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Expert Review of Gastroenterology & Hepatology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierh20

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To cite this article: Nadir Abbas, Neil Rajoriya, Ahmed M Elsharkawy & Abhishek Chauhan (2022): Acute-on-chronic liver failure (ACLF) in 2022: have novel treatment paradigms already arrived?, Expert Review of Gastroenterology & Hepatology, DOI: 10.1080/17474124.2022.2097070

To link to this article: https://doi.org/10.1080/17474124.2022.2097070

Published online: 07 Jul 2022.

EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY
https://doi.org/10.1080/17474124.2022.2097070

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REVIEW

Acute-on-chronic liver failure (ACLF) in 2022: have novel treatment paradigms already arrived?

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ABSTRACT

Introduction: Acute-on-chronic failure (ACLF) is a recognized syndrome in patients with chronic liver disease and is characterized by acute decompensation, organ failure(s), and a high short-term mortality. ACLF is often triggered by ongoing alcohol consumption, gastrointestinal bleeding and/or infections, and is pathophysiologically characterized by uncontrolled systemic inflammation coupled with paradoxical immunoparesis. Patients with ACLF require prompt and early recognition. Management requires extensive utilization of clinical resources often including escalation to intensive care.

Areas covered: Currently, there are no specific targeted treatments for established ACLF, and management revolves around treating underlying precipitants and providing organ support. In this article, we review the epidemiology and pathophysiology of ACLF and summarize recent advances in management strategies of this syndrome, focusing specifically on novel emerging therapies.

Expert commentary: ACLF is a challenging condition with rapid clinical course, high short-term mortality and varying clinical phenotypes. Management of ACLF is broadly focused on supportive care often in an intensive care setting with liver transplantation proving to be an increasingly relevant and effective rescue therapy. This disease has clear pathogenesis and epidemiological burden, thus distinguishing it from decompensated cirrhosis; there is clear clinical need for the development of specific and nuanced therapies to treat this condition.

ARTICLE HISTORY
Received 27 January 2022
Accepted 29 June 2022

KEYWORDS
Inflammatory response; Acute-on-chronic liver failure; liver transplantation; acute decompensation; multiorgan failure

1. Introduction

Advanced liver fibrosis (traditionally termed liver cirrhosis) represents end-stage liver disease and is associated with disruption of hepatic synthetic function and portal hypertension. Cirrhosis is a continuum ranging from the relatively stable and largely asymptomatic 'compensated phase' to the more advanced 'decompensated phase,' characterized by the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy, and jaundice [1]. The development of a decompensating event increases mortality amongst patients with cirrhosis; median survival falls from 12 years in compensated cirrhosis to 2 years with decompensation [1]. Investigators have defined a distinct syndrome within acutely decompensated cirrhotic patients called Acute-on-Chronic Liver Failure (ACLF) [2] which carries a 90-day mortality in excess of 50% [3–5]. ACLF is characterized by the development of extrahepatic organ failure (OF) in a patient with preexisting cirrhosis [6]; it is associated with a high 28-day mortality [4]. The discovery of ACLF as a distinct syndrome has led to novel insights into disease pathogenesis and has the potential to allow identification of new therapeutic targets to ameliorate the excess mortality seen in this patient population.

2. Defining ACLF

Controversy exists regarding a consensual definition and diagnostic criteria for ACLF with up to 13 noted definitions of ACLF each with variable scope and differing prognostic values [7]. Whilst there are notable differences between definitions by various major societies, the two most widely accepted definitions are the Asian Pacific Association for the Study of the Liver (APASL) criteria and the European Association for the Study of Chronic Liver Failure (EASL-CLIF) criteria. (Table 1). APASL defines ACLF as 'an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR [international normalised ratio] ≥1.5) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. It is associated with a high 28-day mortality.' Patients with prior decompensation and those with acutely decompensated cirrhosis are not included in the definition. Extrahepatic insults such as gastrointestinal hemorrhage and sepsis are considered complications of the syndrome, rather than precipitating events [5]. The EASL criteria require an acute decompensation (ascites, bacterial infection, gastrointestinal bleeding, and/or hepatic encephalopathy) followed by the development of one or more organ failures [4]. The heterogeneity in definition is

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Article highlights

- ACLF is a frequency complication in hospitalized patients with cirrhosis and carries high mortality.
- Heterogenous definitions of ACLF are proposed in different regions of world, leading to difficult to interpret epidemiological data.
- There are no targeted treatments against heightened systemic inflammation and resultant immunoparesis; hallmarks and key drivers of ACLF.
- Recognising and managing sepsis is key and reliable biomarkers are needed for early diagnosis.
- Gut microbiota contributes to systemic inflammation and decompensation, hence role of FMT in ACLF needs further trials.
- Liver transplantation as a last resort remains a viable option; ACLF being a recognized indication for liver transplantation in many countries.

partly due to regional differences in ACLF precipitants; alcoholic hepatitis for the EASL-CLIF ACLF cohort compared to mainly viral infections in Asia (superadded hepatitis E or reactivation of hepatitis B) [8]. Thus, cirrhosis is not a pre-requisite for the APASL diagnosis of ACLF but remains a key criterion for the EASL-CLIF ACLF diagnosis. Also, there is focus on liver failure by the former and extra-hepatic organ failure by the later definition. This raises the question whether both definitions refer to different time points in the pathophysiological journey of ACLF. The North American Consortium for the Study for End-Stage Liver disease (NACSELD) and the Chinese Group on the Study of Severe Hepatitis (COSSH) have also provided definitions, which although not consistent, lay groundwork for future research [9,10].

Mahmud et al. compared both widely accepted definitions to ascertain ACLF incidence and mortality in a diverse cohort of patients with compensated cirrhosis, in a retrospective study in the US [11]. Unsurprisingly, incidence and prevalence of ACLF varied based on the definitions used with a significant proportion of patients classified as having ACLF by one criterion alone. In total 4296 patients qualified as having any grade of ACLF by the EASL-CLIF criteria and 574 individuals met the APASL ACLF criteria (10.2%). The short-term mortality of those meeting the APASL ACLF criteria was similar to patients with grade 2 EASL-CLIF ACLF in the cohort. Whilst these findings highlight the heterogeneity in defining ACLF around the world, it remains unclear whether nuanced geographical definitions or a cogent universally accepted, international definition would be best for patient care; the latter would certainly help standardize international, multicenter datasets.

3. Epidemiology

Predicting the worldwide prevalence of ACLF is challenging due to the lack of a universal definition. Previously, prevalence of ACLF in hospitalized patients was estimated to be between

Table 1. Definitions of acute on chronic liver failure (ACLF).

	APASL	EASL CLIF	NACSELD	CHINESE
Definition	Acute hepatic insult manifesting as jaundice (Bilirubin >5 mg/dL) and coagulopathy (INR>1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed CLD including cirrhosis	An acute deterioration of preexisting chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 months due to multi-organ failure	A syndrome characterized by acute deterioration in a patient with cirrhosis due to infection presenting with two or more extra-hepatic organ failures.	**A complicated syndrome with a high short-term mortality rate that develops in patients with HBV-related chronic liver disease regardless of the presence of cirrhosis and is characterized by acute deterioration of liver function and hepatic and/or extrahepatic organ failure.**
Study Cohort	**First consensus was expert opinion**	Prospectively studied in 1343 patients	Prospectively studied in 507 patients	**Prospective study of 1322 hospitalized patients with acute decompensation of cirrhosis or severe liver injury due to chronic HBV.**
Inclusion	• Compensated Cirrhosis • CLD but no cirrhosis • Acute insult directed to liver • Presentation with liver failure	• Patients with AD or cirrhosis • Patients with prior decompensation of cirrhosis	• Patients with prior decompensation of cirrhosis • Patients with infection at admission or during hospital stay	• **Patients with severe liver injury (TB≥5 mg/dL and INR≥1.5) from chronic hepatitis B or acute decompensation of cirrhosis (Ascites/HE/UGIB/bacterial infections)**
Exclusions	• Patients with bacterial infections • Patients with cirrhosis and known prior decompensation who develop acute deterioration are considered to have acute decompensation but not ACLF	• HCC outside Milan criteria • Severe chronic extrahepatic diseases • HIV infection and on-going immunosuppressive treatments	• Outpatients with infection • HIV infection • Prior organ transplant • Disseminated malignancies	• **Age <18 and >80 years** • **Pregnant women** • **Other liver malignancies** • **Severe extra-hepatic disease** • **Receiving immunosuppressive drugs for indications other than chronic liver disease**
Priority criteria for severity	Experts consider the failing liver as predictor of severity	Pre-specified criteria for organ failure(s) according to the CLIF-SOFA score	Prespecified criteria for organ failure(s)	**Chinese group on the Study of Severe Hepatitis B-ACLF (COSSH-ACLF) criteria**

Abbreviations: AD, Acute Decompensation; APASL, Asian Pacific Association for the Study of the Liver; CLD, Chronic liver disease; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; EASL-CLIF, European Association for the Study of Liver-Chronic Liver failure; **HBV**, **Hepatitis B**; HCC, Hepatocellular carcinoma; **HE**, **hepatic encephalopathy**; HIV, Human immunodeficiency virus; INR, International normalized ratio; NACSELD, North American Consortium of End-stage Liver Disease; SOFA, Sequential Organ Failure Assessment; **UGIB: Upper gastrointestinal bleed**.

24% and 40% [12–14]. A recent systematic review and meta-analysis, constituting the largest epidemiological study on this subject to date, estimated the global prevalence of ACLF to be 35% of hospitalized patients with cirrhosis (95% CI: 33% to 38%) using the EASL-CLIF criteria [15]. The authors found the 90-day mortality rate to be 58% (95% CI: 51% to 64%), with marked regional variation. (ACLF 90-day mortality was 41%, 56%, 68%, and 73% in North America, Europe, South Asia, and South America, respectively). Alcohol was the most frequent etiology worldwide (45%), showing the highest prevalence in Europe. Similar to the European PREDICT trial (Predicting Acute on Chronic Liver Failure) data, bacterial infection, and severe alcoholic hepatitis, either alone or in combination, resulted in acute decompensation and ACLF in 96% of patients included in the analysis [16]. Mezzano et al al confirm that the most frequent ACLF triggers globally were bacterial infections (35%), followed by gastrointestinal bleeding (22%) and alcohol (19%).

4. Animal models of ACLF

Animal models of ACLF aim to mimic human disease with techniques resulting in chronic liver injury, followed by a precipitating event, usually through administration of D- galactosamine/lipopolysaccharide (LPS). These models exhibited a very high short-term mortality and lacked the clinicopathological manifestations of true ACLF; including portal hypertension, ascites, and multiorgan failure [17–20] Recently, Nautiyal et al. reproduced ACLF in mice by intraperitoneal administration of carbon tetrachloride (CCL4) for 10 weeks followed by an acute injury with acetaminophen (APAP) and LPS. This CCL4/APAP/LPS (CALPS) model replicated the clinical, biochemical, and pathological features of ACLF including hepatocellular injury and necrosis, liver failure, jaundice, ascites, and organ dysfunction [21]. This model is the closest one available to human ACLF and could aid in development of stage specific treatments in this dynamic syndrome.

5. Pathophysiology

Portal hypertension, intestinal dysbiosis, and enhanced gut permeability are key cirrhosis phenomenon [22] (Figure 1); these set the stage for bacterial translocation and drive the subsequent local and systemic iterative inflammation that is characteristic of cirrhosis [23]. Cirrhotic individuals are thus 'primed' to enter catastrophic cycles of inflammation.

The systemic inflammation hypothesis proposes that the clinical features of acute decompensated cirrhosis and organ failure share a common pathophysiological mechanism. Traditionally, systemic inflammation is known to cause organ dysfunction through stimulating NO production, resulting in worsening of preexisting circulatory dysfunction and activation of immune cells. This then results in tissue damage and impaired organ function [24]. An additional mechanism involving mitochondrial metabolic dysfunction associated with systemic inflammation has recently been proposed [25].

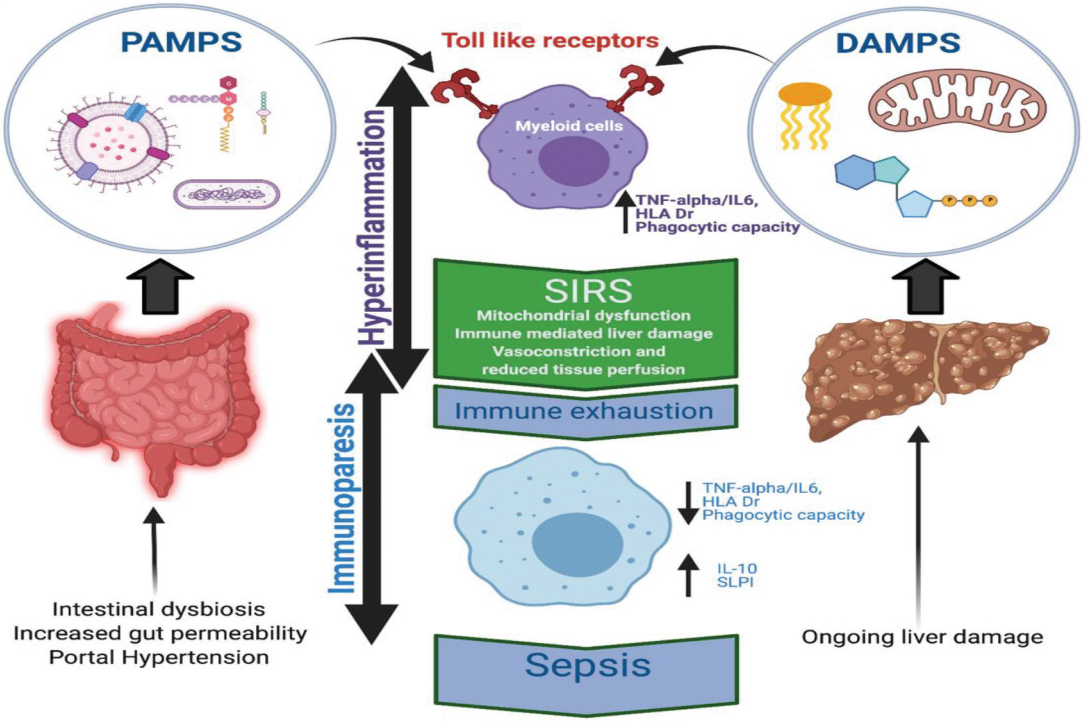

Figure 1. Pathophysiology of ACLF.

Intestinal dysbiosis, enhanced gut permeability, and ongoing liver damage contribute to a large circulating pool of immunogenic motifs including PAMPs (LPS, peptidoglycan, nucleic acids, unmethylated CPG motifs) and DAMPs (HMGB-1, histones, DNA) in decompensated cirrhosis. These drive uncontrolled myeloid cell activation via the toll-like receptors resulting in continual background inflammation typified by the SIRS: this is the hyperinflammatory stage of ACLF with high cytokine levels including IL6 and TNF-alpha. Perpetual immune cell activation results functional reprogramming of these cells which signifies immune exhaustion, this is the immunoparetic phase which portends to sepsis [21,22].**Abbreviations**: ACLF: acute-on-chronic liver failure, DAMPs: damage-associated molecular patterns, DNA: deoxyribonucleic acid, HMGB1: high mobility group box 1, HLA: human leukocyte antigens, IL: interleukin, LPS: lipopolysaccharide, PAMPs: pathogen-associated molecular pattern, SIRS: Systemic Inflammatory Response Syndrome); SLPI: secretory leukocyte peptidase inhibitor, TNF: tumor necrosis factor.

Untargeted blood metabolomics obtained from a large series of patients with AD of cirrhosis, with or without ACLF, alongside immunology data in the context of sepsis [26,27] suggest preferential allocation of circulating nutrients (amino acids, fatty acids, and glucose) to innate immune cells as a result of high metabolic demands. This process is supported by inhibiting nutrient consumption in peripheral organs resulting in decreased mitochondrial energy production and the eventual organ dysfunction/failure seen in individuals with ACLF [28].

ACLF precipitating events vary with geographical location [1] but broadly include infections and GI bleeding [22]. Such triggers initially drive decompensation events such as renal failure or ascites and then hepatic and extrahepatic OFs. Whilst it is clear that an exaggerated inflammatory response is a key feature underlying ACLF pathophysiology, what is less well understood is the associated paradoxical immunoparesis which portends to overwhelming sepsis, multiple OF and poor short-term survival [29]. Inflammation and immunoparesis are thus key pathophysiological features of ACLF (Figure 1).

6. Pre-ACLF state

The PREDICT study identified three distinct clinical courses in acute decompensated cirrhosis after hospital admission. In this prospective, multicenter, observational study, the investigators noted that the development of systemic inflammation was the key driver of disease progression and stratified patients into three groups with distinct clinical trajectories. The first group defined was the patients with 'pre-ACLF.' This cohort developed ACLF within 90 days and had a 3-month and 1-year mortality of 53.7% and 67.4%, respectively. The second group exhibited a clinical course of unstable decompensated cirrhosis, whilst they did not develop full blown ACLF, these patients were noted to have low-level systemic inflammation and portal hypertensive bleeding complications. This group had a 1-year mortality of 35.6%. Finally, the patients with stable decompensated cirrhosis with no systemic inflammation had a 1-year mortality rate of 9.5% and comprised almost two-third of all patients admitted to hospital with AD [16].

7. Management of ACLF

Currently, there are no specific treatments available for patients with ACLF and management centers on supportive treatment; treating precipitating factors; prevention of complications whilst providing organ support and increasingly liver transplantation. Due to both an improved understanding in the pathogenesis of ACLF and increasing commercial interest from pharmaceutical companies, there are currently several novel therapies being trialed in both clinical and purely experimental settings.

7.1. Managing sepsis and novel biomarkers

Bacterial infections are common in ACLF, either as a complication or as a precipitating event [30]. In infection triggered ACLF, the likelihood of death is four times higher than all other precipitating events [31]. Early diagnosis of sepsis is thus vital and can improve prognosis. Conventional laboratory markers such as C-reactive protein (CRP) and procalcitonin (PCT) can help in diagnosis but levels of both markers are noticeably lower in patients with cirrhosis and infections compared to patients without liver disease [32]. It is clear that effective biomarkers for early diagnosis of sepsis in ACLF are needed and a number of these have been proposed. Interleukin-6 (IL-6) is an acute-phase protein that predicts outcome of patients (90-day and 1-year mortality) with cirrhosis comparable to MELD score and better than CRP and white cell count [33,34].

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) (immune cell surface marker, elevated in infections and sepsis) [35,36] and Presepsin (novel inflammatory biomarker stimulating monocyte phagocytosis) [37] have been studied as early diagnostic tests in ACLF-associated sepsis [38]. Both biomarkers demonstrated higher diagnostic efficacy in diagnosing sepsis in ACLF patients compared to traditional markers including white cell count, procalcitonin, and CRP. Furthermore, a combination of presepsin with the traditionally used CLIF-SOFA score revealed the highest diagnostic accuracy in diagnosing sepsis in ACLF patient [38].

7.2. Emerging treatments

7.2.1. Inhibition of toll-like receptor 4 (TLR-4)

TLR-mediated immune cell activation plays a pivotal role in the innate immune response [39]. By recognizing pathogen-associated molecular patterns (PAMPs), including LPS (lipopolysaccharides) and Damage-Associated Molecular Protein (DAMPs) (Figure 1) TLRs activate innate immune cells including macrophages and neutrophils thus initiating inflammatory processes critical to host defense [40]. The liver is continually exposed to a high antigen load from the gut, so hepatic TLR distribution and function is designed to fundamentally facilitate tolerance rather than immune induction. This balance is disrupted in cirrhosis. Furthermore, there is an abundance of both PAMPs and DAMPs in cirrhosis due to a breakdown of the gut-blood barrier, intestinal dysbiosis, and ongoing hepatocyte necroptosis [41]. The resultant uncontrolled TLR-driven innate cell activation is instrumental in driving the low- and high-grade inflammation characteristic of ACLF. (Figure 1)

7.2.2. TAK-242

Rodent models of ACLF (both bile duct ligation and CCL4 [chemokine ligands 4] plus LPS) confirm that TLR-4-mediated signaling is a key step in the pathogenesis of ACLF. TAK-242 inhibits TLR-4 activation [42,43], thus effectively blocking LPS and DAMPs triggered pro-inflammatory cytokine production (Figure 2). Whilst this therapy is promising [39], human *in vivo* data are currently lacking. A randomized-controlled trial (RCT) has been assessing efficacy, safety, and pharmacokinetics of TAK-242 in cirrhotic patients with acute alcoholic hepatitis (AH) and a trial in ACLF is being set up. The primary outcome is changed in CLIF-ACLF score at day 8 of treatment. (NCT04620148)

7.2.3. Recombinant alkaline phosphatase

Another novel method of blocking TLR4 is by neutralizing a key PAMP in ACLF; LPS. High serum LPS levels in patients with AH and ACLF are associated with increased risk of death [44] (Figure 2). LPS is an endotoxin from the cell wall of gram-negative bacteria and can be rendered nontoxic by recombinant alkaline phosphatase (recAP)-mediated dephosphorylation [45,46]. Engelmann *et al* used a rat model of bile duct ligation with co-administration of LPS to demonstrate that recAP reduced hepatic TLR 4 expression, blunted the inflammatory response and improved organ failures in ACLF [47]. This approach awaits validation in human subjects with ACLF.

7.2.4. gDNA, DAMPs and pan-caspase inhibitor Emricasan

In addition to PAMPs, products from necrotic and apoptotic hepatocyte death (DAMPs) also drive the development of SIRS in the pathogenesis of ACLF [48] (Figure 1). Whilst end products of apoptotic pathways such as fragmented chromatin, the M-30 component of KRT-18 (keratin) and g-DNA (low molecular weight DNA with size laddering) are seen in patients with ACLF [49], the dominant mode of cell death in ACLF appears to be necrosis. This was confirmed by a subset analysis of 337 patients from the CANONIC dataset by Macdonald et al. [50] Caspase-cleaved keratin 18 (cK18) and Keratin 18(k18) which are derived from apoptotic and necrotic cell death, respectively, were measured in the plasma of patients from this CANONIC subset and the resultant cK18: k18 ratio (apoptotic index) was calculated. There was a statistically significant reduction in cK18:K18 ratio seen in ACLF patients as compared to AD [50], indicating greater hepatocyte necrosis in ACLF. Zheng *et al* corroborated these findings in chronic HBV (hepatitis B virus) patients. They demonstrated that patients with ACLF had significantly raised levels of both M-30 (derived by caspase-mediated cleavage of Ck18; marker of apoptotic hepatocyte death) and M-65 (marker of total hepatocyte death; necrosis and apoptosis) and decrease in the M30/65 ratio associated with poorer clinical outcomes [51]. Other investigators hypothesize that the dominant mode of cell death driving ACLF is apoptosis with Adebayo *et al* demonstrating a high apoptosis index (M-30/M-65 ratio) in patients with ACLF. It is important to note, however, that the comparison group was patients with acute liver failure in this study, where far higher levels of necrosis are to be expected [49].

Studies involving the caspase inhibitor Emricasan support necrosis as the dominant cell death modality in ACLF [52] (Figure 2). Caspase inhibitors block apoptosis and have a hepato-protective effect in rodent models of cholestatic and fatty liver disease [53]. Frenette et al demonstrated that oral administration of Emricasan for 3 months in patients with cirrhosis resulted in improved liver function (MELD score, Child-Pugh score; INR and total bilirubin) compared to placebo [54]; this RCT excluded patients with advanced liver disease (CTP-C) and advanced organ failure, thus effectively excluding ACLF patients [54]. When Emricasan was studied in ACLF (phase 2 multicenter, double-blind, randomized trial) [55], an

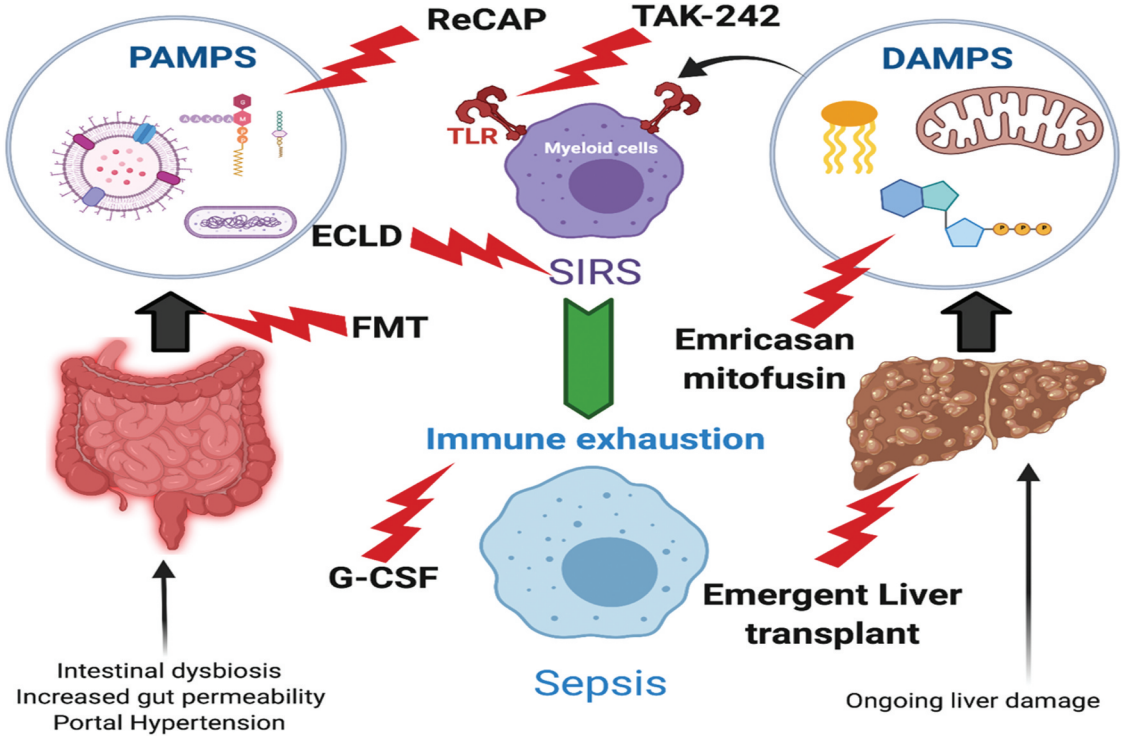

Figure 2. Novel interventions for ACLF.

FMT has the potential to alter the gut microbiome to alter the nature of bacterial translocation. ReCAP and TAK-242 reduce LPS-driven TLR activation. Emricasan and mitofusin modulate apoptosis products thus potentially reducing the immunogenic pool of DAMPS. G-CSF is hypothesized to reduce immunoparalysis by resetting immune exhaustion whilst ECLDs reduce the inflammatory cytokine burden driving the initial SIRS.

Abbreviations: DAMPS: damage-associated molecular pattern, ECLD: extracorporeal liver support devices, FMT: fecal microbiota transplantation, G-CSF: granulocyte-colony stimulating factor, LPS: lipopolysaccharides, PAMPS: pathogen-associated molecular pattern, ReCAP: recombinant alkaline phosphatase, SIRS: systemic inflammatory response syndrome, TLR: toll-like receptor.

expected reduction in apoptotic markers was observed but there was no improvement in either the MELD or CLIF-C ACLF/CLIF-C AD scores.

7.2.5. Mitofusin-2 – a protective target in the liver

Mitochondrial fusion protein 2 (Mfn2) has multiple biological functions including vital effects on apoptosis and autophagy [56]. The balance between the two is mediated via the BNIP3 (BCL2 and adenovirus E1B 19-kDA-interacting protein 3)-mediated signaling pathway [57]. Xue *et al* conducted a study using an ACLF animal model and a hepatocyte autophagy model by delivering Mfn2 to liver cells using adenovirus and lentivirus. Anti-apoptotic effects of Mfn2 overexpression were demonstrated by increased and decreased Bcl-2 (inhibitor of apoptosis) and Bax (inducer of apoptosis) levels, respectively. Autophagy was triggered with Mfn2 via the P13k/Akt/mTor signaling pathway, signaling a role in alleviating liver injury in ACLF [58]. Whilst necrosis is likely the key driver of ACLF, there is likely a contribution from apoptotic cell death and thus Mitofusin-2 may be part of future combination therapies in these patients (Figure 2).

7.2.6. Oxysterol sulfates: 25-hydroxycholesterol 3-sulfate (25HC3S)

Oxysterol sulfates are a new class of anti-inflammatory drugs under clinical evaluation and play an important role in lipid metabolism, inflammatory response, and cell survival through epigenetic modification [59]. A phase 2a, open-label study is underway studying the oxysterol sulfate DUR-928 in moderate-severe AH. (NCT03917407) If efficacy is demonstrated, then the role of this in the management of ACLF is likely to be explored.

7.2.7. Statins

Statins are established treatment agents for hypercholesterolemia. In addition, they have antioxidative, antiproliferative, and anti-inflammatory properties [60]. Statins, in studies from the early 2000s, have been shown to increase hepatic nitric oxide release and decrease hepatic resistance in patients with portal hypertension and cirrhosis [61]. Additional hepatoprotective and anti-inflammatory properties were demonstrated in subsequent experimental studies [62,63]. Investigators have also demonstrated that statins decrease portal pressure (measured by hepatic venous pressure gradient) in patients with cirrhosis [64,65], with beneficial effects on survival noted in patients presenting with variceal bleeding [66]. As clinically significant portal hypertension (CSPH), perhaps more specifically rising portal pressures, heralds the onset of ACLF [67], it is unsurprising therefore that the effects of statins in patients with decompensated cirrhosis is an active area of ACLF research. Currently, two RCTs, one comparing Simvastatin (20 mg/day) and Rifaximin (1200 mg/day) with placebo in patients with Child-Pugh B/C cirrhosis to prevent ACLF (NCT03780673), and another examining the effects of Atorvastatin (20 mg per day) on survival and hospitalization in patients with cirrhosis and CSPH (NCT04072601), are underway. These trials will also address the safety concerns surrounding statin use in advanced liver disease; this remains a particularly relevant outcome when examining statin use in liver disease given the early results from the LIVER-HOPE SAFETY trial. This trial revealed that simvastatin 40 mg/day plus rifaximin in patients with decompensated cirrhosis was associated with significant increase in adverse events (rhabdomyolysis being the most common) requiring treatment withdrawal, compared with simvastatin at 20 mg/day plus rifaximin [68].

7.2.8. Granulocyte colony stimulating factor (G-CSF)

Perpetual inflammation and the resultant immune cell exhaustion contribute to the immunoparesis seen in ACLF [69].(Figure 1) G-CSF or Granulocyte colony stimulating factor, with its ability to stimulate proliferation and differentiation of neutrophil progenitor cells, thereby potentially resetting a paralyzed immune system is an attractive proposition in ACLF. (Figure 2) G-CSF is hypothesized to drive hepatic regeneration in ACLF in a stem cell-dependent mechanism; in animal models of liver failure G-CSF enhanced mobilization of hematopoietic stem cells and then proliferation of hepatic progenitor cells [70]. The results in human cirrhosis are however less convincing; small RCTs' in patients with stable decompensated cirrhosis have generated different outcomes and drawing firm conclusions is challenging due to heterogeneity of the studies [71–74], and this point is further highlighted in a recent meta-analysis which revealed conflicting outcomes between European and Asian studies [75].

G-CSF therapy in patients with HBV-associated ACLF improved liver function and 3-month survival (48.1% compared to 21.4% in the control group; P = 0.018; n = 28) [76]. Survival benefits have also been noted with G-CSF in alcoholic cirrhosis and concomitant biopsy-proven alcoholic steatohepatitis (ASH) [77]. In a double-blind, randomized, placebo-controlled trial, G-CSF was co-administered with darbepoetin α (GDP group) for 4 weeks (n = 29), or only placebo (n = 26). All patients also received standard medical therapy. At 12 months, higher proportion of patients in the GDP group survived in comparison with controls (68.6% vs 26.9%: 0.003). The GDP group demonstrated reduced liver severity scores (CTP reduction of 48.6% vs 39.1%; p = 0.001, MELD score reduction by 40.4% vs 33%; p = 0.03) and developed less ACLF [78].

More recently, G-CSF was evaluated in patients with ACLF. In a prospective, open-label phase II study 176 patients with ACLF (EASL-CLIF criteria) were randomized to receive either G-CSF plus standard medical therapy (SMT) (n = 88) or SMT alone. G-CSF in comparison with SMT had no significant effect on 90-day transplant-free survival (34.1% vs 37.5%: HR1.05; 95% CI:0.71–1.55; p = 0.805). G-CSF also did not improve liver function scores and occurrence of infections [79]. At present, there is therefore insufficient evidence to recommend use of G-CSF to treat patients with decompensated cirrhosis or ACLF.

7.2.9. Mesenchymal stem cells (MSCs) transplantation

MSCs are multipotent cells with ability to regenerate and differentiate into various type of cells, including hepatocytes [80], and possess immunomodulatory properties [81]. Studies have shown bone marrow-derived MSCs ameliorate liver

fibrosis and protect against fulminant hepatic failure in mice [82,83]. Umbilical-cord derived MSCs in Hepatitis B associated ACLF were given in an open-label-controlled study. The results showed improvement in liver function tests and decreased MELD score indicating increased survival rates [84]. A systematic review on stem MSC transplantation in ACLF due to hepatitis B (Three studies, 198 patients [91 treated with MSC and 107 on standard medical therapy]) concluded a significant reduction in the mortality rate and bilirubin at three months with a good safety profile [85]. Another systematic review and meta-analysis assessing clinical performance of MSC therapy in ACLF (4 RCT and 6 non-randomized controlled trials) showed short-term improvement in liver function tests and MELD scores [86]. In conclusion, the use of MSC therapy in ACLF in real-world settings requires more studies as current evidence confines the use to research and experimental use.

7.2.10. N-Acetylcysteine (NAC)

NAC is a glutathione precursor and well-established treatment option in paracetamol-induced ALF [87]. NAC has the effect of scavenging free radicals and antioxidation, helping mitochondrial function, inhibit inflammation and improve hepatic function and promote repair of hepatocytes [88,89]. Wang et al studied the effect of NAC treatment on HBV-related ACLF in a retrospective study in a total of 90 patients (42 and 48 patients in NAC treated and control group, respectively). NAC treatment improved intrahepatic cholestasis, coagulation function, and liver biochemistry [90].

7.2.11. Albumin

Albumin use in decompensated cirrhosis is well established in an acute/short-term setting to address hypovolemia and associated complications. It is universally recommended in treating spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and for patients undergoing large volume paracentesis (LVP) [91]. Recent data have highlighted the non-oncotic properties of albumin, making it a biologically plausible treatment agent in decompensated cirrhosis. These functional features include homeostatic effects, antioxidation by scavenging-free radicals, immunomodulation, endothelial stabilization, and binding toxic metabolites including bile acids [92]. Use of albumin in the setting of decompensated cirrhosis and ACLF has evolved dramatically over the last decade albeit without a consensus on dosage, duration, and frequency of administration. Long-term albumin administration in the setting of decompensated cirrhosis has generated interest, resulting in three large RCT's in the last 3 years [93–95].

The ATTIRE trial (Albumin to prevent infection in chronic liver failure) was published recently [94]. This multicenter RCT included 777 adult patients with cirrhosis, hospitalized for acute decompensation with or without ACLF and hypoalbuminemia (serum albumin <30 g/L). The mean MELD score was 20, and 66% of patients were admitted because of new-onset or worsening ascites. Patients were randomized to receive 20% human albumin (median 200 g; IQR 140–280 g) to target albumin level ≥30 g/L, as compared to standard of care with control group receiving 20 g of albumin (IQR 0–120 g). The composite primary endpoint was new infection, renal dysfunction, or death between days 3 and 16 after initiation of treatment. The percentage of patients with primary endpoint event did not differ significantly between targeted albumin group (29.7%) and standard-care group (30.2%); p = 0.87.

The ANSWER study, a multicentric, open-label study enrolled patients with stable decompensated cirrhosis and uncomplicated ascites. The 18-month survival (primary endpoint) was significantly higher in patients receiving SMT and albumin (77%) as opposed to SMT alone (66%; p = 0.028). Long-term albumin reduced the need for paracentesis (54%) and the incidence of refractory ascites (57%). In addition, rates of SBP, renal dysfunction, HRS type 1, hepatic encephalopathy (grade 3 or 4) and potential diuretics-induced side-effects were significantly reduced by 30–67.5% in patients receiving albumin and SMT. These results were further validated in a prospective, non-randomized study enrolling 70 patients with refractory ascites. Patients receiving SMT and albumin (half the dose of ANSWER trial at 20 g/week) had a lower 24-month mortality (41.6%) vs patients receiving SMT alone (65.5%; p = 0.032). This was coupled with a lower risk of emergency hospitalization from SBP, non-SBP infections, and HE [96].

MACHT trial (midodrine and albumin for cirrhosis patients in the waiting list for liver transplantation) had contrasting results showing no survival benefit or probability of developing complications (primary endpoint) for long-term albumin use in decompensated cirrhosis patients, listed for liver transplantation [95]. These contradictory results can be explained by smaller dosage (40 g every 15 days vs 40 g every week in the ANSWER trial) and duration of albumin therapy (mean duration 80 days vs 18 months). Moreover, a loading dose was used in the ANSWER trial resulting in a significant increase of serum albumin 0.6–0.8 g/dL to a median value of nearly 4 g/dL.

There were considerable differences in study design, baseline patient characteristics, dosing and timing of albumin and length of follow-up between the aforementioned three studies. The recent American College of Gastroenterology (ACG) guidelines on ACLF recommend against daily infusion of albumin to maintain albumin >3 g/dL to improve mortality, prevention of renal dysfunction, or infection [97].

PRECOCIA pilot and INFECIR-2 studies by Fernández et al also provide novel insights into the effect of prolonged administration of Human albumin (HA) in patients with decompensated cirrhosis [98]. The PRECOCIA pilot study evaluated the efficacy of long-term HA treatment in prevention of ACLF and mortality. The aim was to identify the HA dose that could normalize serum albumin concentration during 12 weeks of treatment, and then investigate the effects of administration of this albumin dosage for 12 weeks on hypoalbuminemia, cardiocirculatory dysfunction, portal pressure, and systemic inflammation. Out of 18 patients recruited, 10 patients received 1 g/kg body weight of albumin every 2 weeks (low-albumin dose (LA1bD) group which failed to normalize serum albumin (SA) concentration in majority of the patients. As a result, the HA dosage and frequency was increased to 1.5 g/kg body weight every week (high-albumin dose (HA1bD) group). All six patients of HA1bD group presenting with baseline hypoalbuminemia normalized SA concentration (P < 0.001). HA1bD group also showed significant

improvement in LV function which is an important contributory mechanism in the cardiocirculatory dysfunction seen in decompensated cirrhosis. These findings also highlighted the dose and frequency required to normalize serum albumin concentration is much higher than that used by other therapeutic trials so far performed. Furthermore, the HA1bD group (not LA1bD) induced a reduction of >20% of IL-6 concentration. This finding prompted extension of the investigation to 13 additional pro-inflammatory cytokines which were suppressed in the HA1bd group. To confirm these results, the investigators also analyzed the blood samples collected in the INFECIR-2 study [multicenter, randomized clinical trial assessing the effect of short-term albumin concentration (1.5 g/kg at diagnosis and 1 g/kg on the third day) in addition to antibiotic therapy, in patients with cirrhosis and acute bacterial infections unrelated to SBP]. A significant reduction in circulating cytokines alongside renin concentration was observed only in patients receiving HA plus antibiotics compared to the antibiotics alone group. Both studies provide useful insights on the dose and frequency of albumin administration to attenuate systemic inflammation and improve cardiocirculatory dysfunction. Implementation of this in real-world settings will be challenging given the cost and utilization of clinical services.

Use of albumin in ameliorating paracentesis-induced circulatory dysfunction (PICD) in setting of ACLF was studied in a RCT. In total, 80 patients undergoing <5 L paracentesis were randomized to receive albumin (8 g/dL, n = 40) or no albumin (n = 40). Non-albumin group experienced higher PICD (I70% v 40%; p = 0.001), higher incidence of hepatic encephalopathy (50% v 27.5%; p = 0.04), hyponatremia (67.5% v 22.5%; p < 0.001), acute kidney injury (62.5% v 30%; p = 0.001), and inpatient mortality (62.5% v 27.5%; p = 0.003) [99].

Additional clinical trials are needed to identify patient groups who would benefit most from long-term albumin administration. To this effect, the ASIA trial is currently underway assessing efficacy of albumin with SMT as compared to SMT in improving patients' survival and immune modulation in ACLF. (NCT03754400)

7.3. Role of gut microbiome in ACLF

The gut microbiota plays a cardinal role in development of complications associated with cirrhosis [100]. Increased gut permeability, release of products such as endotoxins, small bowel bacterial overgrowth and translocation predispose individuals to infections ultimately leading to complications of end-stage liver cirrhosis such as spontaneous bacterial peritonitis, hepatic encephalopathy, and ACLF [101] Figurse(Figures 1 and 2). The gut microbiome is altered in patients with liver cirrhosis with quantitative metagenomics analyses demonstrating 75,234 distinct microbial genes in cirrhosis in comparison t healthy controls [102]. Manipulation of the gut microbiota to alleviate gut dysbiosis and immune dysfunction by fecal microbiota transplantation (FMT) from a healthy donor may influence the course of liver disease. To this effect, FMT has been evaluated in severe AH (alcoholic hepatitis), PSC (primary sclerosing cholangitis), NAFLD (nonalcoholic fatty liver disease), and HBV infection [103–107]. In a randomized trial by Bajaj et al., FMT was shown to be associated with short-term reduction in alcohol craving and alcohol misuse-related events over six months [108]. An open-label randomized controlled trial by Ahmad *et al* evaluating FMT as an adjunctive therapy with antiviral therapy (tenofovir) vs antiviral therapy alone in patients with ACLF (defined by the APASL criteria as MELD>18 with <2 organ failures) due to reactivation of HBV, demonstrated significantly improved transplant-free survival in the FMT + tenofovir group (75% vs 37.5%; P = 0.01) [109]. More recently, the efficacy and safety of FMT was studied in patients with severe alcoholic hepatitis (SAH) ACLF in an open-label clinical trial. Thirty-three patients (13 in the FMT arm; 20 in the standard of care (SOC) arm) with SAH-ACLF were administered FMT and followed on days 7, 28, and 90. FMT improved survival at 28 days (100% v 60%; p = 0.01) and 90 days (53.8% v 25%; p = 0.02) [110]. Larger trials assessing safety and efficacy of FMT in ACLF including other settings of chronic liver diseases are required.

Carbalive™ is a novel-engineered microporous carbon bead, administered orally, and is designed to absorb and clear LPS and other toxins from the gut thus preventing translocation into blood and liver. The goal being to attenuate LPS-driven immune overactivity and eventually paresis. Preliminary results from an RCT assessing the safety, tolerability, and efficacy have shown promising data but official results are awaited (www.carbalive.eu).

7.4. Emergent transplantation for ACLF

Whilst super-urgent transplantation in acute liver failure with multiorgan failure is an established therapy [111,112], this has not been universally accepted standard of care for critically ill patients with cirrhosis (ACLF patients) for a variety of reasons. Diminished physiological reserve, higher recipient age, concerns about recidivism in those with ethanol as an etiology, and the presence of comorbidities are commonly seen amongst patients with end-stage liver disease. Superadded critical illness in this cohort (i.e. additional hit of ACLF) has traditionally thus been viewed as a contraindication to emergent transplantation due to poor survival.

Emerging data challenge this concept as multiple studies have now demonstrated good post-transplant outcomes in ACLF patients (Figure 2). 4.9% and 15% of patients from the CANONIC study received liver transplantation for ACLF within 28 and 90 days of admission. The survival for ACLF-2 and ACLF-3 was around 20% without liver transplantation and 80% with transplantation [4]. Further data from studies have consistently shown that one-year survival rates after transplantation for ACLF are above 70% [113,114]. Interrogation of the UNOS database by American investigators confirms findings from the CANONIC experience; Sundaram et al. demonstrated improved survival odds in ACLF-3 patients when transplanted within 30 days of placement to the transplant waiting list, whilst Thuluvath et al found that even in the presence of six organ failures, transplantation resulted in an 81% survival chance at 1 year [115]. Building upon these retrospective analyses that likely included super-selective patients in interested centers, Leary et al prospectively studied around 2800

patients admitted with cirrhosis in a multi-center North American study and found that outcomes after transplantation were identical between stable or decompensated cirrhosis and those that were critically ill with ACLF [116].

A common theme emerging from these studies is how traditional liver disease scores such UKELD, MELD and CTP lack the robustness required to prognosticate patients with ACLF. The CLIF-ACLF score which incorporates the SOFA score arguably provides the most dynamic measurement system to predict outcome in ACLF [3], but again needs validation in wider cohorts of patients. Other critical points that need addressing through further study is timing of transplantation in patients with ACLF and the definition of futility. It is clear that decisions with regard to transplantation need to be taken early but what is perhaps less apparent is what exactly constitutes 'early' and what the specific contraindications may be. Artru et al excluded advanced pulmonary and circulatory failure, as well as active sepsis and GI bleeding [113]; other groups have noted better outcomes if patients on renal replacement therapy were excluded. Furthermore, the CANONIC investigators demonstrate that the final grade of ACLF within 81% of ACLF patients occurred between the 3rd and 7th day post-diagnosis [117]; suggesting this may be the best time to take such decision. Ethical debates that address how best to prioritize these patients on national waiting lists whilst maximizing transplant utility and benefit overall also need to take place. Ultimately a rapid but bespoke assessment within an MDT setting that considers patient and disease specific nuances will result in the best overall care, organ allocation, and resource utilization. Recently, a UK wide service evaluation of transplantation for patients with ACLF-2 and −3 has started. As of 8 November 2021, patients have been enrolled in the scheme with seven patients receiving a transplant and six surviving to the last follow up. Further data from around the world should help define futility criteria and lead to clear inclusion and exclusion criteria for the use of this precious resource.

7.5. Artificial liver devices (ECLD)

Liver failure and the resultant OF is in part due to accumulating toxins (including ammonia, urea, bile acids, branch chain aromatic amino acids) and the pro-inflammatory cytokines that DAMPS and PAMPS elicit including cytokines from the Tumor Necrosis Factor (TNF) and Interleukin families (Figure 1). These cytokines and substances can be removed by artificial liver support systems (Figure 2). Thus, replacing or complementing the work of a failing liver using an artificial device in ACLF has generated a sizable amount of interest and research [118]. Given the worldwide shortage of organ donors, there has been an understandable focus on possible utility of these devices. However, there is little concrete evidence for recommending these devices in ACLF currently [119]. Table 2 summarizes the most comprehensively studied ECLD therapies in ACLF.

Whilst there is strong evidence to suggest use of plasma exchange in ALF to improve transplant free survival, there is lack of robust evidence to use plasma exchange in ACLF. Qin et al reported the use of plasma exchange compared to SMT in a prospective controlled trial in patients with HBV-associated ACLF [135]. Plasma exchange had improved 90-day (60% v 47%; p = 0.016) and 5-year (43% v 31%; p = 0.013) mortality compared to SMT. The study used the Chinese definition of ACLF which does not require cirrhosis of multiorgan failure as a pre-requisite hence the studied population was highly heterogeneous. (52% patients were non-cirrhotic) A systematic review of plasma exchange in ACLF showed improved 30- and 90-day survival in non-transplanted individuals but further well designed RCTs are required to ascertain the optimal duration and amount of plasma exchange required in the setting of ACLF [136]. APACHE trial is a phase III, multicenter, randomized, open-label trial in ACLF, aimed to determine whether plasma exchange with 5% albumin improves 90-day survival, in comparison with standard medical therapy. (NCT03702920)

Thus, replacing or complementing the work of a failing liver using an artificial device in ACLF has generated a sizable amount of interest and research [118]. Given the worldwide shortage of organ donors, there has been an understandable focus on possible utility of these devices. However, there is little concrete evidence for recommending these devices in ACLF currently [119]. Table 2 summarizes the most comprehensively studied ECLD therapies in ACLF.

8. Conclusion

ACLF remains a challenge in modern hepatology with no universally accepted definition, devastating consequences, and limited treatment strategies. ACLF is a dynamic syndrome with systemic inflammation, immune paralysis, and multi-organ failure being the hallmarks. Treatment is based on organ support, prevention, and management of complications. Extracorporeal liver support devices have failed to reduce mortality in ACLF patients. Prognostication is challenging given the dynamic course of ACLF and requires day-to-day assessment. Novel therapies targeting the various pathophysiological mechanisms in development of ACLF are desperately needed.

9. Expert opinion

ACLF is a major cause of mortality in patients with cirrhosis and chronic liver disease worldwide. An international consensus definition for ACLF is currently lacking and thus there is heterogeneity in how these patients are identified and subsequently managed in different settings. Whilst it is clear that early diagnosis, prevention of precipitating factors, and aggressive ICU care with organ support improves prognosis; treatment for ACLF is currently broadly restricted essentially to supportive care. There are no target-specific therapies against heightened systemic inflammation or resultant immunoparesis – key pathophysiological drivers of ACLF. The novel therapies outlined in this review illustrate potentially how rampant inflammation and immune cell paresis can be both minimized and modulated. Artificial liver devices to date have failed to replace endogenous hepatic function but do offer a potential for future research. Reliable biomarkers are needed for early detection and prognostication of ACLF and if used in conjunction with existing ACLF scores, may provide robust predictors of both the trajectory of ACLF and markers of response to gauge early intervention for a precision medicine-based approach. A multidisciplinary approach

Table 2. Artificial extracorporeal liver support devices used in ACLF*.

	Mechanism of action	Study	Biochemical improvement	Survival advantage	Comments
MARS	Albumin dialysis	Retrospective analysis (n = 101) [120]	Yes	No (reduced short-term mortality but effect deteriorated over time after discontinuation of therapy)	Adverse events include thrombocytopenia
		Case-control study (n = 73) [121]	Yes	No	Long follow up period of 6.5 yearsIn a cohort of patients with ALF and graft dysfunction
		Retrospective analysis (n = 69) [122]	Decreased ammonia -Worsening coagulopathy -Decreased phosphate and magnesium.	No	Both pediatric and adult patients. Median treatment time – 27 hours
		Prospective, observational study (n = 64)	Yes (RR in bilirubin – 25%) -No improvement in cytokine levels	No	Patients clinical characteristics on starting MARS predicted outcomes
		Prospective analysis (n = 53) [123]	Yes		Reduction in HE grades from grade 3 to 1 (n = 6, p < 0.001)
ELAD	Hepatoblastoma-derived C3A cells expressing growth factor and anti-inflammatory properties	Prospective, RCT (n = 203) [124]	No	No survival benefit in severe AH population with MELD scores ranging from 18–35.	In a subgroup of patients with MELD<28, ELAD was associated with non-significant trend of higher overall survival at 3 months (P = 0.08). Elevated INR and creatinine were predictors of a negative response to therapy.
Single pass albumin dialysis	Albumin dialysis	Retrospective analysis (n = 14) [125]	Weak correlation of decrease in total bilirubin induced by SPAD and amount of extracted total bilirubin -Strong correlation between SPAD and bile acid changes	No	Patients received *n*-acetylcysteine, antioxidant vitamins, terlipressin or norepinephrine.
		Retrospective analysis (n = 101) [126]	Yes (decrease in bilirubin and ammonia levels)	Reduced 30-day mortality in SMT+ECLS subgroup (p = 0.0238) but no difference in 3-month mortality.	High mortality (73.74%) but lower in comparison to SMT group (83.02%)
		Retrospective case control study (n = 13) [127]	Patients with paracetamol overdose but no improvement in clinical, physiological and biochemical parameters.	No	No anticoagulation was used. Observation period of 3 years
Plasma exchange		**Randomized, controlled trial (Single-center study) (n = 34) of HBV-associated ACLF** [135]		**Reduced 90-day (60% v 47%; p = 0.016) and 5-year (43% v 31%; p = 0.013) mortality compared to SMT**	**Definition of ACLF according to the Chinese guidelines; cirrhosis and multiorgan failure were not taken as mandatory criteria.**
SEPET™	Selective plasma filtration therapy	Case report [128]	Bilirubin reduction from 23.5 ± 3.7 to 16.4 ± 2.5 mg/DL and reduction of creatinine.		Only case control study in a 74-year-old man with hepatorenal syndrome. Lack of data for SEPET in literature.
Hemodiafiltration	Form of renal replacement therapy utilizing convective in combination with diffusive clearance.	Prospective study (n = 19) [129]	Improvement in bilirubin and ALT levels (p < 0.05)		Hemodiafiltration used only in combination with other plasma clearance techniques such as plasma exchange and hemoperfusion.
		Retrospective analysis (n = 110) [130]	Not analyzed and discussed.	Not mentioned	Analysis of recovery of consciousness receiving hemodiafiltration compared to plasma exchange.
Prometheus	Plasma separation, adsorption, resin and anion adsorbent	Randomized controlled trial (n = 145) [131]	Decreased serum bilirubin levels	No	
		Retrospective analysis (n = 114) [132]	Yes	Mortality in FPSA+OLT –33% vs 68% for FPSA without OLT.>90% mortality without FPSA and OLT	Improvement in GCS scale.
		Retrospective analysis (n = 23) [133]	Yes (reduction of median bilirubin levels 23.7 mg/dL to 15 mg/dL; P < 0.001)		ALF patients had better survival compared to AoCLF patients (44% vs 22%; p = 0.022)
		Prospective observational cohort (n = 12) [134]	Biochemical improvement in total bilirubin, cholic acid, ammonia, bile acid concentration, IL2 and IL6.		Broad inclusion criteria for AoCLF.

*Studies included have a minimum of 10 patients

Abbreviations: **ACLF, acute-on-chronic liver failure**; ALF, acute liver failure; ECLS, extracorporeal liver system; FPSA, fractionated plasma separation and absorption; GCS, Glasgow coma scale; HE, hepatic encephalopathy; IL, interleukin; MARS, molecular adsorbent recirculatory system; OLT, orthoptic liver transplantation; RR, relative risk; SMT, standard medical therapy; SPAD, single pass albumin dialysis

between hepatologists, allied health staff, intensive-care teams and palliative-care physicians remains paramount however in providing personalized care to patients with ACLF. The role of emergent liver transplant in settings where it is available needs to be comprehensively defined and validated with a particular focus on what constitutes futility. Current organ allocation systems clearly disadvantages patients with ACLF and national or even international strategies are required to prioritize ACLF patients with inherent high mortality for earlier access to transplantation. The role of liver transplantation in the management of this cohort is gaining traction, with increased acceptance of the benefits that can be derived by employing this judiciously. With improving understanding of pathophysiology, increased physician awareness and interest from pharmaceutical companies, a bright future to in management of this devastating syndrome look increasingly near.

Declaration of interests

A Chauhan is recipient of a Wellcome trust clinical fellowship and an NIHR clinical lectureship. A Chauhan has received consultation fees from Principia biopharma (now part of Sanofi). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This paper was not funded.

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