NARRATIVE REVIEW

Artificial liver support in patients with liver failure: a modified DELPHI consensus of international experts

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Abstract

The present narrative review on albumin dialysis provides evidence-based and expert opinion guidelines for clinicians caring for adult patients with different types of liver failure. The review was prepared by an expert panel of 13 members with liver and ntensive care expertise in extracorporeal liver support therapies for the management of patients with liver failure. The coordinating committee developed the questions according to their importance in the management of patients with liver failure. For each indication, experts conducted a comprehensive review of the literature aiming to identify the best available evidence and assessed the quality of evidence based on the literature and their experience. Summary statements and expert's recommendations covered all indications of albumin dialysis therapy in patients with liver failure, timing and intensity of treatment, efficacy, technical issues related to the device and safety. The panel supports the data from the literature that albumin dialysis showed a beneficial effect on hepatic encephalopathy, refractory pruritus, renal function, reduction of cholestasis and jaundice. However, the trials lacked to show a clear beneficial effect on overall survival. A short-term survival benefit at 15 and 21 days respectively in acute and acute-on-chronic liver failure has been reported in recent studies. The technique should be limited to patients with a transplant project, to centers experienced in the management of advanced liver disease. The use of extracorporeal albumin dialysis could be beneficial in selected patients with advanced liver diseases listed for transplant or with a transplant project. Waiting future large randomized controlled trials, this panel experts' statements may help careful patient selection and better treatment modalities.

Keywords: Artificial liver support, Acute liver failure, Acute on chronic liver failure, Albumin dialysis, Molecular Adsorbent Recirculating System™, Plasma exchange

Introduction

Twenty years after the birth of a novel concept in hemodialysis, extracorporeal albumin dialysis (ECAD) is still currently the main artificial liver support used worldwide. Albumin dialysis devices, linked to a dialysis machine, allowed a great capacity of removal of both hydrosoluble and albumin-binding molecules, drugs and toxins which are often increased in patients with advanced liver disease [1]. Among three currently

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available artificial liver support devices, the molecular adsorbent recirculating system (MARS™, Baxter International Inc., Deerfield, Il, USA), the fractionated plasma separation and adsorption system Prometheus™ (Fresenius Medical Care, Bad Homburg, Germany), and the single pass albumin dialysis, MARS™ is the most studied and used system worldwide [1, 2]. More recently, plasma exchange has shown a major clinical interest in patients with liver failure.

MARS™ has been applied in various types of liver failure: acute liver failure (ALF), acute-on-chronic liver failure (ACLF), liver dysfunction and liver failure after liver transplantation (LTx) and after major hepatectomy, refractory pruritus, drug overdose and secondary liver dysfunction in intensive care unit (ICU) patients. Albumin dialysis with MARS™ has been used in various departments: medical ICU, surgical ICU, nephrology, hepatology, transplant centers and very rarely in ambulatory patients; this could explain in part, differences in practical clinical use. Despite that numerous trials, reviews and meta-analyses [3–6] on the effect of ECAD on short- and medium-term survival has been published, there is still neither a clear consensus on the profile of eligible patients nor on the optimal treatment protocol. In critically-ill patients, multiorgan support therapies (MOST) may provide simultaneous and combined support to failing organ systems [7]. Considering current and future developments of MOST, refining indications of albumin dialysis and modalities of treatment of critically ill patients with end-stage liver disease and organ dysfunction, i.e., ALF and ACLF, are here provided.

Methods

Selection and coordination of the expert panel

The coordinating committee composed of three experts in extracorporeal liver support invited all other panel members to establish an expert opinion panel to address clinical guidance on the use of extracorporeal albumin dialysis in patients with liver failure. The members were selected from different countries based on their large experience in conducting main trials on artificial liver support therapies and their expertise in the management of critically ill patients with liver failure.

The working group of 13 international experts (hepatologists, surgeons, intensivists, and nephrologists) individually performed a comprehensive review of the literature, searching for most relevant articles related to their domain and summarized their findings. Search was performed using Pubmed, Medline and Embase databases from January 2000 to May 31, 2019. Articles were selected using text words including mainly: albumin, artificial liver support, liver failure, acute liver failure, acute on chronic liver failure, albumin dialysis,

> ### Take-home message
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> Extracorporeal albumin dialysis is the most studied and used system worldwide. It showed a beneficial effect on hepatic encephalopathy, refractory pruritus, renal function, reduction of cholestasis and jaundice. The technique is safe, and its use should be limited to centers experienced in the management of advanced liver disease and to patients with a transplant project. Panel experts' statements reported in this manuscript may help careful patient selection and better treatment modalities.

molecular adsorbent recirculating system, fractionated plasma separation and adsorption, single pass albumin dialysis, hemadsorption, plasma exchange. Only English language studies were included. Main indications and outcomes of randomized controlled trials (RCTs) and large retrospective comparative and non-comparative trials of clinical interest on albumin dialysis with MARS are illustrated in Table 1. As liver support use and benefit, through various indications, are supported by limited evidence, it might have been difficult to achieve group consensus. Hence, other methods such GRADE or DELPHI used to establish guidelines with strong recommendations may be inappropriate to apply to the current document. A modified Delphi process was employed to establish statements in this position paper. The scientific committee generated a list of clinical questions focused on the following list of clinical questions in different situation of liver failure:

1- What is the rationale for the use of albumin dialysis in liver support therapy?
2- Which patients are eligible for albumin liver dialysis?
3- What is the optimal timing of albumin liver dialysis in disease course?
4- What are the best technical and practical conditions of use of albumin liver dialysis?
5- How should patients undergoing albumin liver dialysis be monitored considering safety issues?

These questions were discussed in the context of relevant clinical syndromes (ALF, decompensated cirrhosis and ACLF, refractory pruritus, hypoxic liver injury, post-hepatectomy liver failure, graft dysfunction after LTx and other rare diseases). Each expert elaborated in his field of expertise summary statements based on the relevant paper in the literature and suggested recommendations to the above predefined questions based on perceived importance to patients for clinical decision-making. The panel experts met twice via a virtual conference to discuss the statements. The final statements were modified based on discussions and feedback from all the experts until consensus was

obtained. Statements were classified according to the quality of evidence graded following a simplified adaptation of the GRADE system (EASL clinical practice guidelines), as high (data derived from multiple RCTs), moderate (data derived from a single RCT or multiple comparative and non-comparative studies) or low (data derived from retrospective observational studies); the grade of recommendation (wording associated with the grade of recommendation) strong ("must" or "should" or "Experts recommends") weak ("can, "may" or "Experts suggests") [8].

The rationale for albumin dialysis uses in liver support therapy

Human serum albumin metabolism

Human serum albumin (HSA) is a water-soluble 67 kDa protein, negatively charged at neutral pH, exclusively synthesized by the hepatocytes and has a prolonged half-life of approximately 20 days [9]. HSA is an important transport molecule for a variety of fatty acids, lipophilic toxins, hormones, vitamins, metals, metabolites,and drugs [10, 11] (Supplemental Fig. 1).

The total intravascular 120 g amount of albumin circulate through the organism and are exchanged with 240 g albumin in the extravascular space at a 4–5% per hour rate. HSA escapes the blood by fenestrated capillaries, such in the sinusoidal endothelium, e.g., in the liver and to a small extent in the glomerular filter. Organs with continuous endothelium (except the brain) display the 60 kDa glycoprotein receptor gp60 (albondin) which leads to internalization and caveolin-dependent transcytosis [12, 13]. Albumin also escapes by pinocytosis involving the membranal neonatal Fc receptor FcRn which binds it in endosomes for transcytosis [14], a process that is faster for cargo-carrying albumin [15]. The recycling of albumin from the extracapillary space via the lymphatic system and the recycling from glomerular filtered albumin by receptor complex formation with cubilin and megalin [13, 14] contribute to a long half-life and allow for up to 28 trips during the lifetime [10]. A therapeutic approach to acute and chronic liver failure including hepatorenal syndrome is the removal of such "albumin-bound toxins" (ABTs) by means of extracorporeal techniques based on the principles of adsorption, dialysis, and plasma filtration. Therapeutic plasma exchange and various forms of plasma adsorption have been explored as extracorporeal liver support therapies [16, 17].

Albumin dialysis-based therapy

ECAD using MARS™ device is a hemodialysis-like technique to facilitate the semi-selective removal of ABTs. To the contrary of standard hemodialysis, the dialysate fluid is enriched with HSA as a scavenger for ABTs. The method has higher selectivity than plasma exchange as the dialysis membranes used greatly exclude molecules larger than 30 kD. The mechanism of action comprises the detachment of ABTs from HSA, intermittent binding to the dialysis membrane, directed surface diffusion of ABTs towards the dialysate site of the dialysis membrane, detachment, and binding to dialysate albumin. The driving force is a transmembrane concentration gradient for the ABTs between the blood and dialysate space. To maintain this gradient, dialysate albumin is constantly replaced in the dialysate space of the dialyzer by fresh albumin (Fig. 1).

MARS™ uses three different fluid compartments, i.e., the blood circuit, an albumin circuit and a regular dialysate circuit (Fig. 1). It can be performed intermittently (typically for 6–8 h per day) or continuously. The blood flow rate is 150–250 ml/min, depending on the hemodynamic status of the patient. The dialysate albumin, pumped with 150 ml/min, is online-regenerated by dialysis against a bicarbonate-buffered dialysate, followed by sequential passage through a charcoal and an anion exchanger column. Either regional citrate or systemic heparin is used as an anticoagulant [18].

ECAD using MARS™ in different indications of liver failure

ECAD has been used in most situations of liver failure (Fig. 2) as a rescue therapy or a bridge to transplantation or recovery of acute liver decompensation presenting with progressive cholestasis. The place of liver support therapy in patients with liver failure and its objective are illustrated in Fig. 3. In most indications, patients with liver failure require a clinical and biological assessment, screening for etiology, infection and other decompensating events, management, and optimization of medical treatment prior to use of liver support therapy. The aim of ECAD is to provide local and systemic environment for liver regeneration. The timing of MARS™ indication, should consider the fibrosis stage severity of the liver disease, the remaining liver function and the potential of liver regeneration (Fig. 4) in addition to the presence of multiple organ failures. The perspective of LTx as a curative therapy should be discussed with the transplant team.

Acute liver failure

Acute loss of liver function results in a devastating and life-threatening condition. It is related to high circulating levels of endogenous harmful molecules that escape from the splanchnic area into the systemic circulation. Some of these compounds act like toxins such as ammonia, others are bigger in size, are lipophilic in nature and have a large distribution volume. These latter molecules mainly consist of proinflammatory

Table 1 Main trials of clinical interest on albumin dialysis with MARS™

First author, year	Design	Indication	No. of patients	Main results
Mitzner, 2000 [41]	RCT	ACLF—HRS	13	Survival improvement at 28 days Increase urine output. Decrease creatinine levels Removal of albumin bound and water-soluble substances
Heemann, 2002 [40]	RCT	ACLF—severe cholestasis	24	Survival improvement at 28 days Improvement of HE, hemodynamics, renal function, and reduction of bilirubin
Schmidt, 2003 [97]	RCT	ALF	13	Improvement of systemic hemodynamics Reduction of MAP and SVRI Reduction of Cardiac Index and heart rate
Sen, 2004 [27]	RCT	ACLF	18	Significant improvement of HE Significant decrease of NOx levels
Novelli, 2005 [98]	Retrospective	ALF, ACLF, PNF, PDF	116	Significant decrease of bilirubin, ammonia, lactates and creatinine Significant improvement of Glasgow coma scale
Laleman, 2006 [29]	RCT	ACLF	18	MARS™ significantly attenuates the hyperdynamic circulation in ACLF Significantly reduces SVRI and MAP, associated to a decrease of NOx levels
Hassanein, 2007 [39]	RCT	ACLF—HE	70	Significant improvement of 2 grades of HE Significant faster improvement of HE Not designed to assess survival improvement
El Banayosy, 2007 [99]	RCT	ALF due to cardiogenic shock	40	Trend to higher survival at 28 days ($p < 0.061$) in the MARS treated group
Kantola, 2008 [22]	Comparative retrospective	ALF	159	No statistically significant difference in survival between the MARS™ and the control group patients at 28 days Trend to higher 6-months survival in the MARS™ group ($p = 0.07$) and in transplanted patients ($p = 0.06$) Survival without LTx was significantly higher in the MARS™ group ($p = 0.03$)
Parés, 2010 [53]	Pilot	Refractory pruritus in cholestatic liver	20	Important decrease in pruritus in 75% of the patients (72% in the VAS) Significant bile acids reduction (41% after treatment and 37% after 1 month)
Leckie, 2012 [54]	Pilot	Refractory pruritus in cholestatic liver diseases	15	Immediate and complete response in 11 patients (73.3%), partial response in 2 and no response in 2 patients Mean VAS and itchiness score improved significantly (both $p < 0.001$) with improvement in the patient's perception of their quality of life Duration of acceptable relief in responders was 3.3 months (range 2–5)
Saliba, 2013 [19]	RCT	ALF	102	No significant improvement in 6- and 12-months survival Significant improvement of transplant free survival in patients that received ≥ 3 MARS™ sessions Significant improvement in the probability to be transplanted
Banares, 2013 [38]	RCT	ACLF	187	No significant improvement in 28- and 90-days survival Significant decrease of bilirubin and creatinine levels Short term beneficial effects in hepatic encephalopathy and HRS
Gerth, 2017 [100]	Comparative Non-randomized	ACLF	101	Significant reduction of 14-days mortality rate in the MARS™ group ($p = 0.004$), especially in patients with ACLF grades 2 and 3) Significant decrease of bilirubin and creatinine
Banares, 2019 [32]	Meta-analysis of individual patient data from 3 RCT's	ACLF	285	Significant survival improvement in patients receiving HIT both in the entire cohort (10-day survival: 98.6% vs. 82.8%, $p = 0.001$; 30-day survival: 73.9% vs. 64.3%, $p = 0.032$), and within the ACLF patients (10-day survival: 97.8% vs. 78.6%, $p = 0.001$; 30-day survival: 73.3% vs. 58.5%, $p = 0.041$) HIT increased survival independently of ACLF grade Independent predictors of survival were age, MELD score, ACLF grade, number of MARS™ sessions received and intensity of MARS™ therapy
MacDonald, 2021 [25] Crit Care Med	Propensity-score matched controls 1:4	ALF	520	Significant 21-day transplant-free survival improvement in patients receiving MARS™. Significant improvement (pre vs. post MARS™) in mean arterial pressure, creatinine, lactate, and ammonia for all. In non-acetaminophen ALF ($n = 53$), MARS™ significantly improved bilirubin, creatinine and ammonia

ACLF acute-on-chronic liver failure, *ALF* acute liver failure, *RCT* randomized controlled trial, *MAP* mean arterial pressure, *SVRI* systemic vascular resistance index, *NOx* nitric oxide, *HIT* high intensive treatment, *HRS* hepato-renal syndrome, *HE* hepatic encephalopathy, *VAS* visual analogic scale

cytokines and damage-associated molecular proteins (DAMPs) that are released from the failing and necrotic liver [16]. The lack of urea synthesis with hyperammonemia, together with release of DAMPS, causes a "endogenous intoxication syndrome" with development of multiple organ failure. In this fragile medical situation, it would be highly desirable to have a procedure that ensures rapid purification of the blood for both hydrophilic and lipophilic substances to reverse the critical condition.

ECAD with the MARS™ device in ALF ensured both albumin dialysis and hemodialysis, and was shown to be safe and to reduce the circulating levels of both water-soluble and lipophilic substances such as ammonia, aromatic amino acids, creatinine, amino-transaminases, bilirubin and various proinflammatory cytokines [19–21]. This blood-cleaning effect of MARS™ resulted in alleviation of hepatic encephalopathy [21, 22] and systemic circulatory shock, but it remained unclear if and how MARS™ affected nitrogen turnover and the levels of DAMPS.

Though it is likely that MARS™ therapy made patients with ALF less intoxicated, the question is whether MARS™ may improve survival [19–21, 23, 24]. Only one RCT was carried out to address this question in patients with ALF. The study could not demonstrate a survival benefit with MARS™ ($n=53$) compared to a control group ($n=49$) that received the same kind of standard medical therapy, at 6 months and 1 year (i.e., 85% in the MARS™ arm vs. 76% in the control arm at 6 months, and 83% vs. 76% at 1 year, respectively). In patients with paracetamol-related ALF, the 6-month survival rate was 68.4% (CI 43.5–86.4%) with conventional treatment and 85.0% (CI 61.1–96%) with MARS ($p=0.46$). Subgroup analyses of transplant-free survival at 6 months (19% in MARS™-treated patients vs. 27% in controls) also found no significant difference. However, it is important to note that all patients were only enrolled into the study if they were considered candidates for emergency LTx. This narrow inclusion criteria caused a central and critical problem in the interpretation of study results since two-thirds of the included patients were grafted before the planed number of interventions with MARS™ could be implemented, i.e. the median time to grafting was only 16 h [19]. In support of this view, a secondary analysis showed that the dosing of MARS™ influenced outcome: survival was significantly improved in patients who received ≥ 3 MARS™ sessions ($n=16$), compared to those who received <3 sessions ($n=88$). This significant signal

suggests that MARS™ therapy may be of value to patients with ALF who were not listed for emergency LTx. This finding is comparable with a similar study in patients with ALF where blood cleaning with plasmapheresis was shown to improve the survival of patients who were not candidates for LTx [16].
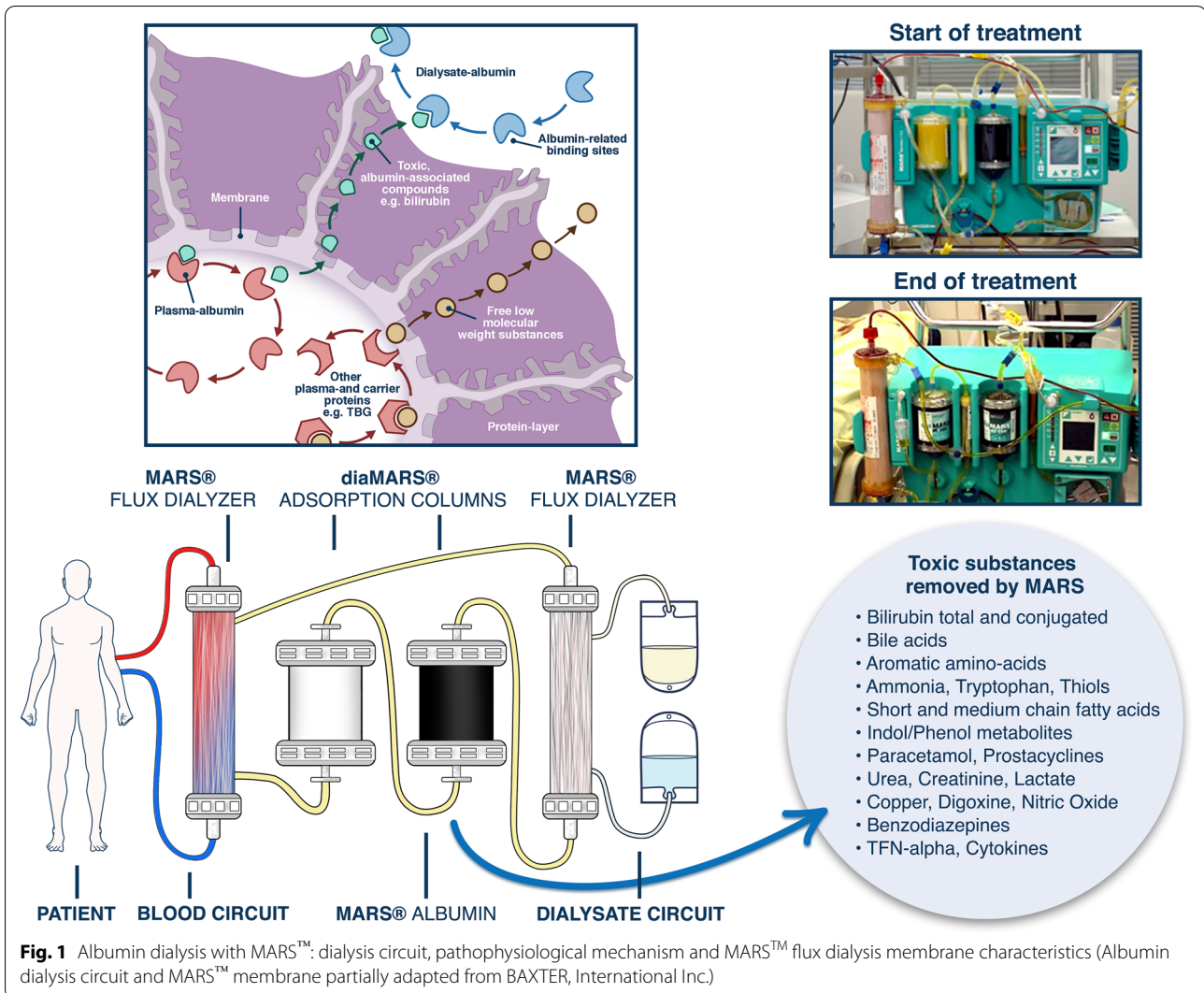
Interestingly, the data provided by the FULMAR study [19] suggested that liver support with ≥ 3 MARS™ sessions may be considered for patients with ALF who are not candidates for emergency LTx, due to definitive or temporary contraindications. This is especially true in countries with a short transplant waiting time from listing to LTx, until a graft becomes available. On the other hand, initiation of MARS™ therapy may indeed be important in situations where rapid LTx is not an option due to shortage of donor organs [19].

Another important issue to note is that MARS™ sessions may have an optimal effect if initiated early during ALF, when hepatic encephalopathy becomes clinically overt.

In a multicenter study from the U.S. Acute Liver Failure Study Group registry, 104 ALF patients who received MARS™ were propensity-scored matched to 416 controls. The multivariable conditional logistic regression adjusting for ALF etiology (acetaminophen: $n=248$; vs non-acetaminophen: $n=272$), age, vasopressor support, international normalized ratio, King's College Criteria, and propensity score showed that MARS™ was significantly associated with increased 21-day transplant-free survival [25]. Treatment with MARS™ has been associated with significant improvements (post vs pre) in hemodynamics, creatinine, lactate and ammonia particularly in acetaminophen-ALF [25].

High volume plasma exchange (HVPE)

In patients with ALF, HVPE for three days was compared to standard medical treatment (SMT), in a multicenter RCT of 182 patients. The study demonstrated an improvement in overall hospital survival (58.7% vs. 47.8%; HR 0.56; 95% CI 0.36–0.86; $p=0.008$). HVPE prior to transplantation did not improve survival compared with patients who received SMT alone (CI 0.37–3.98; $p=0.75$). The survival of those patients who fulfilled poor prognostic criteria but were not listed for transplantation due to contraindications (such as severe psychiatric disease or medical comorbidity) was significantly higher in those who received HVPE ($n=28$) as compared to those in receipt of SMT alone ($n=36$) [16].

Fig. 1 Albumin dialysis with MARS™: dialysis circuit, pathophysiological mechanism and MARS™ flux dialysis membrane characteristics (Albumin dialysis circuit and MARS™ membrane partially adapted from BAXTER, International Inc.)

Summary statements

In patients with ALF, extra-corporeal albumin liver dialysis:

Is associated with a significant improvement of 21-day survival in acetaminophen ALF etiology

Is not associated with a significant improvement of 6- and 12-months survival.

Is not beneficial at late stages of ALF, when multiple organ failure is already expressed

Is contraindicated in patients with an ongoing uncontrolled severe sepsis.

In patients with ALF, HVPE:

Is associated with an improvement in overall hospital survival and transplant-free survival

Experts' recommendations

HVPE may be considered as a bridge to LT in ALF patients (*moderate evidence*)

ECAD may be considered as a bridging therapy in patients meeting the criteria and waiting for liver transplantation particularly in acetaminophen patients (*moderate evidence*)

ECAD is preferably to be started at an early stage of hepatic encephalopathy (grade 2–3) once the criteria for liver transplantation are met (*moderate evidence*)

ECAD Is preferably administered in three or more 8 h sessions to induce a significant improvement of hepatic encephalopathy and hemodynamics (*moderate evidence*)

Fig. 2 Indications: different situations of liver failure treated with ECAD using MARS™
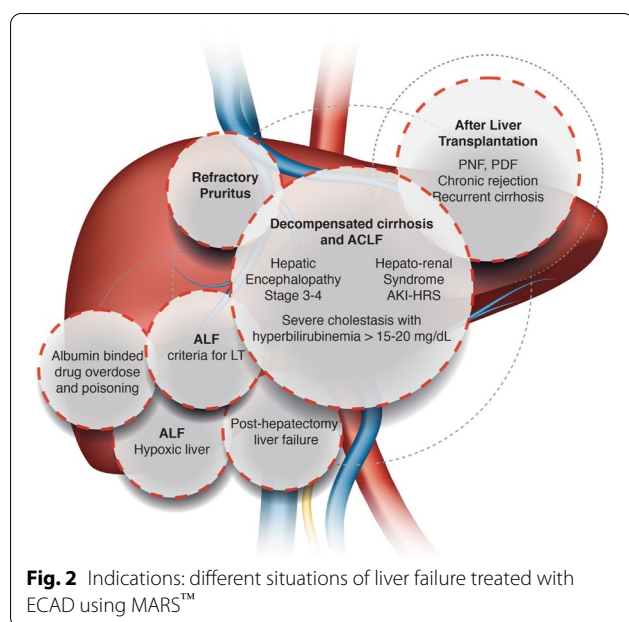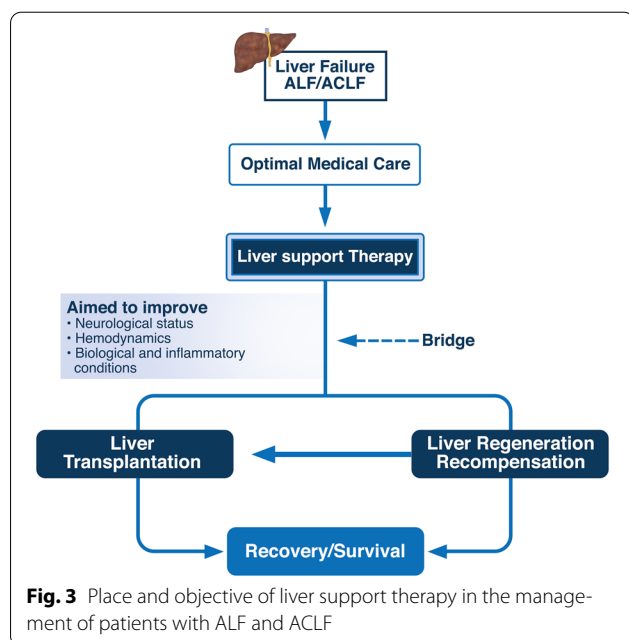
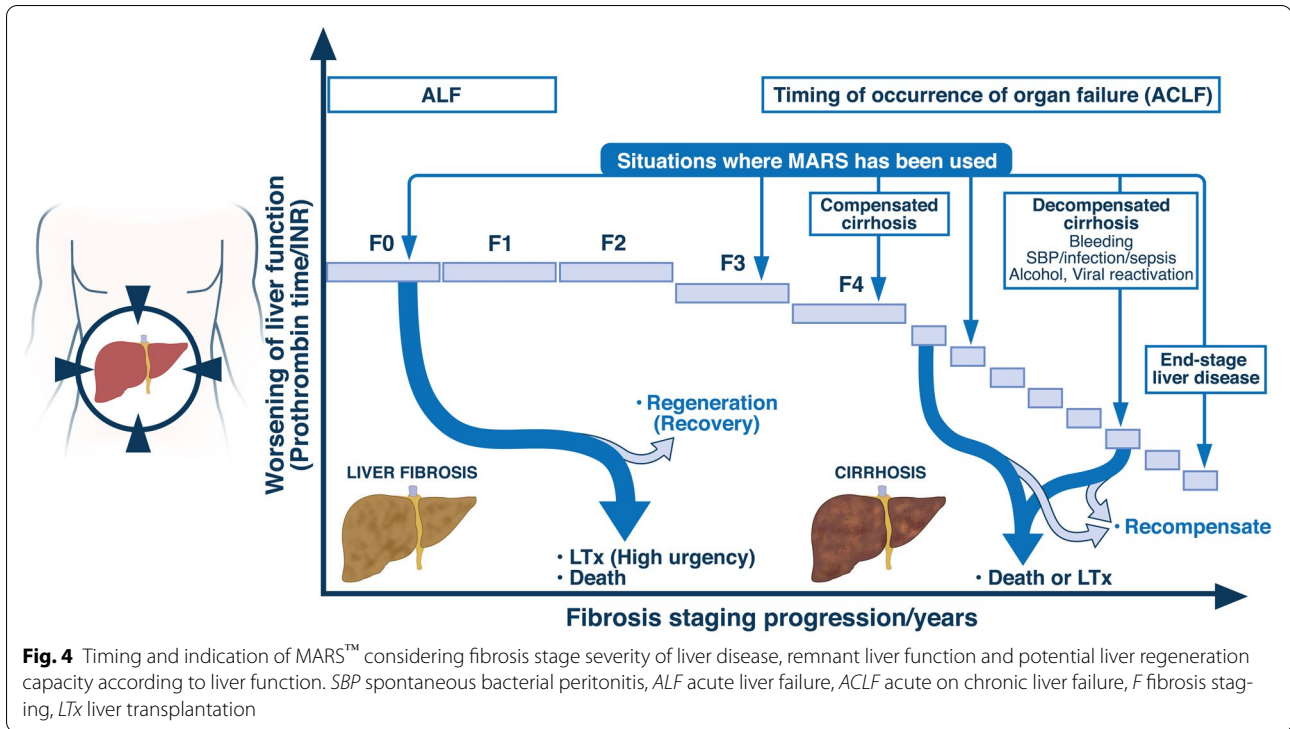## Decompensated cirrhosis and acute-on-chronic liver failure

The pathogenesis of decompensated cirrhosis and ACLF is extremely complex, with an incompletely known interplay of several mechanisms that are characteristically associated with a high incidence of organ dysfunction and failure. Excessive inflammation, strongly related with multiple organ failure, albumin dysfunction,

Fig. 3 Place and objective of liver support therapy in the management of patients with ALF and ACLF

immune-exhaustion and mitochondrial damage are especially intense in ACLF [26].

Several studies have shown that the MARS™ device removed significant amounts of various substances that accumulate in patients with ACLF such as bilirubin, bile acids, ammonia, protein breakdown products (aromatic amino acids, phenol, mercaptans), lactate, glutamine, mediators of oxidative stress, free fatty acids, endogenous benzodiazepines and pro-inflammatory cytokines [27]. MARS™ was also able to remove vasoactive mediators and to improve systemic and hepatic hemodynamics [28–30]. Stadlbauer et al. [31] showed that various cytokines were cleared from plasma by both MARS™ and Prometheus™, but neither system was able to change serum cytokine levels, probably reflecting the intensity of inflammation in ACLF patients.

The clinical effects of albumin dialysis in ACLF patients have been evaluated in several RCTs and meta-analyses [32–42]. The first study evaluated the effect of albumin dialysis in patients with type I hepatorenal syndrome [41]. In this small pilot study, 13 patients were randomized to receive either MARS™ ($n = 8$) or hemodiafiltration ($n = 5$). Patients allocated to the MARS™ group presented significant decreases in serum bilirubin and creatinine as compared with patients treated with hemodiafiltration. In addition, the 7-day survival rate was significantly better in MARS™-treated patients (27.5% vs. 0%). In an uncontrolled study in patients with hepatorenal syndrome unresponsive to vasoconstrictors, MARS™ therapy decreased nitric oxide plasma levels and serum creatinine, but without improving the glomerular filtration rate [43]. A second controlled study included 24 patients with ACLF that were randomly allocated to receive MARS™ or standard medical therapy (SMT) [40]. The primary endpoint was a 3-day stable reduction of serum bilirubin below 15 mg/dL. MARS™ therapy was significantly associated not only with a decrease in serum bilirubin levels but also with lower mortality. These results, however, should be interpreted cautiously because the trial was not designed to detect differences in mortality and the inclusion criteria were poorly defined. A third controlled trial evaluated the effects of MARS™ in patients with cirrhosis and severe hepatic encephalopathy [39]. Albumin dialysis significantly improved the recovery rate from hepatic encephalopathy as compared to SMT, which included conventional hemofiltration when indicated (58% vs. 37% at 72 h; $p = 0.045$). A large RCT, involved 189 patients with ACLF (RELIEF study) who were randomized to receive either MARS™ plus SMT ($n = 95$) or SMT alone ($n = 94$) [38]. The primary endpoint was 28-day survival. Patients in the MARS™

Fig. 4 Timing and indication of MARS™ considering fibrosis stage severity of liver disease, remnant liver function and potential liver regeneration capacity according to liver function. *SBP* spontaneous bacterial peritonitis, *ALF* acute liver failure, *ACLF* acute on chronic liver failure, *F* fibrosis staging, *LTx* liver transplantation

arm received up to ten 6–8 h sessions. Remarkably, the mean number of MARS™ sessions was 6.5 and the median time under MARS™ therapy was only 42 h. At day 4, a stronger decrease in serum creatinine ($p = 0.02$) and bilirubin ($p = 0.001$) was observed in patients treated with MARS™. Improvement of hepatic encephalopathy was also more frequent in the MARS™ arm. These beneficial effects on intermediate variables were not translated to an improvement of 28-day survival, which was comparable in both groups in intention-to-treat and per protocol population analyses. After adjusting for confounders, a significant beneficial effect of MARS™ on survival was not observed either. The MELD score and hepatic encephalopathy at admission and the increase in serum bilirubin at day 4 were independent predictors of mortality. Severe adverse events were similar in both groups, a fact that has been observed across other studies. However, non-clinically relevant bleeding episodes were more frequent in MARS™-treated patients in the RELIEF study [38].

In the HELIOS trial, a large multicenter RCT performed in Europe, using the fractionated plasma separation and adsorption (FPSA) (Prometheus® system, Fresenius Medical Care AG, Hamburg, Germany), 145 patients with acute decompensation of a chronic liver disease were recruited. ACLF was defined as cirrhotic patients with a Child–Pugh score >10 and a bilirubin >5 mg/dL. In an intent-to-treat analysis, the probabilities of survival on day 28 were 66% in the FPSA group and 63% in the control group ($p = 0.70$); on day 90, they were 47% and 38%, respectively ($p = 0.35$). The study showed that the approach was safe and well tolerated, although there was no overall significant survival benefit [42].

The results of conventional meta-analyses are heterogeneous. While some studies suggested a lack of effect of artificial liver support on ACLF survival [35, 36], other suggested a beneficial effect [37]. Two studies have evaluated this issue considering retrospectively the new ACLF definition. Gerth et al. [24] assessed the impact of MARS™ in a case–control study in patients with ACLF using the CANONIC study definition [44]. Interestingly, the authors excluded patients with respiratory failure. The study suggested that MARS™ may improve short-term survival and benefit to patients with more severe disease. Bañares et al. [32] evaluated, in a meta-analysis of individual patient data from three larger RCTs [38–40], the potential impact of the number of MARS™ sessions on survival. Age, MELD score, ACLF grade and the number of MARS™ sessions independently predicted survival, indicating that the intensity of the MARS™ therapy may influence clinical outcomes. Therefore, future studies should be designed considering risk stratification and intensity of the therapy. There are currently no available evidence-based data indicating how albumin dialysis

should be used in clinical practice. However, the literature suggests several relevant points:

-Albumin dialysis should be performed in reference sites with trained personnel experienced in the use of extracorporeal support in patients with advanced liver diseases.

-A careful evaluation of bacterial infection and a high suspicion for its diagnosis and aggressive therapy are mandatory before starting MARS™ treatment.

-Safety evaluation is essential considering specifically coagulation disturbances. Therefore, frequent clinical evaluation and testing coagulation parameters are mandatory.

Efficacy and safety of the treatment and the decision to continue or to stop the treatment should be evaluated on an individual basis.

Summary statements:

ECAD using MARS™ device:

Induces significant changes in systemic and portal hemodynamics and in vasoactive mediators, bile acids and bilirubin levels, but without changes in albumin function and inflammatory profile

Improves hepatic encephalopathy and renal failure in patients with ACLF

Is not associated with a significant improvement of 28–90 days survival in patients with acute decompensation of cirrhosis and ACLF

MARS™ may improve short-term survival (14 days) and efficacy appears to be correlated with patient selection and intensity of treatment

Experts' recommendations

In patients with decompensated cirrhosis and ACLF, ECAD using MARS™ device:

Should be considered in patients with hepatic encephalopathy refractory to 24–48 h of SMT (*moderate evidence*)

May be considered in patients with hepato-renal syndrome not responding to terlipressin plus albumin as a bridge to liver transplantation (*low evidence*)

Should be considered in patients with progressive cholestasis secondary to ACLF (*moderate evidence*)

Should not be considered in patients with either severe infections, sepsis, septic shock, acute respiratory distress syndrome or ACLF-OF grade > 3 (*low evidence*)

The decision to stop or to continue extracorporeal therapy after a minimum of three sessions should be based on a careful individual clinical assessment of efficacy and safety (*moderate evidence*)

Refractory pruritus

Pruritus is a common and very upsetting symptom in patients with cholestasis. Itch has a marked negative impact on the quality of life of these patients and, when severe, it can lead to suicide ideation. Therefore, intractable pruritus is an indication for liver transplantation [45, 46].

Both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend a stepwise approach in the management of cholestatic pruritus [45, 46]. This symptom can usually be alleviated using cholestyramine or colestipol. The next step for the management of pruritus is rifampicin, which is widely used as a second-line treatment and it has a notable effect in most cases [47]. Other agents such as naltrexone [48] and sertraline [49] reduce cholestatic itching but the effects are less prominent and constant. Studies indicates that fibrates [50] and an ileal bile acid transporter inhibitor [51] alleviate cholestatic itch. Older therapeutic interventions including phototherapy, charcoal hemoperfusion, plasmapheresis, external diversion of bile, and ileal bypass have been used in patients with cholestasis and intractable pruritus [52]. Some of latter techniques are far from being clearly favorable.

In patients with cholestatic pruritus, the ECAD with MARS™ has beneficial effects in relieving itch for a prolonged period. In a series of 20 patients with resistant pruritus, albumin dialysis resulted in a significant decrease of itch assessed by a visual analogue scale (VAS) [53]. Compared with baseline values, the VAS decreased by 72% immediately after treatment, and by 51% after 1 month. Pruritus decreased in all, but one patient and the overall itch improvement was reported satisfactory by 15 patients. Other studies also showed marked improvements in pruritus and quality of life after MARS™. The safety and efficacy of "out-patient" albumin dialysis using MARS™ in the treatment of intractable pruritus in cholestatic patients referred for liver transplantation was assessed in 15 patients [54]. In this study, three 6-h MARS™ sessions were performed per admission. Treatment was associated with immediate and complete response in 11 patients (two patients had a partial response, and two patients had no response). Mean VAS values decreased significantly while patients' quality of life improved. The median duration of acceptable relief in responders was 3 months. The efficacy of MARS™ on pruritus has also been reported in both adult and pediatric patients with cholestatic conditions and after LTx [55–60]. No significant adverse events have been described, including no serious infections, bleeding or hemodynamic changes.

Hypoxic liver injury

Hypoxic liver injury (HLI) is one of the most common types of liver failure and it is observed in up to 15% of critically ill patients. HLI is usually defined as a massive increase of aminotransferase levels (many studies used a cut-off of ≥ 20 times the upper limit of normal) in the context of cardiac, circulatory or respiratory failure. Although other potential causes should be explored, patients in the ICU displaying a massive raise of aminotransferase levels should be considered as having HLI until the opposite has not been proven [61].

Extracorporeal support therapies represent a cornerstone of therapeutic measures in HLI. Initiation of continuous renal replacement therapy was associated with improved survival in a large observational study of patients with HLI [62]. Albumin dialysis systems like MARS™ can remove albumin-bound substances in addition to conventional renal replacement properties. Case reports [63] and one RCT reported a trend toward an improved survival [64] in MARS™-treated patients with HLI. Preliminary results of another RCT showed that MARS™ significantly reduced the need for vasopressor support in patients with HLI [65]. However, future larger studies are needed to validate these results and to compare MARS™ with other dialysis devices.

Post-hepatectomy liver failure

Post-hepatectomy liver failure (PHLF) is a life-threatening complication following partial hepatectomy. The main reason is a small-for-size situation leaving the patient with an insufficient amount of liver parenchyma to maintain sufficient liver function and facilitate liver

regeneration at the same time. However, even complications in the early post-operative course might harm liver regeneration leading to liver failure [66].

So far, there is, besides LTx with all its limitations, no definitive treatment available for these patients. In patients with ALF or ACLF, the MARS™ system demonstrated several effects on patient physiology that might be beneficial in PHLF also (e.g. decrease of portal pressure, decrease of pro-inflammatory cytokines) [67–69]. A bi-institutional retrospective review of patients treated with MARS™ due to PHLF suggested a tendency for favorable patient outcome if patients were treated early (first week following hepatectomy) and more frequently (5 consecutive treatment cycles) [70]. So far, only one prospective pilot trial investigated the effect of MARS™ in PHLF according to a systematic treatment protocol [71]. The key features of this trial were early (treatment decision on post-operative day 5, based on Balzan 50:50 criteria [72]) a frequent, consecutive treatment (between 5 and 7 full treatment cycles) and exclusion of untreated surgical complications. Despite promising results in this trial (feasibility, liver function improvement and unexpectedly low mortality rates compared to a historical control in some patients), current evidence for the use of MARS™ in PHLF is weak. In a systematic review, a survival benefit related to MARS™ treatment was found in patients with primary PHLF [73]. However, only five studies with a total of 34 patients have investigated specifically the role of MARS™ in PHLF. Even though there were no concerns regarding safety and feasibility, a general treatment recommendation could not be given. Still, there are unsolved questions like the start of treatment in the post-operative course, number, duration of sessions and, most importantly, adequate patient selection.

Acute or chronic graft failure after liver transplantation

Only case reports or small retrospective cohorts have been reported on the use of MARS™ in different situations of graft failure after LTx. These consisted of the use of MARS™ either, in early complications post-LTx such as primary non-function or primary dysfunction

of the graft, and in few exceptional cases, intra-operatively during the "anhepatic" phase, or in late complications post-LTx of graft dysfunction mainly related to chronic rejection or primary disease recurrence or other rare graft failures. In all reports, the graft function was severely impaired like situations of ALF and ACLF, severe cholestasis and refractory pruritus reported above in the non-transplant setting. The MARS™ was often used as a rescue therapy or as a bridge therapy awaiting liver retransplantation with different results.

In the absence of prospective trials and the extreme difficulty to perform RCTs in this setting, albumin dialysis might be considered only when such situations are associated with liver failure and in those patients listed for liver retransplantation.

Experts' recommendations

In patients with acute or chronic graft failure after LTx:

Albumin dialysis might be considered in individual cases, after careful assessment based on similar criteria as in the non-transplant population, and only in patients listed for liver retransplantation (*low evidence*)

Drug overdose

Few reports on the use of albumin dialysis in drug overdose with calcium channel inhibitors (amlodipine, diltiazem, verapamil), benzodiazepines, fentanyl, phenytoin or intoxication related to mushroom poisoning, cupper (acute form of Wilson disease), with hemodynamic improvement and clinical success [74–77].

Experts' recommendations

In patients with drug overdose of compound highly linked to albumin:

Albumin dialysis might be considered in individual cases/if no therapeutic alternative and the drug/poison has a high degree of albumin binding (*low evidence*)

Practical, technical and safety aspects

Technical issues

Technical issues can arise at any place of the different parts of the dialysis circuit. The time for setting up of the dialysis and MARS circuits range from 60 to 120 min according to the expertise of the nursing team. The system is primed with albumin and saline through specific tubes and filters and needs close monitoring. By using a double-lumen catheter of at least 13 Fr in a central venous access and within the range of the recommended pump flows, frequent pressure alarms can be avoided as well as early circuit failure. During MARS™ treatment mean arterial pressure and systemic vascular resistance usually remain stable or improve, both in ACLF and

ALF. However, hypotension during treatment may occur and can be improved by either reducing blood and circuit flow speed, or ultrafiltration or, preferably, providing modest volume expansion or low-dose noradrenalin. Air or blood leakage are very rare. In vitro, the presence of specific stabilizers in different albumin solutions affects the stability of albumin binding properties [78]. In vivo, there is no evidence for a relevant clinical effect between different albumin solutions.

Anticoagulation

The most frequent technical complication of MARS™ is clotting in the extracorporeal circuit. The complex balance of coagulation in patients with liver failure and the lack of appropriate monitoring parameters make it difficult to use anticoagulation in patients under extracorporeal therapy. Clotting results in a premature discontinuation of the MARS™ session and loss of blood clearance efficacy. Different approaches have been described in small case series including unfractionated heparin with or without epoprostenol [79], heparin minimization [80] and regional citrate anticoagulation [81], without relevant differences between them. Unfractionated heparin is the standard anticoagulation regimen in many centers. Targets for anticoagulation are either activated partial thromboplastin time of 2–2.5 times the upper normal limit, or activated clotting time between 150 and 200 s. In very severe coagulation disorders, some studies have reported on MARS™ treatment without any anticoagulation. However, even with the use of anticoagulation, circuit clotting may occur in up to 23% of sessions [82, 83]. Regional citrate anticoagulation (RCA) for periods of 6–8 h has been shown to be safe [82, 84, 85] and most effective to prevent clotting. In a retrospective series, the probability of filter survival for a given treatment session was 94% with RCA versus 82% with heparin anticoagulation. In experienced centers, RCA is the preferred strategy for MARS™ anticoagulation [85]. Running the blood and albumin pumps at 200 ml/min rather than 150 ml/min also reduces the risk of circuit clotting. Considering the risk of bleeding, different factors including the severity of liver disease, the etiology of liver disease (ALF, ACLF…), the presence of severe coagulation disorders, the circuit anticoagulation type and dosage (heparin, fractioned heparin, citrate…) might influence this risk. However, in the two mains large RCTs in ALF and ACLF (FULMAR and RELIEF), the risk of bleeding from any source didn't differ from the standard medical treatment. Therapeutic guidance using viscoelastic tests is promising in other complex situations such as LTx [86] but has not been evaluated yet in the context of extracorporeal liver support.

Treatment intensity

Treatment intensity is determined by the number of hours for each treatment session and by the sequence and total number of treatment sessions. Treatment for more than 6 h offers no or little benefit in terms of blood clearance of ABTs [87]. Larger RCTs in ACLF and in ALF have reported treatment session spans of 6–8 and 8 h, respectively [19, 29, 38, 39]. The sequence and total number of treatment sessions varies depending on the indication and the aim of MARS™ therapy. In a recent meta-analysis, 165 patients with ACLF who received at least 5 sessions had a 30-day survival of 73.3% versus 58.5% in those who had less than 5 sessions ($p = 0.041$) [32]. In most studies of ACLF patients, 3 to 4 sessions were planned in the first 5 days and then continued depending on the response and clinical endpoint. In one RCT assessing MARS™ in ALF patients, transplant-free survival was 57.1% in patients receiving ≥ 3 sessions on consecutive days, versus 17% in those who received ≤ 2 sessions [19].

Experts' recommendations
Albumin dialysis is not recommended in patients with high-risk of bleeding (platelets counts < 40.000/mm³, INR > 2.5 and fibrinogen < 1 g/L), because of the risk of fibrinolysis and DIC) (*low evidence*)
Circuit anticoagulation with unfractionated heparin should be used to avoid circuit and membrane clotting (*moderate evidence*)
Regional citrate anticoagulation could be an alternative option to unfractionated heparin use, is safe and is associated with decreased circuit clotting (*moderate evidence*)
6–8 h is the recommended treatment duration of each session (*moderate evidence*)
In patients with ACLF, ≥ 5 treatment sessions should be attempted in the first 7 to 10 days, the first 3 sessions being administered on consecutive days (*moderate evidence*)
In ALF every attempt should be made to reach ≥ 3 consecutive treatment days (*moderate evidence*)

Monitoring and safety aspects

Patients receiving albumin dialysis for hepatic failure should be treated in an ICU. Alarm settings and frequency of evaluation of clinical parameters are not different from those used for liver failure patients receiving other types of extracorporeal support therapies.

Albumin dialysis is considered as a safe procedure. However, complications may occur. Air embolism is very uncommon, and the risks associated with this complication are not different from the risks associated with any central venous access for other purposes than albumin dialysis. Thrombocytopenia and drop in fibrinogen levels are common. The expected decrease before and after a treatment session is 15–20% of baseline value. It is recommended not to initiate MARS™ treatment with values below 50,000/μL and less then 1 g/L of fibrinogen.

Bleeding and thrombosis, though infrequent, need to be monitored. If bleeding occurs, it usually manifests as oozing from the venous access. Thrombosis of the venous access occurs in about 1–2% of cases. While some degree of decrease in hemoglobin, leukocytes or increase in prothrombin time is expected, these changes have not been reported to be of clinical significance.

If RCA is chosen, the patient needs close metabolic monitoring for citrate accumulation or hypocalcemia. Citrate net overload usually manifests itself as metabolic alkalosis, while true citrate accumulation due to incomplete citrate metabolism results in metabolic acidosis with potentially severe hypocalcemia [88]. A safe monitoring approach for citrate toxicity includes determination of the ratio of total to ionized plasmatic calcium before the start of albumin dialysis (normal < 2.5), after about 2 h of dialysis and around the end of the session.

ECAD can influence drug clearance. Regarding antifungals, case reports have described 2.5 to four-fold increased clearance of amphotericin B colloidal dispersion or amphotericin B lipid complex with undecided clinical relevance, while no effect on drug elimination of anidulafungin has been observed [89, 90]. In the case of antibacterial medications, continuous infusion or an extended-infusion strategy of piperacillin–tazobactam will likely prevent the expected steep decline in plasma concentration if a standard infusion of 30 min would be used [91, 92]. Finally, according to one case report, albumin dialysis has no effect on tacrolimus elimination [93].

Experts' recommendations
In patients undergoing MARS™ treatment:
Standard monitoring of patients' hemodynamics, clinical and biological parameters, like other extra-corporeal therapies, is mandatory (*high evidence*)
Antimicrobial medications choice and dosing need to be adapted (when the effect of albumin dialysis on their clearance is known) (*moderate evidence*)

Future directions, research agenda

The Advanced Organ Support system (ADVOS™) represents a new type of albumin dialysis and was introduced in 2013. In contrast to MARS™, the albumin circuit in ADVOS™ is regenerated using both temperature and pH changes; the ADVOS™ showed comparable results to MARS™ in a retrospective comparative in vitro analysis with a good safety [94, 95].

The DIALIVE™ is a novel liver dialysis device, that replaces dysfunctional albumin and removes pathogen and damage associated molecular patterns in patients with liver failure. A phase 2 RCT, in patients with ACLF, has been presented at the EASL 2021 congress and

showed improvement in ACLF grading and safety of the device (NCT03065699).

Albutec device is an adaptation of the MARS™ device using a new filter system is currently in clinical trials (IDE G200071).

Plasma exchange demonstrated in a RCT, improvement in transplant free survival in patients with ALF, together with improvement of SIRS and SOFA score [16]. A large international phase 3 RCT to determine the efficacy and safety of plasma exchange is currently ongoing in patients with ACLF (NCT03702920).

Hemadsorption using either the Oxiris® or the Cytosorb® membranes has been used mainly in critically ill septic patients. Studies including small cohorts or case reports have shown some effects in cirrhotic patients (reduction in bilirubin level or hepatic encephalopathy) of clinical interest but this needs to be confirmed in prospective trials.

Other liver support devices, mainly used in eastern countries in patients with ALF and ACLF due to HBV infection or reactivation, combined two or three different dialysis system that included CVV-HDF, plasma exchange, MARS™ and other devices has been reported, but never evaluated in prospective trials [96].

Conclusion

In the long wait for further clinical development of plasma exchange, new artificial liver support devices, bio-artificial liver devices, mesenchymal stem cells therapies and other exploratory prototypes, ECAD with MARS™ device, is a safe procedure and could be integrated in the management of critically ill patients with liver impairment. The MARS™ combined to renal dialysis machine, in the context of MOST, allowed improvement of different manifestations of liver impairment. The different statements and recommendations elaborated by the expert panel based on the literature and their experience would help a careful and practical selection of patients in terms of indications, timing and treatment modalities for the use of MARS™. ECAD should be reserved to centers experienced in the management of advanced liver disease either listed for transplant or with a transplant project, and/or to clinical trials.

Supplementary Information
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Abbreviations
ABT: Albumin-bound toxin; ACLF: Acute-on-chronic liver failure; ALF: Acute liver failure; DAMP: Damage-associated molecular proteins; HE: Hepatic encephalopathy; HLI: Hypoxic liver injury; HSA: Human serum albumin; ICU: Intensive care unit; LTx: Liver transplantation; MARS™: Molecular Adsorbent Recirculating System; MELD: Model of end-stage liver disease (score); MOST: Multiorgan support organ support therapies; PHLF: Post-hepatectomy liver failure; RCA: Regional citrate anticoagulation; HVPE: High volume plasma exchange; RCT: Randomized controlled trial; SMT: Standard medical therapy; VAS: Visual analogue scale.

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Declarations

Conflicts of interest
FS has received speaker's honoraria and/or research grants from Novartis, Astellas, Chiesi, Gilead, Merck Sharp and Dohme, Neovie, Biotest and Baxter. RB has received speaker's honoraria and/or research grants from Gilead, abbvie, Janssen, Gore Baxter. FL has nothing to declare. AW has no conflict of interest. AP has received grant funding, personal fees, and advisory board fees from Intercept Pharmaceuticals and Genfit; advisory board fees and fees for teaching from Novartis; and personal fees from CymaBay Therapeutics and Inova Diagnostics. SM has received speaker`s honoraria and/or research grants from Amgen, Astellas, Baxter, BMS/Pfizer, CytoSorbents, Pentracor, Vifor. JS is chairman of the board of Albutec GmbH. VF declare presentations for Fresenius, Baxter, ADVITOS, CSL-Behring, Merz, Advisory board. SG declare no conflict of interest. TH is consultant for DIALIVE. On advisory committee and received consultancy from AbbVie, Bristol-Myers Squibb, Gilead, Malinckrodt, Merck, and Organovo. Received research grants from AbbVie, Allergan, Amarex/Cytodyn, Astra Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, CARA, DURECT Corporation, Enanta, Galectin, Gilead, Grifols, Intercept, Merck, Mirum, Novartis, Novo Nordisk, Pfizer, Salix Pharmaceuticals, Sonic Incytes, and Terns

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