encephalopathy and renal function improved in MARS-treated patients, who were also associated with a significant improvement in 30-day survival (11 of 12 vs. 6 of 12 in controls). Sen et al. [18] randomized 18 patients with alcohol-related ACLF to SMT versus MARS therapy over 7 days. Encephalopathy improved significantly with MARS ($p < 0.01$), but not with SMT. Similarly, in a prospective, randomized, controlled, multicenter trial of MARS +SMT ($n = 39$) or SMT ($n = 31$), Hassanein et al. [20] demonstrated better improvement of HE in MARS (mean, 34 %; median, 30 %) versus the SMT group (mean, 18.9 %; median, 0 %) ($p = 0.044$). On the contrary, in an uncontrolled study Rifai et al. [21] showed no improvement in HE by Prometheus in patients with ACLF. In the multicentric RELIEF trial [22] of 189 patients with ACLF, a greater decrease in serum creatinine and bilirubin levels and greater improvement in HE (56 vs. 39 %, $p = 0.06$) were observed in the MARS group even though statistical significance was not achieved. A significant improvement in HE was also demonstrated with MARS in a recent metaanalysis [23]. Selective plasma exchange has showed beneficial effects in the management of acute hepatic encephalopathy in patients with liver failure [24]. In a recent study looking at the effect of plasma exchange on four patients with ALF, a significant decrease in hepatic encephalopathy and IL-18 levels was reported with plasma exchange [25].

## Hepatorenal syndrome in ACLF

The pathophysiological basis of HRS in patients with ACLF is supposed to be multifactorial with inflammation and infection as the hallmarks along with superadded circulatory dysfunction [26]. Another proposed pathogenetic mechanism of renal injury in patients with ACLF could be "cholemic nephrosis" or bile cast nephropathy characterized by tubular damage with intrarenal bile cast formation secondary to bilirubin toxicity [27]. The vasoconstrictors such as terlipressin act by improving the systemic hemodynamics, but do not remove the cytokine burden. In a recent study from our own group comparing renal dysfunction in patients with ACLF (APASL definition) with decompensated CLD, it was noted that patients with ACLF had a significantly increased incidence of tubular dysfunction requiring renal replacement therapy and an inferior response to terlipressin confirming a different pathophysiological basis of renal dysfunction in these patients [28]. Patients with ACLF in this study also had a significantly higher bilirubin level as compared to patients with CLD. Considering the fact that high bilirubin levels decrease the effectiveness of terlipressin in reversal of type 1 HRS [29], a detoxification device that enables reduction of bilirubin and the inflammatory cytokines would result in amelioration of renal injury as against conventional management with vasoconstrictor drugs alone. The preliminary data from the RCTs also suggest liver dialysis could be used as an effective treatment modality for type 1 HRS in patients with ACLF. In the HELIOS trial [30], survival of patients with type 1 HRS was better when treated with FPSA than with SMT (28-day survival 62 vs. 39 %; 90-day survival probability, 42 vs. 6 %, respectively; log-rank test, $p = 0.04$). Similarly, in the RELIEF trial with MARS [22], the proportion of patients with a serum creatinine level below 1.5 mg/dl at day 4 in patients with HRS at baseline tended to be higher in patients who were treated with MARS ($p = 0.07$). Rifai et al. [21] studied ten patients with HRS in a prospective clinical study and reported a significant improvement of serum creatinine and urea concentrations as well as blood pH after two sessions of Prometheus treatment. Similarly, Mitzner et al. [31] looked at eight patients with HRS and found improvement in renal parameters. In a pilot study by Wong et al., the efficacy of MARS in improving systemic and renal hemodynamics in patients with cirrhosis with refractory ascites and type 1 HRS ($n = 6$) not responding to vasoconstrictor therapy was studied. There were no significant changes in the systemic hemodynamics, GFR, neurohormone and cytokine levels following MARS treatment, even though a significant reduction in NO concentrations ($111.5 \pm 18.8$ to $65.1 \pm 8.2$ μmol/l, $p = 0.05$) and a transient reduction in serum creatinine ($p < 0.05$) were noted. Even though four

of the six patients were successfully bridged to liver transplant, the results of this study showed that MARS was not effective in improving renal function in patients with cirrhosis with type 1 HRS with refractory ascites who failed vasoconstrictor treatment [32].

## Circulatory dysfunction in ACLF

Circulatory changes also play a key role in the development of ACLF, and characteristic changes that occur in the circulation of cirrhotics become more exaggerated during ACLF, akin to severe sepsis or septic shock [26]. The improvement in systemic hemodynamics was initially demonstrated by Catalina et al. [33] in four patients in whom MARS was associated with a significant decrease in plasma rennin activity (PRA) and norepinephrine (NE), which correlated with the decrease in HVPG. Similarly, Laleman et al. [34] demonstrated amelioration of the hyperdynamic circulation in patients with ACLF after treatment with MARS. He randomized 12 patients with ACLF to SMT ($n = 6$) or to MARS with SMT ($n = 6$) and showed favorable effects of MARS in comparison to SMT on the mean arterial pressure (MAP), systemic vascular resistance index (SVRI), plasma rennin activity (PRA) and nitric oxide (NO). Sen et al. [35] also showed beneficial effects of MARS on systemic hemodynamics by demonstrating a reduction in portal pressures in patients with severe alcoholic hepatitis with organ failure. Donati et al. [36] studied the acute effect of treatment with the MARS on splanchnic, renal and systemic haemodynamics in 12 patients with end-stage cirrhosis. A significant improvement in hemodynamics was noted with an increase in median portal velocity, mean arterial pressure and vascular resistance and a decrease in the renal resistance index and splenic resistance index.

## Immune dysfunction in ACLF

ACLF patients are known to have impaired immune responses including a reduced frequency of dendritic cells and high IFN-γ production by T cells. These cellular immune responses have showed improvement after G-CSF treatment [37]. Wasmuth et al. [38] had demonstrated that patients with ACLF have immunological 'defects' that are comparable to those in patients with sepsis characterized by a state of severe neutrophil dysfunction that in turn is associated with an increased risk of infection, organ failure and mortality. Guo et al. [39] treated 24 patients with MODS with liver failure with MARS and demonstrated a significant removal of NO and other cytokines such as TNF-α, IL-6, IL-8 and INF-γ, which was associated with an improvement in the overall outcome of patients. Nine patients survived or were successfully bridged to transplantation. Moreover, severe derangements in the albumin functionality, which is proportional to the severity of liver damage, have been well documented in patients with ACLF [40, 41]. The albumin becomes dysfunctional secondary to the accumulated toxins, which physically impair its tertiary structure, leading to an alteration in the binding sites and loss in the functional capacity as shown by a higher ratio of ischemia modified albumin to total albumin. However, the current devices have failed to show improvement in the functionality of albumin [40].

The effect of Prometheus on the cytokine concentration and markers of inflammation and liver regeneration was studied in 11 patients with ALF; it showed a significant decrease in the concentrations of TNFα, CRP, PCT and α(1) fetoprotein, but contrary to this, an increase in hepatocyte growth factor (HGF) was detected [42]. In another recent study by Donati et al. of 64 patients treated with MARS for 269 treatment sessions given as a bridge for orthotopic liver transplantation (OLT) or for liver function recovery, MARS treatment was shown to reduce bilirubin and bile acids; however, HGF values showed a significant increase post-treatment from 4.1 ng/ml (1.9–7.9) to 7.9 ng/ml (3.2–14) [43]. This is important because the HGF-Met pathway has been shown to play a critical role in promoting cell survival and regeneration of tissues as it suppresses and improves chronic inflammation and fibrosis [44].

## Survival in ACLF

In the most recent meta-analyses and systematic reviews, no benefit of MARS treatment in reducing mortality compared to SMT was noted [23, 45], even though both of these meta-analyses have the limitations of enrolling a heterogeneous group of patients. However, contrary results were shown by a systematic review by Kjaergard et al. [46, 47] that included 12 RCTs ($n = 483$); 10 of the trials assessed ALS in ALF and ACLF, and ALS was shown to reduce mortality by 33 % in patients with ACLF as compared to SMT. Jalan et al. [48] reported 50 % survival at 3 months for eight patients treated with MARS suffering from severe alcoholic hepatitis. Faenza et al. studied 56 ACLF patients (278 sessions): 41 out of 191 procedures with MARS and 16 out of 87 procedures with Prometheus. Treatment led to 3-month survival without OLT in just 48.5 % in the MARS group and 33.5 % in the Prometheus groups [49]. In a Chinese study of patients with hepatitis B-related ACLF [50], it was seen that a decrease in the MELD score after treatment with artificial liver support pre-transplantation led to improved survival post-transplantation, which was comparable to that of patients who underwent emergency liver transplantation. This was also significantly better than that of patients who had no decrease in the MELD score post-artificial liver support

therapy. This study highlights that ALS could be an effective form of bridging therapy in patients with ACLF with high MELD scores awaiting liver transplantation. In a retrospective single-center study, the efficacy of MARS for patients with either ALF or ACLF was studied. Of the 50 ALF patients and 26 ACLF patients only 1 patient survived without liver transplantation. Thus, the authors concluded that MARS could only be an effective bridging therapy, and it is a futile exercise in the absence of a liver transplant [51]. These results have been substantiated by two large randomized multicentric controlled trials from Europe, i.e., the recently published HELIOS (for Prometheus) and RELIEF trials (for MARS), which failed to show any benefit on short-term transplant-free survival with these modalities, which was the primary end point of these studies [22, 30].

### Cost-efficacy analysis

In a prospective cohort of ACLF patients ($n = 149$), Hessel et al. [52–54] showed MARS to be cost-effective with a mean difference of 19.835 euros (95 % CI 13.308–25.429) with 35,639 euros for MARS-treated patients and 15,804 euros for controls. Similar results were shown by Kantola [55] for MARS when used in patients with ALF. The cost of a single 7-h session of MARS is approximately € 2,165 [serum albumin (20 %) € 300–600, € 1,740-for the MARS treatment kit and € 125 for disposables used by the dialysis machine], which is almost the same as for a single Prometheus session. However, the cost of SPAD is approximately € 656, which is 30 % of the cost of MARS therapy [56].

Proposed modifications of the current systems

To overcome the potential weaknesses of the currently available artificial liver support systems, several modifications have been tried. To exclude the limitations of the anion exchange polymers that are used in the current systems, i.e., binding of heparin and activation of coagulation, Weber et al. prepared two series of neutral polystyrene divinylbenzene resins with average pore sizes of 5–6 and 8–9 nm, respectively. In vitro experiments showed that neutral polystyrene divinylbenzene polymers with a pore size larger than 5–6 nm acted as efficient adsorbents for albumin-bound toxins without inducing generation of thrombin-antithrombin complexes [57]. In another in vitro study by Dominik et al. [58], three novel membranes of different pore sizes were compared with the MARS Flux membrane for cytokine removal and detoxification qualities in vitro. Albumin-bound toxins were removed more efficiently using novel large (Emic2) to super-large pore size membranes (S20; HCO Gambro). Clearance of cytokines IL-6 and tumor necrosis factor-α was also drastically improved using super-large pore membranes. Coupled plasma filtration adsorption (CPFA) has been developed to remove larger mediators during systemic inflammation with an extracorporeal circuit consisting of a plasma filter, a resin cartridge and a high-flux dialyser, which is mainly used as an extracorporeal therapy for sepsis and has proved to be effective as a liver assist device in a few preliminary reports [59]. The efficacy and safety of CPFA combined with continuous veno-venous hemofiltration (CVVH) for the treatment of multiple organ dysfunction were studied in 11 cases of ALF. There was an increase noted in MAP along with a significant decrease in inflammatory cytokines, i.e., TNF-alpha, IL-1 beta, IL-6 and IL-8, with a significant decrease in the biochemical parameters and APACHE II scores. There were no adverse reactions, and the overall survival rate of patients was 45.5 % (5/11 cases). Marangoni et al. [60] modified the MARS albumin circuit with the insertion of double adsorption units in parallel (high-efficiency MARS, HE MARS), which was studied in four patients: It was seen that bilirubin and bile acid levels decreased more with HE MARS than standard MARS, and treatment success was inversely proportional to the MELD scores at baseline. Novelli et al. [61] demonstrated removal of endotoxin using polymyxin-B hemoperfusion-based (PMX-DHP) treatment along with MARS, which enabled removal of endotoxin and halted the development of multiorgan failure secondary to the sepsis cascade. In a recent study of ten critically ill ALF patients with unstable hemodynamics, continuous plasma diafiltration (CPDF) showed survival in nine patients without any major adverse events [62].

### Perspectives

Even though the multicentric HELIOS and the RELIEF trials were adequately powered, they were fraught with a number of limitations. First, both trials took some 7–9 years for completion, and consequent to this, the

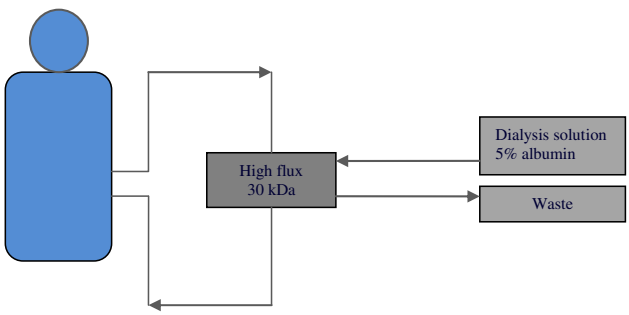


**Fig. 4** Schematic diagram of Single pass albumin dialysis [SPAD] involves adding albumin with a concentration of 4–5% to standard dialysis.The membrane used is a high-flux dialysis membrane which allows molecules up to 30 kDa topass through [4, 63]

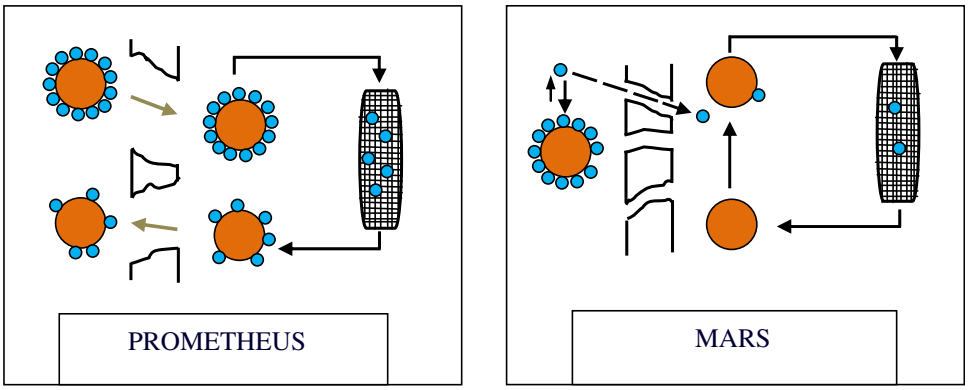


**Fig. 5** Depicting membranes in MARS and Prometheus. In Prometheus there occurs direct adsorption as the albumin with its bound toxins crosses directly through the membrane, however in MARS there is indirect adsorption as the toxins first dissociate from the patient's albumin, cross the membrane and then bind to the albumin in the MARS circuit and are subsequently removed [64]

enrollment of a heterogeneous patient cohort was unavoidable. It is also noteworthy that over the years there has been an obvious change in the diagnostic criteria for ACLF, and to date, controversy still exists concerning how this entity is defined. The pathophysiology and evolution of this syndrome still remain an enigma. Even in the West, it was only recently redefined by the CANONIC study [2]. In the RELIEF trial, the patients were enrolled within 24–48 h of presentation; however, in HELIOS, the patients were enrolled at varied time points, which is a major limitation to assessing which patients would best benefit from therapy. Furthermore, the majority of patients in both trials had sepsis as a precipitating event and hence were enrolled quite late in the natural course of their disease. Many patients even suffered worsening of bacterial infections because of the treatment. Sepsis, as is well known, is the major cause of mortality in patients with ACLF that culminates in multiorgan dysfunction and death. Also, active uncontrolled sepsis is a definite contraindication for albumin dialysis, and there are reports of worsening of coagulopathy and sepsis with treatment. Hence, it is essential to explore the role of albumin dialysis as one of the modalities in the currently available therapeutic options in these patients before the onset of sepsis. In this regard, the APASL definition allows for screening of patients before the onset of sepsis providing for a "golden window" of treatment. If introduced after the onset of sepsis, it also becomes imperative to study its role in patients with single organ failure or patients with ACLF grade 1 [2]. The other option would be to consider improvement in the design of the currently available systems so as to incorporate higher cytokine removal efficiency as in CPFA or endotoxin-removing strategies as suggested by Novelli et al. or albumin exchange properties that might translate into improved survival if introduced after the onset of sepsis [2, 61]. It is also important to look at the role of this modality in combination with conventional dialysis in the management of renal failure as the high cost of the therapy is a major deterrent to its repeated use (Figs. 4, 5).

The foremost reason for no demonstrable survival benefit with the currently available artificial liver support systems is the functional incompetence as most of these provide only the detoxification function of the entire armamentarium of liver functions. Second, as of now there is still no 'magic bullet' that can restore the dysregulated immune system in patients with ACLF that highlights the complexity of the immune response in terms of its magnitude, duration and trajectory, which remains completely elusive. Hence, the timing and choice of patients for intervention with liver support in patients with ACLF are of critical importance to achieve the maximal therapeutic benefit. This is because by the time multiorgan failure is manifest, the benefits of intervention with these devices is not to be expected. Incorporation of synthetic function by living hepatocytes, i.e., the "bioartificial liver" or therapies to potentiate hepatic regeneration, however, look more realistic. Considering the wide heterogeneity in the clinical presentation and etiological profile of patients with ACLF, RCTs from across the world are urgently needed [1, 2].

In summary, artificial liver support systems provide improvement in biochemical and clinical parameters and transiently support the failing liver in patients with ACLF. Patients who develop massive hepatocyte loss with impaired regeneration can be salvaged until a donor liver is available. Liver transplant remains the primary treatment modality for patients with ACLF; however, artificial liver support can rescue properly selected patients waiting for liver transplant or spontaneous regeneration [65]. Larger prospective randomized controlled trials are needed before these modalities can be recommended for routine incorporation into standard clinical practice.

**Compliance with ethical requirements and Conflict of interest** This article does not contain any studies with human or animal subjects. Rakhi Maiwall, Jaswinder Maras, Suman Lata Nayak and Shiv Kumar Sarin have declared no conflict of interest.

## References


1. Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hepatol Int. 2009;3:269–282
2. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426–1437
3. Jalan R, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif. 2002;20: 252–261
4. Hassanein TI, Schade RR, Hepburn IS. Acute-on-chronic liver failure: extracorporeal liver assist devices. Curr Opin Crit Care. 2011;17(2):195–203
5. Stange J, Ramlow W, Mitzner S, et al. Dialysis against a recycled albumin solution enables the removal of albumin-bound toxins. Artif Organs. 1993;17:809–813
6. Abe T, Shono M, Kodama T, Kita Y, Fukagawa M, Akizawa T. Extracorporeal albumin dialysis. Ther Apher Dial. 2004;8(3): 217–222
7. Rozga J. Liver support technology—an update. Xenotransplantation. 2006;13(5):380–389
8. Abe T, Kobata H, Hanba Y, Kitabata Y, Narukawa N, Hasegawa H, et al. Study of plasma exchange for liver failure: beneficial and harmful effects. Ther Apher Dial. 2004;8(3):180–184
9. Falkenhagen D, Strobl W, Vogt G, Schrefl A, Linsberger I, Gerner FJ, et al. Fractionated plasma separation and adsorption system: a novel system for blood purification to remove albumin bound substances. Artif Organs. 1999;23(1):81–6
10. Evenepoel P, Laleman W, Wilmer A, Claes K, Kuypers D, Bammens B, et al. Prometheus versus molecular adsorbents recirculating system: comparison of efficiency in two different liver detoxification devices. Artif Organs. 2006;30:276–284
11. Krisper P, Haditsch B, Stauber R, Jung A, Stadlbauer V, Trauner M, et al. In vivo quantification of liver dialysis: comparison of albumin dialysis and fractionated plasma separation. J Hepatol. 2005;43:451–457
12. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology. 1999;29: 648–653
13. Mans AM, Biebuyck JF, Shelly K, Hawkins RA. Regional blood-brain barrier permeability to amino acids after portacaval anastomosis. J Neurochem. 1982;38:705–717
14. Ryska M, Laszikova E, Pantoflicek T, Ryska O, Prazak J, Koblihova E. Fractionated plasma separation and adsorption significantly decreases intracranial pressure in acute liver failure: experimental study. Eur Surg Res. 2009;42:230–235
15. Koivusalo AM, Teikari T, Höckerstedt K, Isoniemi H. Albumin dialysis has a favorable effect on amino acid profile in hepatic encephalopathy. Metab Brain Dis. 2008;23(4):387–398
16. Kobashi-Margáin RA, Gavilanes-Espinar JG, Gutiérrez-Grobe Y, et al. Albumin dialysis with molecular adsorbent recirculating system (MARS) for the treatment of hepatic encephalopathy in liver failure. Ann Hepatol. 2011;10(Suppl 2):S70–S76
17. Heemann U, Treichel U, Loock J, Philipp T, Gerken G, Malago M, et al. Albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. Hepatology. 2002; 36:949–958
18. Sen S, Davies NA, Mookerjee RP, Cheshire LM, Hodges SJ, Williams R, et al. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver Transpl. 2004;10:1109–1119
19. Kjaergard LL, Liu J, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. JAMA. 2003;289(2):217–22
20. Hassanein TI, Tofteng F, Brown RS Jr, McGuire B, Lynch P, Mehta R, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 2007;46(6):1853–1862
21. Rifai K, Ernst T, Kretschmer U, et al. The Prometheus device for extracorporeal support of combined liver and renal failure. Blood Purif. 2005;23(4):298–302
22. Banares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology. 2013;57:1153–1162
23. Vaid A, Chweich H, Balk EM, Jaber BL. Molecular adsorbent recirculating system as artificial support therapy for liver failure: a meta-analysis. ASAIO J. 2012;58(1):51–59
24. Stenbøg P, Busk T, Larsen FS. Efficacy of liver assisting in patients with hepatic encephalopathy with special focus on plasma exchange. Metab Brain Dis. 2013;28(2):333–335
25. Nakae H, Igarashi T, Tajimi K. Selective plasma exchange with dialysis in patients with acute liver failure. Ther Apher Dial. 2012;16(5):467–471
26. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, et al. Acute-on chronic liver failure. J Hepatol. 2012;57:1336–1348
27. Van Slambrouck CM, Salem F, Meehan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. Kidney Int. 2013. doi: 10.1038/ki.2013.78
28. Maiwall R, Kumar S, Vashishtha C, et al. Acute kidney injury in ACLF is different from patients with cirrhosis. Hepatology. 2013;58(S1):36A–91A
29. Angeli P, Gines P. Hepatorenal syndrome, MELD score and liver transplantation: an evolving issue with relevant implications for clinical practice. J Hepatol. 2012;57:1135–1140
30. Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz C, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology. 2012;142:782–789
31. Mitzner SR, Stange J, Klammt S, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl. 2000;6:277–286
32. Wong F, Raina N, Richardson R. Molecular adsorbent recirculating system is ineffective in the management of type 1 hepatorenal syndrome in patients with cirrhosis with ascites who have failed vasoconstrictor treatment. Gut. 2010;59(3):381–386
33. Catalina MV, Barrio J, Anaya F, Salcedo M, Rincón D, Clemente G, et al. Hepatic and systemic haemodynamic changes after MARS in patients with acute on chronic liver failure. Liver Int. 2003;23(Suppl 3):39–43
34. Laleman W, Wilmer A, Evenepoel P, Elst IV, Zeegers M, Zaman Z, et al. Effect of the molecular adsorbent recirculating system and Prometheus devices on systemic haemodynamics and vasoactive agents in patients with acute-on-chronic alcoholic liver failure. Crit Care. 2006;10:R108
35. Sen S, Mookerjee RP, Cheshire LM, Davies NA, Williams R, Jalan R. Albumin dialysis reduces portal pressure acutely in patients with severe alcoholic hepatitis. J Hepatol. 2005;43:142–148
36. Donati G, Piscaglia F, Colì L, et al. Acute systemic, splanchnic and renal haemodynamic changes induced by molecular adsorbent recirculating system (MARS) treatment in patients with end-stage cirrhosis. Aliment Pharmacol Ther. 2007;26(5): 717–726

37. A Khanam, N Trehanpati, V Garg et al. Altered frequencies of dendritic cells and IFN-c-secreting T cells with granulocyte colony-stimulating factor (G-CSF) therapy in acute-on-chronic liver failure. Liver Int. 2014;34(4):505–513
38. Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghoner A, Vidacek D, Siewert E, et al. Patients with ACLF display "sepsis-like" immune paralysis. J Hepatol. 2005;42:195–201
39. Guo LM, Liu JY, Xu DZ, Li BS, Han H, Wang LH, et al. Application of molecular adsorbents recirculating system to remove NO and cytokines in severe liver failure patients with multiple organ dysfunction syndrome. Liver Int. 2003;23(Suppl 3):16–20
40. Jalan R, Schnurr K, Mookerjee RP, Sen S, Cheshire L, Hodges S, et al. Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. Hepatology. 2009;50:555–564
41. Garcia-Martinez R, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. Hepatology. 2013;58(5):1836–1846
42. Rocen M, Kieslichova E, Merta D, Uchytilova E, Pavlova Y, Cap J, et al. The effect of Prometheus device on laboratory markers of inflammation and tissue regeneration in acute liver failure management. Transpl Proc. 2010;42(9):3606–3612
43. Donati G, La Manna G, Cianciolo G, Grandinetti V, Carretta E, Cappuccilli M, et al. Extracorporeal detoxification for hepatic failure using molecular adsorbent recirculating system: depurative efficiency and clinical results in a long-term follow-up. Artif Organs. 2013;38(2):125–134
44. Nakamura T, Sakai K, Nakamura T, Matsumoto K. Hepatocyte growth factor twenty years on: much more than a growth factor. J Gastroenterol Hepatol. 2011;26(Suppl 1):188–202
45. Khuroo MS, Khuroo MS, Farahat KL. Molecular adsorbent recirculating system for acute and acute-on-chronic liver failure: a meta-analysis. Liver Transpl. 2004;10(9):1099–1106
46. Kjaergard LL, Liu J, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. JAMA. 2003;289(2):217–222
47. Liu J, Kjaergard LL, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for liver failure: a Cochrane Hepato-Biliary Group Protocol. Liver. 2002;22(5):433–438
48. Jalan R, Sen S, Steiner C, Kapoor D, Alisa A, Williams R. Extracorporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. J Hepatol. 2003;38:24–31
49. Faenza S, Baraldi O, Bernardi M, Bolondi L, Coli L, Cucchetti A, et al. Mars and Prometheus: our clinical experience in acute chronic liver failure. Transplant Proc. 2008;40(4):1169–71
50. Ling Q, Xu X, Wei Q, Liu X, Guo H, Zhuang L, et al. Downgrading MELD improves the outcomes after liver transplantation in patients with acute-on-chronic hepatitis B liver failure. PLoS One. 2012;7(1):e30322
51. Wai CT, Lim SG, Aung MO, Lee YM, Sutedja DS, Dan YY, Aw MM, Quak SH, Lee MK, Da Costa M, Prahbakaran K, Lee KH. MARS: a futile tool in centres without active liver transplant support. Liver Int. 2007;27(1):69–75
52. Hessel FP, Bramlage P, Wasem J, Mitzner SR. Cost-effectiveness of the artificial liver support system MARS in patients with acute-on-chronic liver failure. Eur J Gastroenterol Hepatol. 2010;22(2):213–220
53. Hessel FP, Mitzner SR, Rief J, Guellstorff B, Steiner S, Wasem J. Economic evaluation and 1-year survival analysis of MARS in patients with alcoholic liver disease. Liver Int. 2003;23(Suppl 3):66–72
54. Hessel FP. Economic evaluation of the artificial liver support system MARS in patients with acute-on-chronic liver failure. Cost Eff Resour Alloc. 2006;4:16
55. Kantola T, Mäklin S, Koivusalo AM, Räsänen P, Rissanen A, Roine R, et al. Cost-utility of molecular adsorbent recirculating system treatment in acute liver failure. World J Gastroenterol. 2010;16(18):2227–2234
56. Brown K. Liver Dialysis: Molecular Adsorbent Recirculating System (MARS) BME 281 Second Presentation, November 27, 2012
57. Weber V, Linsberger I, Hauner M, et al. Neutral styrene divinylbenzene copolymers for adsorption of toxins in liver failure. Biomacromolecules. 2008;9(4):1322–1328. doi:10.1021/bm701396n
58. Dominik A, Stange J, Pfensig C, Borufka L, Weiss-Reining H, Eggert M. Reduction of elevated cytokine levels in acute/acute-on-chronic liver failure using super-large pore albumin dialysis treatment: an in vitro study. Ther Apher Dial. 2013. doi:10.1111/1744-9987.12146
59. He CS, Shi W, Ye ZM, Liang XL, Zhang B, Liu SX, et al. Efficacy and safety of coupled plasma filtration adsorption combined with continuous veno-venoushemofiltration for multiple organ dysfunction syndrome patients with acute liver failure. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2007;19(1):47–49
60. Marangoni R, Bellati G, Castelli A, Romagnoli E. Development of high-efficiency molecular adsorbent recirculating system: preliminary report. Artif Organs. 2014. doi:10.1111/aor.12250
61. Novelli G, Morabito V, Pugliese F, Ferretti G, Novelli S, Ianni S, et al. Management of sepsis during MARS treatment in ACLF. Transpl Proc. 2011;43:1085–1090
62. Komura T, Taniguchi T, Sakai Y, Yamashita T, Mizukoshi E, Noda T, et al. Efficacy of continuous plasma diafiltraion therapy in critical patients with acute liver failure. J Gastroenterol Hepatol. 2014;29(4);782–786 doi:10.1111/jgh.12440
63. Peszynski P, Klammt S, Peters E, et al. Albumin dialysis: single pass vs.recirculation (MARS). Liver. 2002;22(Suppl 2):40–42
64. Rademacher S, Oppert M, Jörres A. Artificial extracorporeal liver support therapy in patients with severe liver failure. Expert Rev Gastroenterol Hepatol. 2011;5(5):591–599. doi:10.1586/egh.11.59
65. Xu X, Liu X, Ling Q, Wei Q, Liu Z, Xu X, et al. Artificial liver support system combined with liver transplantation in the treatment of patients with acute-on-chronic liver failure. PLoS One. 2013;8(3):e58738