Review

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Abstract: Acute-on-Chronic Liver Failure (ACLF) refers to the deterioration of liver function in individuals who already have chronic liver disease. In the setting of ACLF, liver damage leads to the failure of other organs and is associated with increased short-term mortality. Optimal medical management of patients with ACLF requires implementing complex treatment strategies, often in an intensive care unit (ICU). Failure of organs other than the liver distinguishes ACLF from other critical illnesses. Although there is growing evidence supporting the current approach of ACLF management, mortality associated with this condition remains unacceptably high. In this review, we discuss considerations for ICU care of patients with ACLF and highlight areas for further research.

Keywords: cirrhosis; hemostasis disorder; ICU treatment; hemodynamic disorder; infection

1. Introduction

The concept of Acute-on-Chronic Liver Failure (ACLF) was introduced by Jalan and Williams in 2002, which describes a condition with significant systemic inflammation and single or multiple organ failure (other than the liver) in the setting of acutely decompensated cirrhosis.[1] The concept was refined in 2006 by D'Amico et al. These investigators performed a systematic review of almost 120 publications examining prognostic indicators of survival in patients with compensated and decompensated cirrhosis.[2] Since then, several Chronic Liver Failure (CLIF) consortia, including Asian, European, North American, and Chinese groups, have developed different definitions and criteria for ACLF.[3]

Despite some differences, all research groups agree that the main differentiating factor between decompensated liver failure and ACLF is extrahepatic organ failure.[4]

ACLF and acute liver failure (ALF) have some similarities. About 50% of patients with ACLF may experience *recompensation*. If that is not achieved, they will require a liver transplant (LT) in the near future, similar to ALF patients.

The PREDICT study proposes to select 'Pre-ACLF' patients as a subpopulation of patients with cirrhosis who have an unstable clinical course and require hospitalization due to decompensation.[5] This could be sufficient for the subpopulation of patients that exhibit signs of significant inflammation or sepsis in combination with liver or/and kidney dysfunction.[6] Currently, Pre-ACLF is not a condition that is routinely identified, diagnosed, or treated.

Consequently, many patients prone to developing ACLF are not going to be identified and initially admitted to a medical floor instead of being promptly cared for in an intensive care unit (ICU) for more specialized care. Typical triggers for developing ACLF are alcohol consumption and infections, which are responsible for a significant number of acute decompensation (AD) cases

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associated with ACLF.[3,5] Identifying the inciting event(s) when signs of decline appear is important. Many infections leading to ACLF may not exhibit the typical signs of sepsis and can only be recognized after an AD progresses or kidney function begins to deteriorate.[5] Although infection plays a very important role in ACLF, AD, and disease progression, an infectious organism frequently cannot be identified. Infections are often hospital-acquired and may have a broad spectrum of resistance. For patients with chronic liver disease (CLD) who subsequently develop sepsis, timely administration of antibiotics is essential to prevent the development of ACLF.[7] The connection between survival rates and prompt administration of appropriate treatment emphasizes the fact that any delay in treatment has a negative effect on patient outcomes.[8]

Many patients with ACLF require the administration of vasopressors to maintain a mean arterial pressure (MAP) within a range of 65-70 mmHg while avoiding fluid overload.[6] The development of grade III or IV hepatic encephalopathy (HE), indicates a poor outcome and is often linked to some type of infection.[9] Other considerations that should be addressed in this patient population include coagulation management and prevention/treatment of acute kidney injury (AKI).

2. Essentials of Cardiovascular Care

Chronic liver disease is always associated with systemic inflammation and endothelial dysfunction. As a result, cirrhotic patients develop severe vasoplegia, which leads to stagnation of blood flow, particularly in the portal system.[10,11] Vasoplegia in patients with cirrhosis is related to the release of nitric oxide, which leads to an increased cardiac output (due to a lower systemic vascular resistance) and hypotension in combination with a decrease in systemic blood volume.[3,4] Furthermore, individuals with this condition may also develop a related end stage liver disease specific cardiomyopathy and/or portopulmonary hypertension which can further affect the cardio-pulmonary system. Several events including infection, alcohol consumption, trauma, bleeding, and surgical procedures, can lead to cardiovascular system failure.[6] The main goal of volume resuscitation is to ensure efficient tissue oxygen delivery by maintaining an adequate perfusion pressure. Studies on patients with cirrhosis associated with septic shock have demonstrated that having a MAP higher than 70 mmHg provides no benefit.[3] A recent evaluation in septic patients did not find any difference in mortality between the high-pressure target group (aiming for MAP 80-85 mmHg) and the low-pressure target group (aiming for MAP 65-70 mmHg) at 28 and 90 days. Adverse events were similar in both groups, but the high-pressure target group had a slightly higher rate of new onset atrial fibrillation. It was demonstrated that patients in the high-pressure target group with known hypertension more frequently required renal replacement therapy (RRT) although this did not affect mortality.

Data regarding patient management demonstrated that these patients were most frequently cared for in the ICU. Fluid overload is a significant problem in this patient population due to increased portal pressure. Assessment of fluid responsiveness is recommended before beginning resuscitation, and crystalloids have been demonstrated to be the preferred fluid.[12] It has also been shown that administration of balanced electrolyte solutions is preferable in comparison to 0.9% saline. Normal saline causes an imbalance in chloride levels, which can lead to acidosis, hyperkalemia, and a higher risk of developing AKI.[13,14] Using starch-based solutions for resuscitation is also not recommended due to an increased risk of developing AKI.[15-17] Based on current knowledge, it is still being determined if the administration of albumin is beneficial,[18] although some studies indicate that if hemodynamic stability is not achieved following the administration of crystalloids, albumin may be helpful to achieve better hemodynamics.[19,20] Albumin administration is logical, considering that albumin is important in medication binding, exhibits antioxidant properties, and helps regulate both the immune system and endothelial activity.[21] However, studies in patients with cirrhosis fail to demonstrate any survival benefit for albumin administration, with the exception being in patients with spontaneous bacterial peritonitis in the setting of sepsis.[22,23]

If tissue perfusion is inadequate or blood pressure remains low despite fluid administration, it is advisable to use vasopressors. There is evidence from studies performed in patients with septic shock having hemodynamic characteristics similar to those seen in patients with ACLF that strongly

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supports norepinephrine as the preferred vasopressor.[24] Epinephrine administration is often associated with deterioration of tissue perfusion and subsequent increases in lactate production.[25] However, in a randomized controlled trial (RCT) investigating patients with sepsis, no significant distinction was found between the administration of epinephrine and the combination of norepinephrine and dobutamine.[26] At day 28, the epinephrine group had a 40% mortality rate, while the norepinephrine plus dobutamine mortality rate was 34% (p=0.31). Mortality rates upon ICU discharge, hospital discharge, and by day 90 were similar between the two groups. Additionally, the time to achieve stability after discontinuation of vasopressors and the progression of SOFA scores were comparable. Both groups demonstrated similar rates of adverse events. Despite side effects associated with vasopressin and its derivatives, the Surviving Sepsis Guidelines recommend using vasopressin as an additional agent for managing septic shock after other options have been exhausted. This recommendation is based on clinical studies and meta-analyses that indicate a reduction in catecholamine use and a noticeable increase in blood pressure if vasopressin was added to the treatment protocol.[20] Currently, there is no evidence suggesting that this approach can significantly improve survival.

The use of β -blockers in patients with sepsis or ACLF is still a topic of discussion.

Non-selective beta blockers (NSBBs) are frequently prescribed for patients with cirrhosis to manage portal hypertension and prevent variceal bleeding. The CANONIC study, which included 349 patients, demonstrated that patients with ACLF admitted to the hospital and managed with NSBBs had improved survival at 28 days. This improvement may be attributed to reduced bacterial translocation in the intestine, decreasing systemic inflammation.[27] There is debate regarding the cardiac protection of β-blockers.[28] A recent meta-analysis performed by Tan et al. suggested that administering β-blockers before the development of sepsis might potentially reduce mortality rates.[29] Based on current knowledge, there are no definitive reasons to stop the use of NSBBs.[30]

3. Acute Kidney Injury: Intervention and Care

AKI often develops as a complication of ACLF, impacting about half of patients with CLD admitted to the hospital. It serves as an indicator of decreases in both long- and short-term survival.[31]

Hepatorenal syndrome (HRS) is frequently associated with ACLF and historically has been divided into two subtypes: HRS Type 1 and Type 2. HRS Type 1 usually appears suddenly within a two-week period and is associated with a poor prognosis. HRS Type 2 usually has a prolonged course and is associated with moderate kidney dysfunction and ascites that do not respond well to diuretics.[32] The definition of HRS has been updated to align with the criteria for AKI. The International Club of Ascites adjusted the terminology and diagnostic criteria for HRS Type 1, redefining it as HRS-AKI. This change was performed after investigations indicated that elevated serum creatinine levels at treatment onset correlated with a decreased likelihood of reversible HRS.[33] In patients with ACLF who are at risk of developing AKI, it is important to ensure adequate renal blood flow with fluid administration (and inotropes as necessary) to maintain a MAP between 65-70 mmHg along with an appropriate cardiac index. The administration of vasopressors should be prioritized in the situation of volume overload.[34] In these situations, the use of terlipressin as an infusion is generally better tolerated and potentially more effective compared to administering this medication as a bolus. It has been demonstrated that if AKI treatment is initiated early, there is an increased likelihood the kidney will recover, which is associated with improved survival.[35] A comprehensive analysis suggests that in terms of reversing HRS and reducing mortality within 30 days, the effectiveness of norepinephrine is comparable to terlipressin.[36]

The timing of initiating dialysis is important for patient outcome. Over the years, there have been five RCTs attempting to determine when to initiate RRT for patients with AKI II and III. Among these studies the three largest and most comprehensive (AKIKI, IDEAL-ICU, STARRT AKI) demonstrated that starting RRT early did not result in improved survival. Additionally, it was demonstrated there were risks associated with early RRT, including RRT dependency, increased likelihood of bacteremia and catheter related complications, bleeding problems, and higher resource

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consumption.[37-39] However, a smaller, single-center study (ELAIN) in cardiac surgical patients demonstrated significantly improved survival if RRT was started early.[40] (Table 1).

Table 1. Comparision of 4 RCT.

	ELAIN[40] Zarbock et al.	**AKIKI**[41] Gaudry et.al	**IDEAL-ICU**[37] Barbar et. al	**START-AKI**[39] Investigators group
Patients (n)	231	620	477	2927
Setting	95% (Cardiac surgery)	80% Sepsis	100% septic Shock	67% medical patients
Criteria early	AKI II° & NGAL ≥ 150 ng/ml	AKI III	Stage F of RIFLE	AKI II
Criteria late	AKI III	Urgent indicaton for dialys3s	48 h Remaining at Stage F	Urgent indication
Primary endpoint	90 day mortality	60 day mortality	90-day Mortality	90-day mortality
Mortality early group	39% (p = 0.03)	49%	58%	44%
Mortality Late group	55%	50%	54%	44%
Mortality Dialyzed Late Group	NA	62%	68%	NA
Rate of non dialysis in late group	9.2%	49%	38%	38%
Dependence on dialysis on 90-days after randomization	13 vs 15	2 vs 5	2 vs 3	10.4. vs 6; RR 1.74 95% CI [1.24-2.43]

According to current data, the delayed strategy seems justified unless there are life-threatening indications.

The "Artificial Kidney Initiation in Kidney Injury-2" (AKIKI-2) study evaluated patients the impact of two different waiting strategies (length of time) for starting RRT in 278 patients.[41]

In contrast to the original AKIKI study's late arm, AKI was defined by oligo-anuria > 72 h and/or a urea-N concentration > 112 mg/dl. Only then were patients randomized 1:1 into a "late" strategy where RRT was started < 12 h after randomization, or into an "even-later" strategy when RRT was started only under absolute emergency indications (hyperkalemia > 6 mmol/l, metabolic acidosis pH < 7.15, pulmonary edema) or when serum urea-N exceeded 140 mg/dl. Oligo-anuria was not a trigger for starting RRT, even in the "even-later" arm. The primary endpoint of the study was "days alive and without RRT" within the first 28 days if this persisted for more than three days. There was no difference regarding the number of days without RRT. There were also no differences in secondary endpoints such as "ventilation-free days," "duration of ICU stay," or "recovery of kidney function".

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In the IDEAL-ICU study, 17% of patients in the late group had to undergo emergency dialysis and experienced a higher mortality rate. These findings raise the question regarding the appropriate time to start RRT in patients with AKI III without emergency indications.

In the AKIKI, IDEAL-ICU, and STARRT-AKI trials, an early start was compared to waiting up to 72 hours. If urgent indications did not develop after 72 hours, a late start of RRT still can be dangerous as was demonstrated in AKIKI-2 study. In the "even-later" arm of the study, 79% of patients actually had to undergo dialysis. This was very similar to the ELAIN study where over 90% of patients had to be dialyzed after waiting. In both studies, waiting was associated with a worse outcome (Table 1). These studies have clearly demonstrated that patients who inevitably need dialysis do not benefit from waiting because of high rate of complications. However, an individualized approach should be used: patients likely to recover aren't subjected to dialysis, but for those likely to require dialysis, it should be started as soon as practical. This is especially true for patients with ACLF who are already fluid overloaded. Classic dialysis indicators such as high serum potassium may not be accurate due to an increase in the extracellular space.

Patients with ACLF often demonstrate hypercoagulability. Under these circumstances, anticoagulation for any kind of extracorporal therapy, particularly for RRT, is necessary. While laboratory results might indicate a predisposition for bleeding, there is frequent filter clotting in the absence of anticoagulation. Many intensive care specialists, however, are hesitant to employ regional citrate anticoagulation for these patients due to concerns about citrate toxicity. More recently, numerous studies have demonstrated the safety and effectiveness of using regional citrate anticoagulation for RRT in patients with cirrhosis who required RRT while on the waiting list and in newly transplanted patients.[42,43]

4. Infections in patients with ACLF

Management of infectious conditions in patients with ACLF is very complex. Around 46% of individuals admitted to the hospital due to worsening cirrhosis are diagnosed with bacterial infections. In two-thirds of these cases, the infections are identified only upon admission. Recent data indicates that SBP is particularly common in this patient population, accounting for around 20-30% of infections. Urinary tract infections are responsible for up to 20-25%, pneumonia 20%, bloodstream-related infections 8-15%, and infections affecting the skin and soft tissues between 5 and 10%.[44,45]

Prompt initiation of antibacterial agents when bacterial etiology infection is presumed can markedly enhance survival. An investigation including over 600 patients with septic shock demonstrated that postponing antibacterial therapy post-onset of hypotension was associated with increased mortality. The study also demonstrated that the use of inappropriate antibiotics led to an increased risk of mortality (adjusted odds ratio 9.5, 95% CI; 4.5–20.7).[8] During the last twenty years, the spectrum of bacterial infections among patients with cirrhosis has significantly changed. The use of quinolone antibiotics unexpectedly led to an increase in the prevalence of gram-positive infections. Frequent prescriptions of third-generation cephalosporins has unintentionally contributed to a rise in enterococci infections as these bacteria naturally resist cephalosporins. This trend is particularly prominent with nosocomial infections. This concerning development is associated with the increasing occurrence of bacterial resistance due to multiple treatment regimens using antibiotics that are available as opposed to the most appropriate. This evolution demonstrates the need for appropriate antibiotic management and innovative treatment approaches.[44,45] Managing infections effectively in the setting of generally increasing antibiotic resistance requires customization of medication choice and treatment durations. It is also important to transition from broad-spectrum antibiotics to organism and sensitivity-specific treatments as soon as possible.

Patients with cirrhosis often exhibit fungal colonization when hospitalized, but the prevalence of systemic infection remains under 5%. Aspergillosis is a specific concern in patients with cirrhosis. Aspergillosis can significantly compromise the course of the disease and even be fatal. Furthermore, patients with cirrhosis with aspergillosis can also develop candidemia as well as further complications related to cytomegalovirus infection.[46] Regular infection surveillance is essential for success.

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5. How the Brain Responds: Delving into Cerebral Reactions

Hepatic encephalopathy (HE) is frequently associated with cirrhosis and is primarily related to decreased metabolization of ammonia. Patients with HE usually experience confusion and decreased mental status, but can have seizures and even progress to coma. In patients with ACLF, HE is significantly associated with increased mortality. Fortunately, significant cerebral swelling is very rare. It has been demonstrated that the prevalence of cerebral edema was about 4%, but if it occurs, it is associated with a worse outcome.[47] The etiology of HE is very complex, and its presentation depends on several factors. One of these is an increased concentration in serum ammonia, which is primarily produced by intestinal bacteria and not metabolized in the cirrhotic liver. Other factors contributing to the development of HE includes hyponatremia, damage in neurons with disruptions in the blood-brain barrier, and abnormalities in GABAergic and benzodiazepine pathways with subsequent impaired neurotransmission.[48] In patients with ACLF, decreased mental status is not just related to hyperammonemia but also to generalized inflammation that affects cranial blood vessels, endothelium, and astrocytes.[49] Ongoing infections can worsen existing HE even more. If a patient's conscious level decreases (HE ≥ III°), airway protection with endotracheal intubation may become necessary. Factors contributing to the development of HE including infection, constipation, dehydration, and electrolyte abnormalities should be investigated and managed. All medications that can alter a patient's mental status should be discontinued if possible. Treatment of hyperammonemia with lactulose or non-absorbable antibiotics such as rifaximin (that minimizes nitrogen uptake from the intestines) is frequently started, but their efficacy for patients with ACLF remains uncertain.[50] The HELP study compared polyethylene glycol 3350 electrolyte solution (PEG) and the usual lactulose treatment for HE.[51] The findings indicated that PEG might be more effective. Within a 24-hour period, 91% of patients in the PEG group had significant improvement vs. 52% in the standard therapy group. An RCT compared the effects of L-Ornithine L-Aspartate (LOLA) on patients diagnosed with HE. One hundred forty patients were assigned in a 1:1 ratio (70 patients in each group) to receive LOLA in combination with lactulose and rifaximin vs. placebo in combination with lactulose and rifaximin as a control group. LOLA was administered for five days. The primary endpoint was an improvement in HE. The study demonstrated that the LOLA cohort had faster recovery from HE and a significantly lower mortality rate (16.4% vs. 41.8%) than the control group.[52]

A limitation of the protein intake (a hyperammonemia management option frequently applied in the past) proved not to be helpful and even can be associated with deterioration of the patient's nutritional status. If medication therapy fail, RRT should be performed.[53]

6. The Dynamics of Coagulation in Patients with ACLF

Patients with ACLF are prone to both bleeding and clotting complications.[54] Patients with cirrhosis and/or ACLF have a rebalanced hemostasis affecting all branches of the coagulation system. While these patients frequently have thrombocytopenia, other factors may offset the bleeding risks. The concentration of both procoagulants and anticoagulants (proteins C, S, Antithrombin III) are all decreased, while the concentration of liver independent coagulation factors (F) including FVIII and von Willebrand factor (vWF) is 3-4 times higher in patients with ACLF compared to healthy controls. The concentration of ADAMTS13 (produced in the liver and responsible for vWF degradation) is markedly decreased which limits the bleeding risk but increases the risk of clotting.[55,56] It has been demonstrated that in the population of hospitalized patients with CLD that has acutely decompensated, thrombin generation (TG) is significantly increased which significantly increases the risk of thromboses. This is even more pronounced in patients with ACLF.[57] However, significant fibrinolysis driven by sepsis-related organ failure in patients with ACLF might balance this prothrombotic effect.[58]

Standard laboratory tests (SLT) are not designed to predict bleeding or thrombosis. They can only evaluate serum levels of procoagulants and do not reflect global hemostasis.[59] Although SLTs are still commonly employed for coagulation monitoring, these tests are not accurate in predicting spontaneous bleeding risks or procedure-induced bleeding.[60,61] Viscoelastic tests (VETs) such as thromboelastography (TEG) or ROTEM, evaluate whole blood samples and assess the interaction

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between both pro- and anticoagulants and platelets. Indeed, two randomized controlled trials found that using VETs to guide transfusion in patients with ACLF demonstrated a reduction in the use of blood products without an increase in spontaneous or procedure-related bleeding.[62,63] Administering fresh frozen plasma (FFP) to patients with cirrhosis without signs of bleeding is generally not recommended [64] and can lead to an unnecessary increase in circulating volume and increases in portal pressure with subsequent increased risk of bleeding.[65] It has also been demonstrated that FFP administration has a minimal impact on TG.[64] Instead of FFP, the administration of specific coagulation factors can now be considered. The most frequently used compounds are fibrinogen concentrate, prothrombin complex concentrate (PCC) (encompassing factors II, VII, IX, and X, proteins C and S, heparin and antithrombin III), and factor XIII.[66] It has been demonstrated that the use of these factor concentrates leads to significantly increased TG in patients with cirrhosis, which theoretically might increase the thrombotic risk.[67] In clinical settings, however, use of these medications has been demonstrated to be safe. It has been shown that if VETs were used to guide the administration of factor concentrates, the incidence of thrombosis did not increase.[68] PCC, however, should not be administered to patients without bleeding signs and VET monitoring.[69]

7. Beyond Conventional Treatments: The Impact of Liver Assist Devices

7.1. Bioartifical Liver Assist Device

The Extracorporeal Liver Assist Device (ELAD®, developed by Vital Therapies Inc., San Diego, CA) utilizes hepatocytes derived from a hepatoblastoma cell line. A phase III clinical trial involving 203 participants with severe alcoholic hepatitis (AH) was recently performed.[70] The trial protocol randomized participants to receive either a combination of 3-5 days of continuous ELAD therapy and standard care (SOC) or just the SOC. An intent-to-treat analysis demonstrated there was no difference in patient survival between groups (51.0% for ELAD+SOC vs. 49.5% for SOC alone). A subgroup analysis of patients with a MELD score below 28 and age under 46.9 years found a better (but statistically not significant) 90-day survival rate in ELAD group compared to the SOC group (100% vs. 73%, $p = 0.08$). A subsequent evaluation targeting AH patients with more specific patient demographics (n=151) found no significant survival benefit: 90-day mortality rate was 19.2% for ELAD+SOC and 21.9% for SOC alone (p=0.68) (available only as an abstract).[71]

7.2. Non-Biological Devices

The Prometheus® system (Fresenius Medical Care AG, Hamburg, Germany) is using a Fractionated Plasma Separation and Adsorption (FPSA) approach. This system combines plasma separation with adsorption techniques, facilitating the removal of both albumin-bound and water-soluble toxins. In the HELIOS study involving 145 patients with ACLF demonstrated reduced serum bilirubin levels in the study group in comparison to controls. There was, however, no survival benefit.[72]

The Molecular Adsorbent Recirculating System (MARS) (Baxter International Inc., Deerfield, IL) device operates using an external blood circuit with a semi-permeable, albumin-coated membrane. The part of the system is a dialysis circuit containing 600 ml of 20% human albumin with a charcoal column and an anion exchange resin column (to remove albumin-bound toxins) with a conventional hemodialysis filter. The RCT (RELIEF trial) compared MARS treatment in patients with ACLF with SOC.[73] A total of 189 patients with hypoalbuminemia and HE II-IV and/or HRS were recruited for this study. Each patient in the study group received 6.5 ± 3.1 MARS sessions. There was no difference regarding transplant free survival after 28- and 90 days.

These trials, however, did not utilize the ACLF criteria proposed by the CANONIC study. In a recent meta-analysis, data from 285 participants from three RCTs involving MARS treatment in patients with CLD was reassessed.[74] According to the updated ACLF criteria, 165 cases were reclassified as ACLF. In both groups (ACLF and non-ACLF), MARS was able to significantly decrease bilirubin levels and improve HE but failed to demonstrate any difference in 90-day survival.

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8. Conclusion

The concept of ACLF has been around for over a decade, and numerous publications have emerged since then which have helped refine both the definition and criteria related to the condition, as well as inform patient management. Care of this patient population remains extremely challenging. Management of infections and coagulopathy, HE, AKI, and cardiovascular instability frequently require early ICU admission. Prompt administration of appropriate antibiotic therapy and early dialysis for patients with AKI grade II and above is essential. Coagulation management should be guided by VET, and the preemptive use of blood products should be avoided. Liver support devices show promise to serve as a bridge to LT until an appropriate hepatic graft becomes available.

References

1. Jalan R, Williams R: Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif 2002; 20: 252-61
2. D'Amico G, Garcia-Tsao G, Pagliaro L: Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44: 217-31
3. Arroyo V, Moreau R, Jalan R: Acute-on-Chronic Liver Failure. N Engl J Med 2020; 382: 2137-2145
4. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, Amoros A, Titos E, Alcaraz-Quiles J, Oettl K, Morales-Ruiz M, Angeli P, Domenicali M, Alessandria C, Gerbes A, Wendon J, Nevens F, Trebicka J, Laleman W, Saliba F, Welzel TM, Albillos A, Gustot T, Benten D, Durand F, Gines P, Bernardi M, Arroyo V, Consortium CSIotE-C, the European Foundation for the Study of Chronic Liver F: Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology 2016; 64: 1249-64
5. Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, Giovo I, Uschner FE, Jansen C, Jimenez C, Mookerjee R, Gustot T, Albillos A, Banares R, Jarcuska P, Steib C, Reiberger T, Acevedo J, Gatti P, Shawcross DL, Zeuzem S, Zipprich A, Piano S, Berg T, Bruns T, Danielsen KV, Coenraad M, Merli M, Stauber R, Zoller H, Ramos JP, Sole C, Soriano G, de Gottardi A, Gronbaek H, Saliba F, Trautwein C, Kani HT, Francque S, Ryder S, Nahon P, Romero-Gomez M, Van Vlierberghe H, Francoz C, Manns M, Garcia-Lopez E, Tufoni M, Amoros A, Pavesi M, Sanchez C, Praktiknjo M, Curto A, Pitarch C, Putignano A, Moreno E, Bernal W, Aguilar F, Claria J, Ponzo P, Vitalis Z, Zaccherini G, Balogh B, Gerbes A, Vargas V, Alessandria C, Bernardi M, Gines P, Moreau R, Angeli P, Jalan R, Arroyo V, CONSORTIUM PSgotE-C: PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. J Hepatol 2021; 74: 1097-1108
6. Bernal W, Karvellas C, Saliba F, Saner FH, Meersseman P: Intensive care management of acute-on-chronic liver failure. J Hepatol 2021; 75 Suppl 1: S163-S177
7. Piano S, Tonon M, Angeli P: Changes in the epidemiology and management of bacterial infections in cirrhosis. Clin Mol Hepatol 2021; 27: 437-445
8. Arabi YM, Dara SI, Memish Z, Al Abdulkareem A, Tamim HM, Al-Shirawi N, Parrillo JE, Dodek P, Lapinsky S, Feinstein D, Wood G, Dial S, Zanotti S, Kumar A, Cooperative Antimicrobial Therapy of Septic Shock Database Research G: Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology 2012; 56: 2305-15
9. Bajaj JS, O'Leary JG, Tandon P, Wong F, Garcia-Tsao G, Kamath PS, Maliakkal B, Biggins SW, Thuluvath PJ, Fallon MB, Subramanian RM, Vargas HE, Lai J, Thacker LR, Reddy KR: Hepatic Encephalopathy Is Associated With Mortality in Patients With Cirrhosis Independent of Other Extrahepatic Organ Failures. Clin Gastroenterol Hepatol 2017; 15: 565-574 e4
10. Harrison P, Wendon J, Williams R: Evidence of increased guanylate cyclase activation by acetylcysteine in fulminant hepatic failure. Hepatology 1996; 23: 1067-72
11. Mookerjee RP, Vairappan B, Jalan R: The puzzle of endothelial nitric oxide synthase dysfunction in portal hypertension: The missing piece? Hepatology 2007; 46: 943-6
12. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, Mira JP, Dequin PF, Gergaud S, Weiss N, Legay F, Le Tulzo Y, Conrad M, Robert R, Gonzalez F, Guitton C, Tamion F, Tonnelier JM, Guezennec P, Van Der Linden T, Vieillard-Baron A, Mariotte E, Pradel G, Lesieur O, Ricard JD, Herve F, du Cheyron D, Guerin C, Mercat A, Teboul JL, Radermacher P, Investigators S: High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014; 370: 1583-93
13. Hammond DA, Lam SW, Rech MA, Smith MN, Westrick J, Trivedi AP, Balk RA: Balanced Crystalloids Versus Saline in Critically Ill Adults: A Systematic Review and Meta-analysis. Ann Pharmacother 2020; 54: 5-13
14. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillamondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR,

Rice TW, Investigators S, the Pragmatic Critical Care Research G: Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med 2018; 378: 829-839
15. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K, German Competence Network S: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358: 125-39
16. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA, Investigators C, Australian, New Zealand Intensive Care Society Clinical Trials G: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367: 1901-11
17. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Moller MH, Elkjaer JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Soe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjaeldgaard AL, Fabritius ML, Mondrup F, Pott FC, Moller TP, Winkel P, Wetterslev J, Group ST, Scandinavian Critical Care Trials G: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367: 124-34
18. HakanSaner F, Stueben BO, Hoyer DP, Broering DC, Bezinover D: Use or Misuse of Albumin in Critical Ill Patients. Diseases 2023; 11
19. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, Investigators AS: Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014; 370: 1412-21
20. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP: Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med 2017; 45: 486-552
21. Artigas A, Wernerman J, Arroyo V, Vincent JL, Levy M: Role of albumin in diseases associated with severe systemic inflammation: Pathophysiologic and clinical evidence in sepsis and in decompensated cirrhosis. J Crit Care 2016; 33: 62-70
22. Bernardi M, Angeli P, Claria J, Moreau R, Gines P, Jalan R, Caraceni P, Fernandez J, Gerbes AL, O'Brien AJ, Trebicka J, Thevenot T, Arroyo V: Albumin in decompensated cirrhosis: new concepts and perspectives. Gut 2020; 69: 1127-1138
23. China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, Portal AJ, Becares Salles N, Gilroy DW, O'Brien A, Investigators AT: A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis. N Engl J Med 2021; 384: 808-817
24. Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A: Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One 2015; 10: e0129305
25. Gjedsted J, Buhl M, Nielsen S, Schmitz O, Vestergaard ET, Tonnesen E, Moller N: Effects of adrenaline on lactate, glucose, lipid and protein metabolism in the placebo controlled bilaterally perfused human leg. Acta Physiol (Oxf) 2011; 202: 641-8
26. Annane D, Vignon P, Renault A, Bollaert PE, Charpentier C, Martin C, Troche G, Ricard JD, Nitenberg G, Papazian L, Azoulay E, Bellissant E, Group CS: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 2007; 370: 676-84
27. Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J, Bendtsen F, Coenraad M, Sperl J, Gines P, Moreau R, Arroyo V, Jalan R, Consortium CSIotE-C: Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. J Hepatol 2016; 64: 574-82
28. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, Orecchioni A, D'Egidio A, D'Ippoliti F, Raffone C, Venditti M, Guarracino F, Girardis M, Tritapepe L, Pietropaoli P, Mebazaa A, Singer M: Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013; 310: 1683-91
29. Tan K, Harazim M, Tang B, McLean A, Nalos M: The association between premorbid beta blocker exposure and mortality in sepsis-a systematic review. Crit Care 2019; 23: 298
30. Tergast TL, Kimmann M, Laser H, Gerbel S, Manns MP, Cornberg M, Maasoumy B: Systemic arterial blood pressure determines the therapeutic window of non-selective beta blockers in decompensated cirrhosis. Aliment Pharmacol Ther 2019; 50: 696-706

31. Weil D, Levesque E, McPhail M, Cavallazzi R, Theocharidou E, Cholongitas E, Galbois A, Pan HC, Karvellas CJ, Sauneuf B, Robert R, Fichet J, Piton G, Thevenot T, Capellier G, Di Martino V, Group M: Prognosis of cirrhotic patients admitted to intensive care unit: a meta-analysis. Ann Intensive Care 2017; 7: 33
32. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V: Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007; 56: 1310-8
33. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR, Arroyo V, Garcia-Tsao G, International Club of A: Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015; 64: 531-7
34. Yoo JJ, Park MY, Kim SG: Acute kidney injury in patients with acute-on-chronic liver failure: clinical significance and management. Kidney Res Clin Pract 2023; 42: 286-297
35. Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, Gola E, Morando F, Stanco M, Rosi S, Sticca A, Cillo U, Angeli P: Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. Hepatology 2016; 63: 983-92
36. Mattos AZ, Mattos AA, Ribeiro RA: Terlipressin versus noradrenaline in the treatment of hepatorenal syndrome: systematic review with meta-analysis and full economic evaluation. Eur J Gastroenterol Hepatol 2016; 28: 345-51
37. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyere R, Lebert C, Bohe J, Badie J, Eraldi JP, Rigaud JP, Levy B, Siami S, Louis G, Bouadma L, Constantin JM, Mercier E, Klouche K, du Cheyron D, Piton G, Annane D, Jaber S, van der Linden T, Blasco G, Mira JP, Schwebel C, Chimot L, Guiot P, Nay MA, Meziani F, Helms J, Roger C, Louart B, Trusson R, Dargent A, Binquet C, Quenot JP, Investigators I-IT, the CTN: Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. N Engl J Med 2018; 379: 1431-1442
38. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D, de Prost N, Lautrette A, Bretagnol A, Mayaux J, Nseir S, Megarbane B, Thirion M, Forel JM, Maizel J, Yonis H, Markowicz P, Thiery G, Tubach F, Ricard JD, Dreyfuss D, Group AS: Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med 2016; 375: 122-33
39. Investigators S-A, Canadian Critical Care Trials G, Australian, New Zealand Intensive Care Society Clinical Trials G, United Kingdom Critical Care Research G, Canadian Nephrology Trials N, Irish Critical Care Trials G, Bagshaw SM, Wald R, Adhikari NKJ, Bellomo R, da Costa BR, Dreyfuss D, Du B, Gallagher MP, Gaudry S, Hoste EA, Lamontagne F, Joannidis M, Landoni G, Liu KD, McAuley DF, McGuinness SP, Neyra JA, Nichol AD, Ostermann M, Palevsky PM, Pettila V, Quenot JP, Qiu H, Rochwerg B, Schneider AG, Smith OM, Thome F, Thorpe KE, Vaara S, Weir M, Wang AY, Young P, Zarbock A: Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. N Engl J Med 2020; 383: 240-251
40. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, Boanta A, Gerss J, Meersch M: Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA 2016; 315: 2190-9
41. Gaudry S, Hajage D, Martin-Lefevre L, Lebbah S, Louis G, Moschietto S, Titeca-Beauport D, Combe B, Pons B, de Prost N, Besset S, Combes A, Robine A, Beuzelin M, Badie J, Chevrel G, Bohe J, Coupez E, Chudeau N, Barbar S, Vinsonneau C, Forel JM, Thevenin D, Boulet E, Lakhal K, Aissaoui N, Grange S, Leone M, Lacave G, Nseir S, Poirson F, Mayaux J, Asehnoune K, Geri G, Klouche K, Thiery G, Argaud L, Rozec B, Cadoz C, Andreu P, Reignier J, Ricard JD, Quenot JP, Dreyfuss D: Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. Lancet 2021; 397: 1293-1300
42. Saner FH, Treckmann JW, Geis A, Losch C, Witzke O, Canbay A, Herget-Rosenthal S, Kribben A, Paul A, Feldkamp T: Efficacy and safety of regional citrate anticoagulation in liver transplant patients requiring post-operative renal replacement therapy. Nephrol Dial Transplant 2012; 27: 1651-7
43. Schultheiss C, Saugel B, Phillip V, Thies P, Noe S, Mayr U, Haller B, Einwachter H, Schmid RM, Huber W: Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. Crit Care 2012; 16: R162
44. Bunchorntavakul C, Chamroonkul N, Chavalitdhamrong D: Bacterial infections in cirrhosis: A critical review and practical guidance. World J Hepatol 2016; 8: 307-21
45. Piano S, Angeli P: Bacterial Infections in Cirrhosis as a Cause or Consequence of Decompensation? Clin Liver Dis 2021; 25: 357-372
46. Gustot T, Maillart E, Bocci M, Surin R, Trepo E, Degre D, Lucidi V, Taccone FS, Delforge ML, Vincent JL, Donckier V, Jacobs F, Moreno C: Invasive aspergillosis in patients with severe alcoholic hepatitis. J Hepatol 2014; 60: 267-74
47. Joshi D, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, Willars C, Bernal W, Wendon J, Auzinger G: Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. Liver Int 2014; 34: 362-6

48. Bismuth M, Funakoshi N, Cadranel JF, Blanc P: Hepatic encephalopathy: from pathophysiology to therapeutic management. Eur J Gastroenterol Hepatol 2011; 23: 8-22
49. Claeys W, Van Hoecke L, Lefere S, Geerts A, Verhelst X, Van Vlierberghe H, Degroote H, Devisscher L, Vandenbroucke RE, Van Steenkiste C: The neurogliovascular unit in hepatic encephalopathy. JHEP Rep 2021; 3: 100352
50. Wang Z, Chu P, Wang W: Combination of rifaximin and lactulose improves clinical efficacy and mortality in patients with hepatic encephalopathy. Drug Des Devel Ther 2019; 13: 1-11
51. Rahimi RS, Singal AG, Cuthbert JA, Rockey DC: Lactulose vs polyethylene glycol 3350--electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. JAMA Intern Med 2014; 174: 1727-33
52. Jain A, Sharma BC, Mahajan B, Srivastava S, Kumar A, Sachdeva S, Sonika U, Dalal A: L-ornithine L-aspartate in acute treatment of severe hepatic encephalopathy: A double-blind randomized controlled trial. Hepatology 2022; 75: 1194-1203
53. Gupta S, Fenves AZ, Hootkins R: The Role of RRT in Hyperammonemic Patients. Clin J Am Soc Nephrol 2016; 11: 1872-1878
54. Saner FH, Bezinover D: Assessment and management of coagulopathy in critically-ill patients with liver failure. Curr Opin Crit Care 2019; 25: 179-186
55. Lisman T, Porte RJ: Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010; 116: 878-85
56. Tripodi A, Mannucci PM: The coagulopathy of chronic liver disease. N Engl J Med 2011; 365: 147-56
57. Saner FH, Scarlatescu E, Broering DC, Bezinover D: The Yin and the Yang of Hemostasis in End-Stage Liver Disease. J Clin Med 2023; 12
58. Blasi A, Patel VC, Adelmeijer J, Azarian S, Hernandez Tejero M, Calvo A, Fernandez J, Bernal W, Lisman T: Mixed Fibrinolytic Phenotypes in Decompensated Cirrhosis and Acute-on-Chronic Liver Failure with Hypofibrinolysis in Those With Complications and Poor Survival. Hepatology 2020; 71: 1381-1390
59. Saner FH, Kirchner C: Monitoring and Treatment of Coagulation Disorders in End-Stage Liver Disease. Visc Med 2016; 32: 241-248
60. Mallett SV, Chowdary P, Burroughs AK: Clinical utility of viscoelastic tests of coagulation in patients with liver disease. Liver Int 2013; 33: 961-74
61. Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schochl H: Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? Br J Anaesth 2015; 114: 217-24
62. De Pietri L, Bianchini M, Montalti R, De Maria N, Di Maira T, Begliomini B, Gerunda GE, di Benedetto F, Garcia-Tsao G, Villa E: Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology 2016; 63: 566-73
63. Kumar M, Ahmad J, Maiwall R, Choudhury A, Bajpai M, Mitra LG, Saluja V, Mohan Agarwal P, Bihari C, Shasthry SM, Jindal A, Bhardwaj A, Kumar G, Sarin SK: Thromboelastography-Guided Blood Component Use in Patients With Cirrhosis With Nonvariceal Bleeding: A Randomized Controlled Trial. Hepatology 2020; 71: 235-246
64. Saner FH, Abeysundara L, Hartmann M, Mallett SV: Rational approach to transfusion in liver transplantation. Minerva Anestesiol 2018; 84: 378-388
65. Biancofiore G, Blasi A, De Boer MT, Franchini M, Hartmann M, Lisman T, Liumbruno GM, Porte RJ, Saner F, Senzolo M, Werner MJ: Perioperative hemostatic management in the cirrhotic patient: a position paper on behalf of the Liver Intensive Care Group of Europe (LICAGE). Minerva Anestesiol 2019; 85: 782-798
66. Saner FH, Gieseler RK, Akiz H, Canbay A, Gorlinger K: Delicate balance of bleeding and thrombosis in end-stage liver disease and liver transplantation. Digestion 2013; 88: 135-44
67. Abuelkasem E, Hasan S, Mazzeffi MA, Planinsic RM, Sakai T, Tanaka KA: Reduced Requirement for Prothrombin Complex Concentrate for the Restoration of Thrombin Generation in Plasma From Liver Transplant Recipients. Anesth Analg 2017; 125: 609-615
68. Kirchner C, Dirkmann D, Treckmann JW, Paul A, Hartmann M, Saner FH, Gorlinger K: Coagulation management with factor concentrates in liver transplantation: a single-center experience. Transfusion 2014; 54: 2760-8
69. Hartmann M, Walde C, Dirkmann D, Saner FH: Safety of coagulation factor concentrates guided by ROTEM-analyses in liver transplantation: results from 372 procedures. BMC Anesthesiol 2019; 19: 97
70. Thompson J, Jones N, Al-Khafaji A, Malik S, Reich D, Munoz S, MacNicholas R, Hassanein T, Teperman L, Stein L, Duarte-Rojo A, Malik R, Adhami T, Asrani S, Shah N, Gaglio P, Duddempudi A, Borg B, Jalan R, Brown R, Patton H, Satoskar R, Rossi S, Parikh A, ElSharkawy A, Mantry P, Sher L, Wolf D, Hart M, Landis C, Wigg A, Habib S, McCaughan G, Colquhoun S, Henry A, Bedard P, Landeen L, Millis M, Ashley R, Frank W, Henry A, Stange J, Subramanian R, Group VTIS: Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: A multinational, prospective, controlled, randomized trial. Liver Transpl 2018; 24: 380-393

71. Pyrsopoulos N, Hassanein T, Subramanian R, Thompson J, Caldwell S, Al-Khafaji A, Reich D, Sieberhagen C, Stange J: THU-272-A study investigating the effect of extracorporeal cellular therapy with C3A cells on the survival of alcoholic hepatitis designed along the guidelines of the NIAAA. J Hepatol 2019; 40: e282
72. Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz C, Sarrazin C, Hoste E, Van Vlierberghe H, Escorsell A, Hafer C, Schreiner O, Galle PR, Mancini E, Caraceni P, Karvellas CJ, Salmhofer H, Knotek M, Gines P, Kozik-Jaromin J, Rifai K, Group HS: Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology 2012; 142: 782-789 e3
73. Banares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, Saliba F, Sauerbruch T, Klammt S, Ockenga J, Pares A, Wendon J, Brunnler T, Kramer L, Mathurin P, de la Mata M, Gasbarrini A, Mullhaupt B, Wilmer A, Laleman W, Eefsen M, Sen S, Zipprich A, Tenorio T, Pavesi M, Schmidt HH, Mitzner S, Williams R, Arroyo V, group Rs: Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology 2013; 57: 1153-62
74. Banares R, Ibanez-Samaniego L, Torner JM, Pavesi M, Olmedo C, Catalina MV, Albillos A, Larsen FS, Nevens F, Hassanein T, Schmidt H, Heeman U, Jalan R, Moreau R, Arroyo V: Meta-analysis of individual patient data of albumin dialysis in acute-on-chronic liver failure: focus on treatment intensity. Therap Adv Gastroenterol 2019; 12: 1756284819879565