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GUIDELINES

A global consensus on the critical care management of acute-on-chronic liver failure patients: the APASL ACLF Beijing Position Paper

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Abstract

Background and aims Acute-on-chronic liver failure (ACLF) is a severe syndrome in patients with chronic liver disease, marked by rapid multi-organ failure and high short-term mortality. Managing ACLF requires intensive care, but standardized global guidelines were previously lacking. The APASL ACLF Research Consortium (AARC) developed this position paper to establish a unified, evidence-based consensus for its critical care management.

Methods A global collaboration of 109 experts employed a systematic methodology to address key aspects of ACLF care. Sections were drafted by specialist teams, with recommendations developed using the GRADE system. Draft statements underwent iterative review and refinement, followed by an expert panel consensus process consisting of open show-of-hands voting during the APASL Annual Conference in March 2025 in Beijing and a subsequent anonymous online voting round.

Results The consensus delivers 104 position statements. Key recommendations include using prognostic scores (AARC, CLIF-C ACLF, GIC) for ICU transfer and treatment decisions, and aggressively managing precipitating factors or complications like infections. It details organ-specific support for liver, kidney, and brain failure, advocating for early, targeted antibiotics and careful fluid management. The role of bridging therapies (plasma exchange, artificial liver systems) and nutritional support is emphasized. For transplantation, the guidelines provide criteria for patient selection and timing, particularly for alcohol-related ACLF.

Conclusions The APASL ACLF Beijing Position Paper provides a comprehensive, standardized framework for managing critically sick ACLF patients. Integrating multidisciplinary expertise and current evidence, these guidelines aim to optimize care, inform clinical decisions, and improve survival for this high-risk population. As a few recommendations are supported predominantly by data from different continents, they should therefore be interpreted in local contexts.

Keywords Acute-on-chronic liver failure · Critical care · Treatment · Position paper

Abbreviations

AARC	APASL ACLF Research Consortium
AASLD	American Association for the Study of Liver Diseases
ABILI	Age, TBIL, INR, LDH, and sIL-2R score
ACC	American College of Cardiology
ACLF	Acute-on-chronic liver failure
AH	Alcohol-associated hepatitis
AIH	Autoimmune hepatitis
AKI	Acute kidney injury
ALD	Alcohol-associated liver disease
ALSS	Artificial liver support system
AMR	Antimicrobial resistance
ATN	Acute tubular necrosis
BCAA	Branched-chain amino acid
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CHB	Chronic hepatitis B
COSSH	Chinese Group on the Study of Severe Hepatitis B
CMV	Cytomegalovirus
CRRT	Continuous renal replacement therapy
CVP	Central venous pressure
DEXA	Dual-energy X-ray absorptiometry
DM	Diabetes mellitus
EASL-CLIF	European Association for the Study of the Liver-Chronic Liver Failure
EBV	Epstein–Barr virus
ECG	Electrocardiogram
ESBL	Extended-spectrum beta-lactamase

FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FMT	Fecal microbiota transplantation
GI	Gastrointestinal
GIC	Globulin, IL-6, and CRP score
GM	Galactomannan
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV	Hepatitis B virus
HDU	High dependency unit
HE	Hepatic encephalopathy
HNA2	Human nonmercaptalbumin-2
HRS	Hepatorenal syndrome
HSV	Herpes simplex virus
HVPG	Hepatic venous pressure gradient
IA	Invasive aspergillosis
IC	Invasive candidiasis/candidemia
ICU	Intensive care unit
IFI	Invasive fungal infection
IMAR	Ischemia-modified albumin ratio
INR	International normalized ratio
LCMS	Liquid chromatography–mass spectrometry
LDLT	Living donor liver transplantation
LoE	Level of evidence
LT	Liver transplantation
MAFLD	Metabolic dysfunction-associated fatty liver disease
MALDI-TOF	Matrix-assisted laser desorption/ionization time-of-flight
MAP	Mean arterial pressure
MASLD	Metabolic dysfunction-associated steatotic liver disease
MDRO	Multidrug-resistant organism
MELD	Model for end-stage liver disease
MRSA	Methicillin-resistant *Staphylococcus aure*us
MVP	Modest volume paracentesis
NGAL	Neutrophil gelatinase-associated lipocalin
NPO	Nil per oral
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSBBs	Non-selective beta-blockers
PAOP	Pulmonary artery occlusion pressure
PCR	Polymerase chain reaction
PE	Plasma exchange
PICD	Paracentesis-induced circulatory dysfunction
PK/PD	Pharmacokinetics/pharmacodynamics
POCUS	Point-of-care ultrasonography
PT	Prothrombin time
PTFE	Polytetrafluoroethylene
RCT	Randomized controlled trial
REE	Resting energy expenditure
ROTEM	Rotational thromboelastometry
RRT	Renal replacement therapy
SBP	Spontaneous bacterial peritonitis
SCTs	Standard coagulation tests
SIRS	Systemic inflammatory response syndrome
TACO	Transfusion-associated circulatory overload
TEG	Thromboelastography
TIPS	Transjugular intrahepatic portosystemic shunt
TPPM	Tongji Prognosis Prediction Model
TRALI	Transfusion-related acute lung injury
UTI	Urinary tract infection
VETs	Viscoelastic tests
VRE	Vancomycin-resistant Enterococcus
vWF	Von Willebrand Factor

Introduction

Acute-on-chronic liver failure (ACLF) is a severe clinical syndrome that arises in patients with pre-existing chronic liver disease following an acute hepatic insult. This condition is characterized by a rapid progression to hepatic and frequently extrahepatic organ failure, resulting in high short-term mortality. Recent simplifications in classification have led to the categorization of ACLF into types A and B. Type A ACLF includes patients with underlying chronic liver disease or cirrhosis who experience a first acute insult and present with liver failure. Type B refers to patients with decompensated cirrhosis, with prior or current decompensation, presenting with liver failure [1]. It should be recognized that ACLF is a unique clinical syndrome, but its diagnostic frameworks and patient populations may differ across regions. The Asian Pacific Association for the Study of the Liver (APASL) definition emphasizes an acute hepatic insult in patients with chronic liver disease [1], whereas the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) framework focuses on acute decompensation in cirrhosis associated with extrahepatic organ failure and high short-term mortality [2]. North American definitions have similarly placed greater emphasis on extrahepatic organ failures in hospitalized patients with cirrhosis [3]. Although the definitions of ACLF are not unified yet across regions, the intricate pathophysiology and swift clinical deterioration associated with ACLF demand intensive management, ideally within a specialized intensive care unit (ICU). The ICU's role is pivotal, providing a setting for advanced monitoring, sophisticated organ support, and the integration of multidisciplinary expertise.

The core of ACLF is profound hepatic dysfunction, which precipitates a cascade of events including systemic

inflammatory response syndrome (SIRS), coagulopathy, and subsequently failure of other organs (Fig. 1). ICU management, therefore, involves serial assessment of hepatic function, continuous neurological monitoring for hepatic encephalopathy (HE), and aggressive management of renal complications like hepatorenal syndrome (HRS), often requiring continuous renal replacement therapy (CRRT). Cardiopulmonary instability is common, necessitating advanced hemodynamic support with mechanical ventilation and vasopressors. The immunocompromised state of these patients heightens their susceptibility to sepsis, mandating prompt diagnostic cultures and early administration of antibiotics. Furthermore, managing metabolic dysfunction and meeting heightened nutritional demands are fundamental components of comprehensive care.

Beyond initial stabilization, the ICU functions as a critical hub for bridging patients to liver transplantation (LT). It allows for continuous monitoring of organ function, identifying signs of recovery or further deterioration to enable timely listing for transplantation.

In response to the global challenge posed by ACLF, the APASL, through its ACLF Research Consortium (AARC), initiated a worldwide collaborative effort to establish a consensus on critical care management. 109 experts from across the globe were invited to participate. A systematic, multi-layered methodology was employed, with the level of evidence (LoE) and Grade of Recommendations based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 1). Section chiefs prepared preliminary documents and recommendations after detailed deliberations. These were collated, rigorously reviewed, refined, and ultimately presented at the APASL Annual Conference in Beijing on March 29th, 2025. This process culminated in the 'APASL ACLF Beijing Position Paper,' a unified global framework that incorporates the knowledge of 109 international experts.

Methods

To support the preparation of this expert consensus, a narrative literature review was performed in PubMed/MEDLINE for studies published in English up to March 2025. Following comments from the reviewers and subsequent panel discussions, the literature base was further updated to include relevant studies published up to April 2026. Search terms included combinations of keywords related to ACLF and relevant management domains, such as infection, multidrug-resistant organism (MDRO), fungal infection, viral sepsis, acute kidney injury (AKI), HE, coagulation failure, gastrointestinal (GI) bleeding, transjugular intrahepatic portosystemic shunt (TIPS), artificial liver support system (ALSS), LT, obesity, diabetes, underling chronic liver diseases of viral hepatitis, alcohol-associated liver disease (ALD), autoimmune hepatitis (AIH), and metabolic dysfunction-associated steatotic liver disease (MASLD).

The consensus cited studies were derived from Europe (79/222, 35.6%), Asia-Pacific (77/222, 34.7%), North America (37/222, 16.7%), global or multinational studies (25/222, 11.3%), Latin America (3/222, 1.4%), and Africa/Middle East (1/222, 0.5%). This finding indicate that the evidence base for this guideline is geographically broad and includes substantial contributions from regions worldwide.

Priority was given to international guidelines, consensus statements, randomized clinical trials, multicenter cohort studies, systematic reviews, and landmark observational

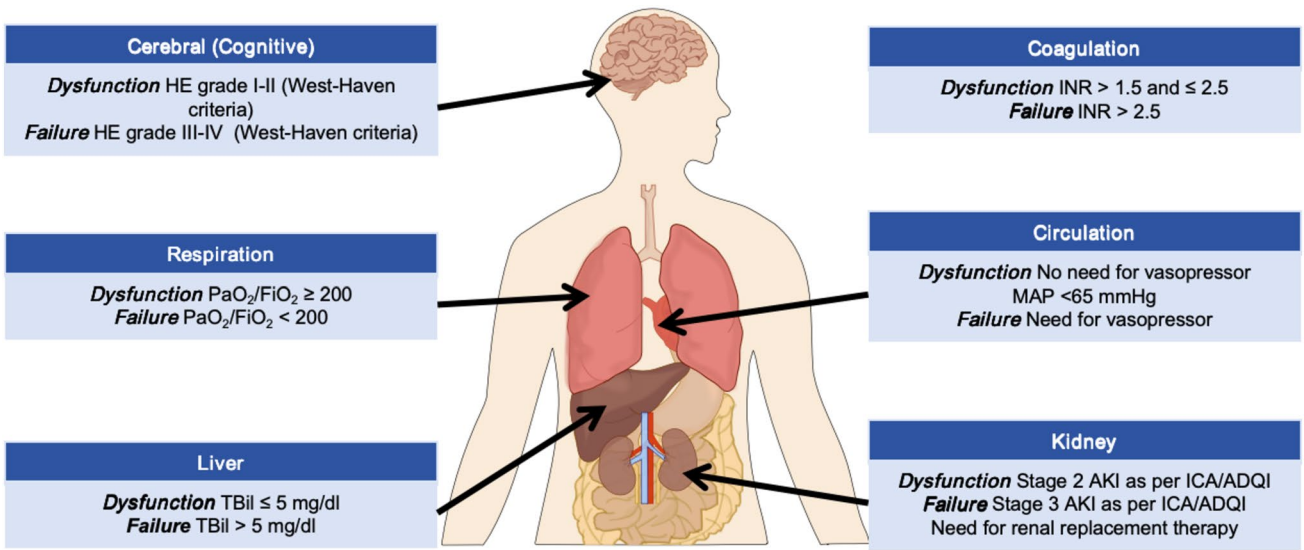

Fig. 1 Organ dysfunction and organ failure in ACLF

studies directly relevant to the clinical questions addressed in this manuscript. In addition, reference lists of selected articles were manually reviewed to identify further relevant studies. The identified evidence was reviewed narratively by section chiefs and panel members and used to inform statement development and expert discussion.

The consensus development began with initial deliberations, after which a concept document was distributed to all contributing experts. This initial step confirmed broad alignment on the necessity to refine diagnostic criteria for early-stage chronic liver disease as a foundational move towards improved patient stratification, optimized clinical trial design, and precision management.

Subsequently, a draft position statement was developed and circulated among the expert panel for review. The document was then refined iteratively based on structured feedback from the panel members. To achieve formal consensus on the proposed criteria, an expert panel consensus process was implemented (Figure S1). In the first round, the proposed diagnostic and treatment items and approaches were discussed during the APASL meeting and subjected to on-site show-of-hands open voting by the expert panel. In the second round, the revised statements were circulated to all participating experts through an anonymous online questionnaire for further voting and comment, with a response rate of 66%. Consensus for each recommendation was predefined as $\geq 75\%$ agreement. Statements requiring further refinement after Round 1 were revised on the basis of panel feedback and then reassessed in Round 2. Statements that did not reach the predefined threshold in Round 2 were further revised or deleted before incorporation into the current version of the manuscript. Detailed Round 2 voting results for individual statements are presented in Table S2, and the demographic and professional characteristics of the experts who participated in Round 2 are summarized in Table S1. In specific statements, the panel deviated from strict GRADE interpretation when the potential benefit was considered sufficiently compelling despite the limited certainty of direct evidence. Statement-specific justifications for this weak-evidence but strong-recommendation pairings are provided in the Supplementary Appendix.

Summary of recommendations and implementation considerations

Prognostic models for treatment decision and ICU transfer in ACLF

The decision to admit a patient with ACLF to the ICU or a general ward from the emergency department can be guided by prognostic models and the presence of organ dysfunctions. It is important to note that the outcome of ACLF patients is more accurately predicted by their clinical course than by the initial grade of ACLF at presentation [4, 5]. Given the severity of ACLF and the established efficacy of LT as a therapeutic option, early and precise prognostic assessment is imperative [6] The Aachen ACLF ICU score has been reported as an easy-to-use tool for predicting ICU mortality in this population, though its predictive performance requires further validation [7].

ACLF patients typically present with a higher incidence of organ dysfunction upon admission compared to the general ICU population [8]. While more patients with cirrhosis are being admitted to ICUs, survival rates are concurrently increasing [9]. A key consideration is that organ dysfunction in ACLF is often reversible, and these patients should be viewed as candidates for survival improvement upon ICU admission [10].

Position statements

1. ACLF patients with advanced encephalopathy, severe GI bleeding, coagulopathy and sepsis, requiring vasopressors, mechanical ventilation system, or renal replacement therapy (RRT) should be managed in the ICU. (LoE—high, recommendation—strong).
2. Prognostic models in ACLF like APASL AARC score, CLIF-C ACLF score, NACSELD ACLF Score, MELD-Lactate Score, TPPM score and COSSH-ACLF score are helpful for treatment decisions and ICU transfer. (LoE—high, recommendation—strong).
3. Dynamic assessment of prognostic models, i.e., serial assessment at days 0, 3, 7, and 14, and when clinically indicated, helps in accurately predicting the need for further organ support. (LoE—moderate; recommendation—strong).

Strategies for identification and prevention of organ failure in ACLF

ACLF is marked by liver and/or other organ failures and carries a high short-term mortality. Systemic inflammation is widely proposed as a major pathophysiological driver [11]. The concept of "Pre-ACLF" [12], as defined by EASL-CLIF, describes a group of patients who are free of organ failure at presentation but develop it during follow-up. These patients are characterized by intense underlying systemic inflammation that drives the development of organ failure in the short term (e.g., within 28 days). This state often correlates with an AARC score of < 5, where only liver failure (bilirubin 5–15 mg/dL) is present without other organ failures. Early recognition and intervention in these "Pre-ACLF" patients could represent a major strategy for preventing full-blown organ failure.

Identifying risk factors for organ failure in patients with decompensated cirrhosis is a critical component of management for prevention. Bacterial infection and systemic inflammation are common independent risk factors [13, 14]. Models such as the GIC score and the ABILI score help identify patients at increased risk of infection and adverse outcomes, thereby facilitating earlier risk stratification and closer monitoring for hepatitis B virus (HBV)-related cases [15, 16]. The exploration of biomarkers through omics technology for predicting "Pre-ACLF" is another promising avenue. The CATCH-LIFE study has developed a liquid chromatography–mass spectrometry (LCMS) test based on novel metabolites for HBV-related cases [17], now being implemented in Chinese labs. Concurrently, the CLIF-SIG score uses immune gene expression to gauge inflammation severity [18].

Position statements

4. Identification and prevention of risk factors for development of organ failure including avoiding use of nephrotoxic antibiotics and drugs is a critical part of management of ACLF patients. GIC score can be used to predict the risk of bacterial infections and ABILI score can be used to predict the risk of mortality in HBV-ACLF complicated with bacterial infections. (LoE—moderate; recommendation—strong).
5. Prompt treatment of precipitating factors like viral hepatitis, alcohol, drug-induced liver injury, infections, and GI bleeding can prevent the progression of ACLF and reduce the risk of organ failure. (LoE—moderate; recommendation—strong).
6. Optimizing hemodynamic stability by vasopressors, cautious use of albumin infusion, and judicious fluid management to maintain tissue perfusion and avoid volume overload is advised. Avoiding cumulative positive balance through excessive fluid resuscitation is encouraged to prevent pulmonary edema. (LoE—moderate; recommendation—strong).
7. Early non-invasive ventilation can prevent hypoxemia-related syndrome in hypoxemic patients. (LoE—moderate; recommendation—strong).
8. Empirical antibiotics based on local antibiogram should be initiated for suspected bacterial infections, such as spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), pneumonia. (LoE—moderate; recommendation—strong).
9. Adequate nutritional support is vital for preventing organ failure in ACLF. Enteral nutrition is preferred to maintain mucosal integrity and reduce the risk of bacterial translocation. (LoE—low; recommendation—strong).
10. Branched-chain amino acid (BCAA)-enriched formulas are preferred in malnourished patients. Avoiding fasting, providing small, frequent meals may prevent catabolism. (LoE—low; recommendation—weak).
11. Non-selective beta-blockers (NSBBs) such as propranolol and carvedilol reduce portal pressure, can prevent variceal bleeding, improve survival, and reduce the severity of systemic inflammation in a subgroup of patients. Decision to start NSBBs in patients with ACLF should be made on a case-by-case basis. (LoE—high; recommendation—strong).
12. Novel biomarkers, e.g., von Willebrand factor (vWF) and CLIF-SIG score may help to assess disease progression or response to treatment. (LoE—low; recommendation—weak).

Ascites and its complications in ACLF—need for new definitions and approach

The management of ascites in ACLF patients is considerably more complex than in those with decompensated cirrhosis. This complexity stems from a more severe pathophysiological state in ACLF, characterized by a greater degree of systemic inflammation and oxidative stress [19]. Consequently, patients exhibit more severe hyperdynamic circulation, microcirculatory disturbances, a marked increase in plasma renin activity, and reduced systemic vascular resistance and arterial pressure [20]. This makes them more prone to ascites-related complications such as refractory ascites, paracentesis-induced circulatory dysfunction (PICD), bacterial infections, and AKI [21].

PICD is common in ACLF and can develop even after modest volume paracentesis (MVP) [22]. Albumin infusion has been shown to significantly decrease the incidence of PICD (30% versus 70%) and is associated with a lower incidence of HE, hyponatremia, AKI, and mortality [22].

AKI in cirrhosis can arise from prerenal, intrarenal, or postrenal causes, with hypovolemia and bacterial infections being the most common precipitating events [2, 23]. Tailoring treatment to the specific cause is essential. For prerenal AKI, volume resuscitation with albumin is recommended [24]. Supportive care and discontinuation of nephrotoxic agents are key for acute tubular necrosis (ATN) or cholemic nephropathy [24]. Vasoconstrictor therapy is the mainstay for HRS-AKI, with responsiveness determined by factors such as timing of initiation, degree of cholestasis, and the number of organ failures [24, 25]. For patients with ACLF and AKI stage 3, initiating early CRRT or plasma exchange (PE) may be beneficial [26].

Current definitions and management strategies for ascites in ACLF are largely based on guidelines for decompensated cirrhosis, which may not fully address the unique challenges

of ACLF. In this context, the term "acute portal hypertension syndrome" may be considered a proposed clinical construct to describe the rapid development of ascites, variceal bleeding, and systemic complications in some patients with ACLF [1]. However, this concept has not yet been formally validated, and standardized diagnostic criteria, prevalence data, and prospective studies are still needed before it can be established as a distinct clinical entity. Nevertheless, this framework may be useful in identifying high-risk patients and guiding early interventions. The approach of MVP, involving the removal of 3–5 l of ascitic fluid to minimize PICD risk, should be incorporated into the management of ascites in ACLF. This strategy, when combined with albumin infusion, can prevent circulatory dysfunction and improve patient outcomes.

Position statements

13. Acute portal hypertension syndrome may be recognized as a pathophysiological feature of ACLF, inducing rapid development of ascites, variceal bleeding, and other complications. (LoE—moderate; recommendation—weak).
14. Albumin should be given even after MVP, i.e., less than 5 l of ascitic fluid to minimize the risk of PICD. (LoE—moderate; recommendation—strong).
15. Early diagnosis and prompt antibiotic therapy are crucial for managing SBP and preventing further complications. (LoE—high; recommendation—strong).
16. Early initiation of terlipressin within 12–24 h for AKI with albumin infusion helps in reducing short-term mortality. (LoE—high; recommendation—strong).
17. In patients with ACLF, ascites, and AKI stage 3, it is advisable to consider initiating early CRRT, in a case-by case selection. (LoE—moderate; recommendation—strong).

The role of high dependency unit (HDU) in the management of ACLF

Currently, ACLF patients are typically managed either in the ICU or the general ward. However, given the scarcity and high cost of ICU resources, and considering that some patients may prefer not to be treated in the ICU, an alternative is needed. The level of care in a general ward is often insufficient for the close monitoring these patients require. HDUs offer an intermediate level of care between general wards and ICUs, functioning as both 'step up' and 'step down' units, and should be considered a viable option for managing select ACLF patients.

Position statement

18. HDU provides an intermediate level of care between general ward and the ICU. HDU care may be most suitable for ACLF patients who do not require mechanical ventilation. (LoE—low; recommendation—weak).

Preventing infection in ACLF

Cirrhosis itself is a significant risk factor for bacterial and fungal infections due to a disrupted immune system, leading to hospitalization and complicating hospital admissions in up to 40% of cases [27]. Infections can exacerbate liver synthetic function and trigger complications like variceal bleeding, HE, AKI, and multi-organ failure, all contributing to high mortality [28]. The development and number of extrahepatic organ failures are key determinants of survival in infection-driven ACLF [29]. Whether the etiology of the underlying liver disease contributes to the risk of infection in ACLF is worth further investigation.

Appropriate first-line antibiotic treatment for documented bacterial infections was associated with a lower rate of ACLF development and lower 90-day mortality [30]. It is noteworthy that while antibiotics control infections, they do not necessarily lower mortality in severe alcohol-associated hepatitis (AH) and ACLF [30–32]. These data support a policy of prompt de-escalation or discontinuation of empirical antibiotics, guided by culture sensitivities at 24–48 h after commencement, if no infection is confirmed and the patient's trajectory is improving [32].

Infection risk in the development of ACLF should also be interpreted in the context of the underlying liver disease etiology. In comparison with chronic hepatitis B (CHB), patients with AIH-related chronic liver disease may develop ACLF either due to hyperacute exacerbation of previously unrecognized AIH or in response to a second exogenous insult, such as viral, drug-induced, or toxic injury, superimposed on established AIH. Because long-term immunosuppressive therapy may increase vulnerability to infection, greater attention to infectious complications is warranted in this subgroup. Reported data suggest that bacterial infection prior to hospital admission may be more common in AIH patients who develop ACLF, especially involving the respiratory tract and peritoneum. Therefore, preventive strategies, including vaccination, early infection surveillance, and avoidance of potentially

hepatotoxic triggers, should be emphasized where appropriate [33].

Position statements

19. Patients with alcohol-associated ACLF are highly susceptible to bacterial and fungal infections, which are linked to the development of organ failures and increased mortality. (LoE—high; recommendation—strong).
20. Patients with alcohol-associated ACLF who are treated with steroid or other immunosuppressant therapies are particularly prone to developing infections, especially fungal infections. (LoE—high; recommendation—strong).
21. Antibiotics reduce infections but do not lower mortality in severe AH and ACLF. (LoE—high; recommendation—strong).
22. In hospitalized patients with acutely decompensated cirrhosis patients, empirical antibiotics do not prevent hospital-acquired infection. (LoE—high; recommendation—strong).
23. Antibiotics should be discontinued for hospitalized patients with ACLF if no infection is identified (guided by culture sensitivities at 24–48 h after commencement) and if the patient is showing improvement. (LoE—high; recommendation—strong).
24. Patients hospitalized with cirrhosis experience a high incidence of antimicrobial resistance (AMR), which justifies antimicrobial stewardship. (LoE—high; recommendation—strong).

Prevention of AKI in ACLF

Preventing AKI in ACLF presents a significant challenge, with limited evidence on specific strategies. However, several key recommendations can be made. First, it is crucial to avoid potentially nephrotoxic medications, particularly nonsteroidal anti-inflammatory drugs (NSAIDs), iodinated contrast agents, and certain antibiotics [34, 35]. Second, optimizing hemodynamics is essential, which includes the judicious use of antihypertensives and beta-blockers [36–38]. Volume status should be managed carefully using intravenous fluids, ideally guided by point-of-care ultrasound to prevent both hypovolemia and volume overload [39]. Avoiding extended periods of nil per oral (NPO) status can prevent iatrogenic harm. Close monitoring for the early initiation of vasopressors is vital when sepsis or cardiovascular dysfunction is present [25, 40]. Third, early recognition and management of infections are paramount [41, 42]. Collectively, these approaches aim to minimize renal injury and improve outcomes in ACLF patients.

Position statements

25. Critical pillars in the management of AKI in ACLF include avoiding nephrotoxic agents, maintaining hemodynamic stability, and ensuring effective infection control. (LoE—high; recommendation—strong).
26. Prevention of AKI requires a multidisciplinary approach that integrates hemodynamic management, infection control, and judicious introduction of procedural interventions to address critical complications in ACLF. (LoE—high; recommendation—strong).

Managing ACLF with obesity and diabetes mellitus (DM) comorbidities

With the rising global obesity epidemic, an etiological shift in ACLF is expected, as MASLD is rapidly becoming the most common chronic liver disease worldwide [43, 44]. Large cohort data from North America have identified severe obesity as a risk factor for ACLF development in patients with decompensated cirrhosis [45]. North American cohort data also suggest that obesity is independently associated with an increased risk of infection in hospitalized patients with advanced liver disease [46], further highlighting the clinical relevance of metabolic dysfunction in this population. Studies have also revealed that DM is associated with higher rates of infections and worse outcomes compared to non-DM patients [47, 48]. Prognostic tools like the metabolic dysfunction-associated fatty liver disease (MAFLD)-MELD-Na and MAFLD-AARC scores have been developed to effectively predict 90-day mortality in this subgroup [45, 49]. Poorly controlled DM and obesity are considered as relative contraindications for LT in some centers [50].

Adequate measures to control blood sugar levels must be implemented, as aggressive management can positively influence outcomes [51]. Post-transplant diabetes and metabolic comorbidities significantly influence post-transplant outcomes, emphasizing the need for vigilant monitoring and early intervention. Significant gaps remain in consensus regarding DM-specific treatment protocols and comparative outcomes data for this patient population.

In patients with MASLD- or obesity-associated ACLF, management should take into account the high burden of metabolic comorbidities, including diabetes, cardiovascular risk, infection susceptibility, and sarcopenic obesity. Clinical care should therefore emphasize individualized glycemic control, early infection surveillance, nutritional assessment, and careful transplant evaluation [52, 53]. However, evidence supporting MASLD-specific

management algorithms in ACLF remains limited, and further studies are needed to develop more specific and actionable recommendations for this growing patient population.

Position statement

27. In patients with ACLF and comorbidities, particularly obesity and DM, management should emphasize early identification and treatment of precipitating events, careful glycemic control, infection surveillance, and tailored nutritional and organ support, along with timely assessment for LT. (LoE—high; recommendation—strong).

Algorithmic management of MDR bacterial infections

The protocol for clinical manifestations and diagnosis of infection in patients with ACLF is as shown in Fig. 2. ACLF patients are particularly susceptible to MDROs such as extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae,

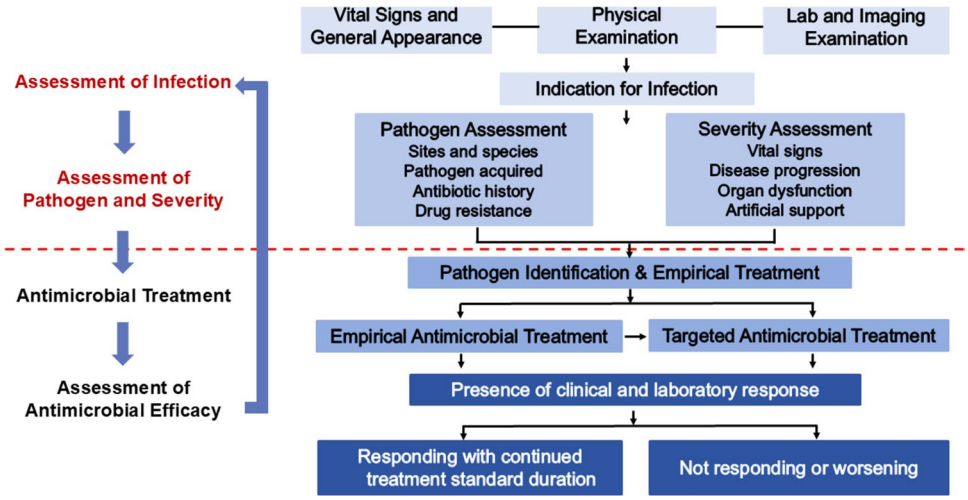

Fig. 2 Protocol for clinical manifestations and diagnosis of infection in ACLF

Table 1 Level of evidence and grade of recommendation used for the guideline development

	Level of evidence[a,b]	Confidence in the evidence
High	Information obtained from meta-analyses or systematic reviews, or from numerous randomized trials that have high-quality data	It is improbable that additional research will significantly alter our level of confidence in the assessment of potential benefits and risks
Moderate	Information obtained from either a singular randomized controlled trial (RCT) or various non-randomized studies	Additional research, if conducted, may potentially alter our estimation of the benefit and risk and have an impact on our level of confidence in the estimate
Low	Studies of limited sample size, observational studies conducted retrospectively, and registries	There is a degree of uncertainty associated with any estimate of the effect
	Recommendations—Grade[c]	Wording associated with the grade of recommendation
Strong	The strength of the recommendation was influenced by several factors, such as the quality of the evidence, the presumed outcomes that are important for the patient, and the cost implications	"must", "should", or "we recommend
Weak	The recommendation may be made with less certainty and may result in higher costs or resource consumption due to variability in preferences and values, or increased uncertainty	"can", "may", or "we suggest

[a]To make the GRADE system more objective, the type of studies from which the evidence are derived have been mentioned in the Level of Evidence

[b]Level was graded down if there was a poor quality, strong bias or inconsistency between studies; level was graded up if there was a large effect size

[c]Recommendations reached by consensus of the members and included the quality of evidence, presumed patient-important outcomes and costs

Carbapenemase-producing Enterobacteriaceae, Carbapenem-resistant non-fermentative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE). Major risk factors include nosocomial episode, recent hospitalization (within 3 months), recent systemic antibiotics exposure (within 1–3 months), recent invasive procedures (within 1 month), ICU admission, and recent infection or colonization by MDROs (within 6 months) [54].

Failure of empirical antibiotic treatment due to AMR leads to poor prognosis and higher mortality. The implementation of aggressive strategies has been suggested, including the prescription of broad-spectrum antibiotics covering all potential pathogens and pharmacokinetic optimization [55, 56]. This approach requires the implementation of epidemiological surveillance programs, including periodic rectal and nasal swabs, to adapt empirical antimicrobials to local resistance patterns [57].

Within 48–72 h after admission, clinicians should re-evaluate the infection and adjust antibiotic strategies based on bacterial culture results. Rapid microbiological tests (polymerase chain reaction [PCR], matrix-assisted laser desorption/ionization time-of-flight [MALDI-TOF]) are essential for implementing these strategies, as they allow for rapid bacterial identification and the initiation of de-escalation policies [54]. In the absence of positive blood cultures, colonization swab results should be used to de-escalate initial broad-spectrum antibiotics, especially if patients are not colonized by MDROs.

Position statements

28. Empirical antibiotic strategies must be adapted to the local ecology covering all potential pathogens in patients with ACLF or septic shock, including MDRO in case of nosocomial infection. (LoE—high; recommendation—strong).
29. Patients with severe infections probably benefit from strategies that optimize the pharmacokinetic/pharmacodynamic (PK/PD) of the antibiotics, especially continuous infusion in the case of beta-lactams and high-loading dose. (LoE—high; recommendation—strong).
30. Epidemiological surveillance programs (assessing potential MDRO carriers) could guide empirical antibiotic strategies. (LoE—moderate; recommendation—strong).

Fungal infection in ACLF-biomarkers for diagnosis and management

Although likely underdiagnosed, invasive fungal infections (IFI) are present in approximately 4% of patients with decompensated cirrhosis and are associated with a poor prognosis. IFIs are observed more frequently in patients with ACLF [2, 57–64].

Invasive candidiasis/candidemia (IC) is the most common IFI (70–90%), followed by invasive aspergillosis (IA) (10–20%, mostly as invasive pulmonary aspergillosis) [2, 57–61]. Furthermore, IFIs are a major contraindication for LT and a frequent cause of delisting. Any clinical deterioration, such as new-onset AKI, altered mental status, or new organ dysfunction/failure, should prompt an immediate evaluation for IFIs [1, 65].

The diagnosis of IFIs is categorized as proven, probable, or possible, based on host factors, clinical features, and mycological evidence, which includes fungal biomarkers [2, 57–60, 66–68]. IC is diagnosed by the isolation of *Candida* species from blood cultures or normally sterile body fluids [2]. Complementary diagnostic biomarkers include serological markers like 1,3-β-D-glucan, mannan, and anti-mannan, as well as molecular assays such as the T2Candida panel [61, 66]. Echinocandins are the first-line antifungal agents for IC [68].

IA diagnosis requires respiratory culture and radiological evidence [2], as serum biomarkers (e.g., 1,3-β-D-glucan/galactomannan [GM]) perform suboptimally [68]. First-line agents for IA include voriconazole, isavuconazole, and liposomal amphotericin B [68–71].

Given the poor prognosis, some experts advocate for antifungal prophylaxis in high-risk populations, though the type and duration remain undefined [61]. Any empirical approach should be followed by rapid de-escalation if fungal infection is not confirmed. Two consecutive negative BDG test results can be used as a criterion to safely discontinue antifungal therapy [2, 72].

Position statements

31. IFI is not uncommon in patients with ACLF and is associated with a high-risk of mortality. Any clinical and biochemical deterioration should prompt an evaluation for infection, including IFI. (LoE—high; recommendation—strong).
32. The diagnosis of IFI in ACLF can be classified as proven, probable, or possible, based on host factors, clinical features, and mycological evidence. (LoE—moderate; recommendation—strong).
33. Fungal biomarkers, including 1,3-β-D-glucan and GM, can support the diagnosis of IFIs and have high negative predictive value. (LoE—moderate; recommendation—strong).
34. Echinocandins are the preferred antifungal agents for the treatment of invasive candidiasis. (LoE—moderate; recommendation—strong).
35. For IA, liposomal amphotericin B should be considered, as with lower hepatic toxicity, but potential

nephrotoxicity. Voriconazole could be adopted with dosage adjustment based on MELD score. (LoE—low; recommendation—weak).

Viral sepsis in ACLF

Recently, viral sepsis has been increasingly recognized as a critical driver of organ failure and mortality [2]. Viral infections complicating ACLF mainly include cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus (HSV), influenza virus, and SARS-CoV-2 [73–76]. Viremia can cause bone marrow suppression, predisposing patients to secondary bacterial or fungal infections. Additionally, viral disruption of the respiratory and intestinal barriers can lead to infections by colonizing pathogens [77, 78].

Early and timely diagnosis and treatment are beneficial. Viral screening in critically ill patients is recommended, and prophylactic antiviral therapy should be considered in high-risk populations. Upon a positive detection, targeted antiviral therapy is strongly recommended (e.g., ganciclovir/valganciclovir for CMV) [79]. Adjustment of antiviral agents is necessary if resistant viruses are detected. Immunomodulation with corticosteroids remains controversial but may benefit patients with hyperinflammation. Supportive care, including oxygen therapy and CRRT, is advised for relevant organ dysfunction.

Position statements

36. Viral infection (e.g., SARS-CoV-2) should be considered when unexplained fever, influenza-like illness, or signs suggestive of specific pathogens (such as cytopenia, ground-glass opacities, upper respiratory tract involvement) are present, particularly if accompanied by elevated lactate levels or worsening organ function. (LoE—high; recommendation—strong).
37. Viral sepsis in ACLF necessitates tailored strategies combining rapid virologic diagnosis, timely therapy, and holistic care. (LoE—high; recommendation—strong).

Management of renal dysfunction or failure

The conventional approach has primarily highlighted HRS-AKI, a functional, vasoconstrictive form of AKI that significantly impacts mortality [80].

Urine biomarkers can serve as point-of-care tests to differentiate between functional (like HRS) and structural (like ATN) causes of AKI. Urinary neutrophil gelatinase-associated lipocalin (NGAL) at a cutoff of > 220 μg/g creatinine demonstrated high accuracy for differentiating ATN from other forms of AKI, including HRS-AKI [81].

Current therapies for HRS-AKI consist of vasoconstrictor therapy combined with albumin. Albumin effectively prevented type 1 HRS in patients with SBP when administered at 1.5 g/kg on day one, followed by 1 g/kg for three days [82]. Terlipressin combined with albumin is recommended as it is more effective than placebo with albumin at reversing HRS-AKI [40, 83–85]. The typical initial dose is 1 mg every 4–6 h, which can be escalated up to 12 mg/day depending on the response, for up to 14 days. A randomized controlled trial (RCT) by Jindal et al. indicated that in ACLF patients, early administration of terlipressin for AKI persisting beyond 12 h of albumin volume expansion reduces short-term mortality and promotes early AKI reversal with concomitant regression of the ACLF stage [39]. A main safety concern of terlipressin is the potential development of respiratory complications, possibly related to diastolic dysfunction from cirrhotic cardiomyopathy and fluid overload from albumin infusion [40].

Position statements

38. In patients with ACLF, a prompt diagnosis of HRS-AKI should be made after ruling out alternate causes of AKI. (LoE—high; recommendation—strong).
39. Terlipressin bolus or infusion combined with intravenous albumin is the first line of treatment for HRS-AKI and must be used with caution in patients with grade 3 ACLF or patients with known cardiac dysfunction or respiratory conditions. (LoE—high; recommendation—strong).

RRT in ACLF: challenges and guidance

The progression of AKI in ACLF is rapid, and a higher proportion of patients develop stage 3 AKI requiring RRT [86]. Elevated NGAL levels, combined with liver severity scores, could accurately identify patients who are non-responders to terlipressin and will require RRT [87, 88]. Apart from terlipressin non-response, RRT is indicated for failure of standard medical treatment, as organ support for persistent encephalopathy and circulatory dysfunction, and as a bridge to LT [42].

Performing RRT in ACLF patients presents several challenges, including a lack of clear survival benefit, an increased risk of intradialytic hypotension, difficulties with safe vascular access and anticoagulation in the context of coagulopathy and thrombocytopenia, and the risk of dialysis disequilibrium syndrome, which may worsen encephalopathy. Furthermore, there are no specific guidelines on dosing,

intensity, exact timing, or assessment of dialysis adequacy, including stopping rules [89].

Ultimately, cost, resource availability, and unit expertise often guide the decision. Anticoagulation-free protocols are generally preferred. The safety of regional citrate anticoagulation is not firmly established in ACLF patients [90, 91].

Position statements

40. RRT should be initiated in patients with ACLF who have non-response to vasoconstrictors and in those with clear indications for RRT (advanced azotemia, metabolic acidosis, hyperkalemia, and volume overload non-responsive to diuretics). (LoE—moderate; recommendation—strong).
41. CRRT is preferred over intermittent modes of RRT in patients with ACLF, especially in those with multiorgan failure and hemodynamic instability. (LoE—low; recommendation—weak).
42. NGAL may be used to identify patients with ATN who may require RRT in cases of terlipressin non-response. (LoE—low; recommendation—weak).

Management of cognitive dysfunction in ACLF patients

Cognitive dysfunction management is complicated by diagnostic challenges, as altered mental status in cirrhosis can result from various conditions beyond HE, including metabolic disorders, infections, neurological events, and drug-related factors [92, 93].

During acute episodes, clinicians must balance effective treatment with avoiding complications like aspiration pneumonia, dehydration from excessive lactulose, and medication discontinuity upon discharge [94, 95]. Laboratory markers provide limited diagnostic certainty. In one study, plasma ammonia levels > 100 µmol/L predicted the onset of severe HE with 70% accuracy [96, 97]. Normal ammonia levels may help exclude HE in patients with altered consciousness [98]. Recent studies suggest that low serum thyroxine (Total T4 and fT4) may be an early biomarker for predicting progression to severe HE in ACLF [99, 100].

Despite its significant impact on outcomes, HE often receives inadequate priority in transplant allocation systems, with research showing that pre-transplant HE severity correlates with post-transplant cognitive impairment [101–103]. Several promising therapeutic approaches are under investigation, including rifaximin soluble solid dispersion (SSD), fecal microbiota transplantation (FMT), golexanolone, intravenous albumin, and LPCN 1148 [93, 104, 98]. Cases of "refractory HE" often involve an incorrect diagnosis, missed precipitating factors, insufficient treatment of underlying causes, or persistent portosystemic shunting that may benefit from embolization in select patients with low MELD scores [105, 106]. Comprehensive evaluation and balanced therapeutic approaches are essential to improve outcomes.

Position statements

43. A comprehensive differential diagnosis is vital for ACLF patients with altered mental status, as HE often coexists with or mimics other critical conditions, such as septic encephalopathy, intracranial hemorrhage, etc. (LoE—low; recommendation—strong).
44. Management of acute HE episodes should focus on preventing complications such as aspiration pneumonia, dehydration from excessive lactulose, timely advanced care planning for transplantation, and ensuring medication continuity upon discharge. (LoE—low; recommendation—strong).
45. Ammonia levels can help exclude HE when normal but are not definitively diagnostic when elevated, while recent evidence suggests low thyroxine levels may predict development of severe HE. (LoE—moderate; recommendation—strong).
46. ACLF patients with bacterial infection on broad-spectrum antibiotics do not acquire survival benefit from the addition of rifaximin. (LoE—moderate; recommendation—weak).

Cardiac assessment in ACLF with shock

In ACLF patients who develop shock, accurate cardiac assessment is crucial as cardiac dysfunction can exacerbate organ failure. Evaluation should begin with a basic assessment, including a detailed history and physical exam, paying particular attention to pre-existing cardiac conditions or heart failure. Routine tests such as cardiac biomarkers, electrocardiogram (ECG), and echocardiography are recommended. For patients with long-standing cirrhosis, dynamic ECG monitoring to assess pulmonary artery pressure is also suggested [107].

Echocardiography is indispensable for evaluating cardiac function, providing rapid assessment of contractility, diastolic function, and pericardial effusion. In shock, hemodynamic monitoring with central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) can help assess volume status and cardiac filling pressures. For complex cases, invasive monitoring via a pulmonary artery catheter can offer a more precise evaluation. Rapid bedside echocardiography is valuable for quickly assessing cardiac filling and function, aiding in differentiating cardiogenic shock from other types108. The 2025 American College of Cardiology (ACC) Concise Clinical Guidance introduced

the "SUSPECT CS" mnemonic to help clinicians identify cardiogenic shock early, which includes laboratory markers and clinical assessment of congestion and low perfusion [109]. Optimal management requires a multidisciplinary team involving cardiology, hepatology, and intensive care medicine. In ACLF patients with stable hemodynamics, cardiac reserve can be preliminarily assessed using exercise tests like the 6-min walk test [110, 111].

Position statements

47. Thorough evaluation of the patient's medical history, especially any pre-existing cardiac conditions, and performance of routine cardiac tests, including cardiac biomarkers, ECG, and echocardiography, can quickly assess cardiac hemodynamics, and rule out dysfunction. (LoE—low; recommendation—strong).
48. Echocardiography and hemodynamic monitoring are used to assess cardiac function and volume status precisely. In complex cases, invasive monitoring can be considered to better guide volume and catecholamine administration. (LoE—low; recommendation—weak).
49. A multidisciplinary team approach involving cardiology, hepatology, and critical care should be employed to manage these complex patients. Technologies or tools like the "SUSPECT CS" mnemonic is encouraged to aid clinicians rapidly identifying and diagnosing cardiogenic shock. (LoE—low; recommendation—strong).
50. Point-of-care ultrasonography (POCUS) should be used for assessment of shock and fluid management. (LoE—high; recommendation—strong).

Fluid management in ACLF with shock—choice and targets

Fluid resuscitation in ACLF with septic shock involves careful consideration of fluid choice, mean arterial pressure (MAP) targets, and monitoring. Studies showed that albumin was beneficial in reversing hypotension and reducing mortality [82, 112–114], but was associated with more pulmonary complications (22% vs. 0%) [113].

The ESICM and EASL favor albumin in cirrhosis. Research has linked the functional quality of albumin to outcomes; Oettl et al. associated oxidative damage (measured by human nonmercaptalbumin-2, HNA2) with survival, and Jalan et al. found that the ischemia-modified albumin ratio (IMAR) was significantly higher in non-survivors and correlated with disease severity and fatty acid binding deficits, enhancing its prognostic utility [115–117]. The TARGET-C trial and other studies support MAP > 65 mmHg (but not advisable to go above 75 mmHg) and lactate < 2 mmol/L as key resuscitation targets [118, 119]. Guidance should be based on these targets, along with dynamic monitoring and potentially functional albumin markers like HNA2 and IMAR.

Position statements

51. Balanced crystalloids (e.g., plasmalyte) is preferred for safety issues. (LoE—high; recommendation—strong).
52. A 5% albumin can be used when MAP < 60 mmHg or lactate ≥ 2 mmol/L or vasopressor 0.2–0.3 mcg/kg/min for hemodynamic recovery and for raising albumin if 2.5–3.0 g/dL. (LoE—high; recommendation—strong).
53. Target MAP should be maintained between 65 and 75 mmHg, aiming for lactate < 2 mmol/L. (LoE—high; recommendation—strong).

Lactate kinetics in ACLF—implications in management

Lactate levels are crucial indicators of tissue perfusion and oxygenation. Elevated levels may suggest circulatory failure, infection, or organ dysfunction [120]. Research indicates that lactate kinetics can serve as key markers for assessing disease severity and prognosis [121]. For instance, lactate is a component of the AARC score used for patient stratification and prognostic evaluation. Continuous lactate monitoring can help identify non-responders to treatment, allowing for timely therapeutic adjustments [122].

A randomized trial showed that targeting a 20% reduction in lactate levels every 2 h significantly decreased in-hospital mortality and ICU stay [123]. Elevated lactate may also indicate the need for more aggressive organ support. Furthermore, in ACLF patients with septic shock, a rapid decline in lactate typically indicates effective infection control [124].

Position statements

54. Serum lactate can be assessed, together with established prognostic models such as the AARC score to support severity stratification and short-term prognostic assessment in patients with ACLF. (LoE—low; recommendation—strong).
55. Serial lactate monitoring should be incorporated into the hemodynamic assessment of ACLF patients with shock or hypoperfusion to help guide fluid resuscitation and overall circulatory support. (LoE—low; recommendation—strong).
56. Changes in lactate levels can indicate treatment effectiveness in infection control in septic shock. Monitoring lactate helps identify patients who do not respond

well to treatment, enabling timely adjustments to therapy. (LoE—low; recommendation—strong).

TIPS in the management of variceal bleed in an ACLF patient

ACLF patients with acute variceal bleeding have higher rebleeding rates and mortality compared to those without. TIPS is indicated for variceal bleeding in four scenarios: pre-emptive (within 72 h, ideally < 24 h) in high-risk patients; salvage for refractory bleeding; rescue for early rebleeding (within 5 days); and elective for secondary prevention [125, 126].

BAVENO VII, APASL, and American Association for the Study of Liver Diseases (AASLD) recommend polytetrafluoroethylene (PTFE)-covered TIPS within 72 h for patients bleeding from esophageal and GOV1/GOV2 varices who meet high-risk criteria (Child–Pugh C or Child–Pugh B with active bleeding or hepatic venous pressure gradient [HVPG] > 20 mmHg) [125, 126]. ACLF is a major independent risk factor for rebleeding, with the risk increasing with the ACLF grade [127]. A study found that pre-emptive TIPS was independently associated with a lower 42-day rebleeding rate and reduced 42-day and 1-year mortality in ACLF patients [127]. Above consortia also recommend TIPS as salvage/rescue treatment, with control of bleeding achieved in 80–100% of cases. However, 6-week mortality remains high (27–55%). Therefore, in patients with a MELD score > 30, lactate > 12 mmol/L, or Child–Pugh > 13, salvage/rescue TIPS should not be used unless it is a bridge to short-term LT [125, 126, 128].

Position statements

57. In patients with ACLF who develop acute variceal bleeding, early risk stratification and intensified monitoring should be considered because of the increased risk of rebleeding and mortality. (LoE—moderate; recommendation—strong).
58. Pre-emptive and salvage/rescue TIPS should be considered in ACLF and variceal bleeding in properly selected patients. (LoE—low; recommendation—weak).
59. Rescue TIPS is recommended for refractory variceal bleeding in ACLF, provided sepsis and multi-organ failure (ACLF-3) are excluded. Pre-emptive TIPS should be prioritized in ACLF patients with acute variceal bleeding and high-risk features (Child–Pugh C, or B > 7 + active bleeding, MELD ≥ 19) to reduce treatment failure and mortality. (LoE—low; recommendation—weak).
60. In patients with ACLF, HE or hyperbilirubinemia may not be considered an absolute contraindication to TIPS. Patient selection requires multidisciplinary evaluation, balancing bleeding severity, ACLF grade, and contraindications (e.g., uncontrolled infections). (LoE—low; recommendation—weak).

Approach to coagulation failure in ACLF

Coagulation failure is a common defining or incident organ failure in ACLF [129]. An elevation in the international normalized ratio (INR) beyond established cut-offs is a key marker for diagnosing ACLF and a target for intervention. Different consortia use varying INR thresholds, from ≥ 1.5 (APASL) [1] to ≥ 2.5 (EASL-CLIF) [130]. Consequently, the prevalence of coagulation failure in ACLF varies by definition, ranging from 24.2% with the APASL definition [131] to 32% with the EASL-CLIF definition [132]. The recent Kyoto Consensus added a tiered definition, naming INR 1.5–2.5 as "coagulation dysfunction" and > 2.5 as "coagulation failure" [1].

While all consortia agree that treating the precipitating insult can reverse coagulation failure, APASL specifically uses coagulopathy within four weeks of an acute hepatic insult to define ACLF, helping to identify a window for intervention and define syndrome reversal [133]. Coagulation failure is an important independent prognostic factor for death [134].

Position statement

61. Coagulation failure should be used as a landmark to define the natural history of ACLF. (LoE—high; recommendation—strong).

Assessment and correction of coagulopathy in non-variceal bleed

The hemostatic imbalance in ACLF is more profound than in compensated cirrhosis or acute decompensation [135–138], and deteriorates further during hospitalization [137, 138]. SIRS and sepsis are linked to a shift towards a hypocoagulable state, which adversely affects mortality irrespective of bleeding [138–141].

Standard coagulation tests (SCTs) like prothrombin time (PT)/INR and platelet count are poor indicators of bleeding risk as they do not reflect the actual in vivo hemostatic balance [142]. Viscoelastic tests (VETs) such as thromboelastography (TEG), rotational thromboelastometry (ROTEM), and Sonoclot, which measure the dynamics of clot formation

and lysis, are more accurate for detecting specific coagulation defects and predicting clinical bleeding risk [134–136, 139, 142, 143].

Correction of coagulopathy in non-variceal bleeding should therefore be based on the specific defects detected by VETs [140]. This allows for selective, targeted transfusion of blood products, effectively halting bleeding while avoiding complications like transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) [134, 142]. While robust, more studies are needed to confirm the efficacy of point-of-care tests in managing non-variceal bleeding in ACLF.

Position statements

62. In patients with ACLF, coagulation abnormalities should be interpreted in the context of systemic inflammation, sepsis, and the overall hemostatic profile. (LoE—high, recommendation—strong).
63. Evidence of hypocoagulability in ACLF should prompt careful prognostic assessment and closer clinical monitoring, even in the absence of overt bleeding. (LoE—moderate, recommendation—strong).
64. Conventional coagulation assessments, including PT, APTT, INR, fibrinogen levels and bleeding time do not consistently predict the risk of bleeding in patients with ACLF. (LoE—moderate, recommendation—strong).
65. VETs such as TEG, Sonoclot and ROTEM provide a more physiological and dynamic evaluation of coagulation, thereby offering improved prediction of bleeding risk in ACLF. (LoE—moderate, recommendation—strong).
66. Viscoelastic tests should be strongly considered to guide blood transfusion strategies in ACLF. (LoE—moderate; recommendation—strong).
67. In managing non-variceal bleeding in ACLF patients, a targeted transfusion strategy based on viscoelastic testing can effectively correct coagulopathy, stop bleeding, and avoid transfusion-related complications. (LoE—low; recommendation—weak).

PE in ACLF—choice, timing and therapeutic end points

With high short-term mortality and LT as the definitive cure, bridging therapies are essential for ACLF patients [1, 2]. PE is a non-biological ALSS that can reduce systemic inflammation, bilirubin, and improve coagulation. It also shows benefit for complications like infections, HE, and HRS, particularly in patients with two or more complications [144–148].

A recent meta-analysis suggests a potential survival benefit with PE for ACLF [149, 150], though individual studies have not uniformly demonstrated this [144, 148, 151–153]. Key aspects such as the timing, volume, number of sessions, technique (centrifugal vs. membrane), and cessation criteria for PE require further study. The replacement fluid is typically fresh frozen plasma (FFP) or a combination of FFP and albumin [152, 153].

Recommendations for PE in ACLF remain controversial among societies. The APASL ACLF Research Consortium's recommendation of PE as a bridge to transplantation aligns with Chinese guidelines, which additionally recommend PE for ACLF stages A1 and A2 [1].

Position statements

68. PE significantly reduces bilirubin, decreases systemic inflammation and improves coagulation function in patients with ACLF. (LoE—moderate; recommendation—strong).
69. PE improves the survival of carefully selected ACLF patients with no infection, shock, and ventilation. (LoE—moderate; recommendation—strong).
70. More clinical data are needed to determine the timing and treatment endpoints for ACLF patients undergoing PE. (LoE—moderate; recommendation—strong).
71. PE may act as a supportive treatment before LT. (LoE—moderate; recommendation—strong).

Adsorption therapy in ACLF—selection of the patient and the filter

Adsorption therapy aims to remove inflammatory mediators and toxins from the blood, potentially benefiting ACLF patients [154]. Its implementation requires careful patient selection and filter choice [155, 156]. Ideal candidates are ACLF patients with a strong inflammatory response who are not responding to conventional treatments, such as those with extremely high bilirubin and inflammatory markers. Liver function reserve, complication risk, and treatment tolerance must be comprehensively assessed. For patients with severe renal insufficiency, adsorption may need to be combined with hemodialysis [156–158].

The choice of filter is critical. Different adsorption materials and designs significantly impact outcomes (Fig. 3 and Table 2). The CytoSorb adsorber has proven effective in removing inflammatory mediators and bilirubin, with good safety in patients with renal failure and hyperbilirubinemia [158–160]. However, a RCT failed to demonstrate its efficiency in ACLF with AKI [161]. Filter parameters like pore size, adsorption capacity, and blood flow rate influence efficacy and safety, with larger pores

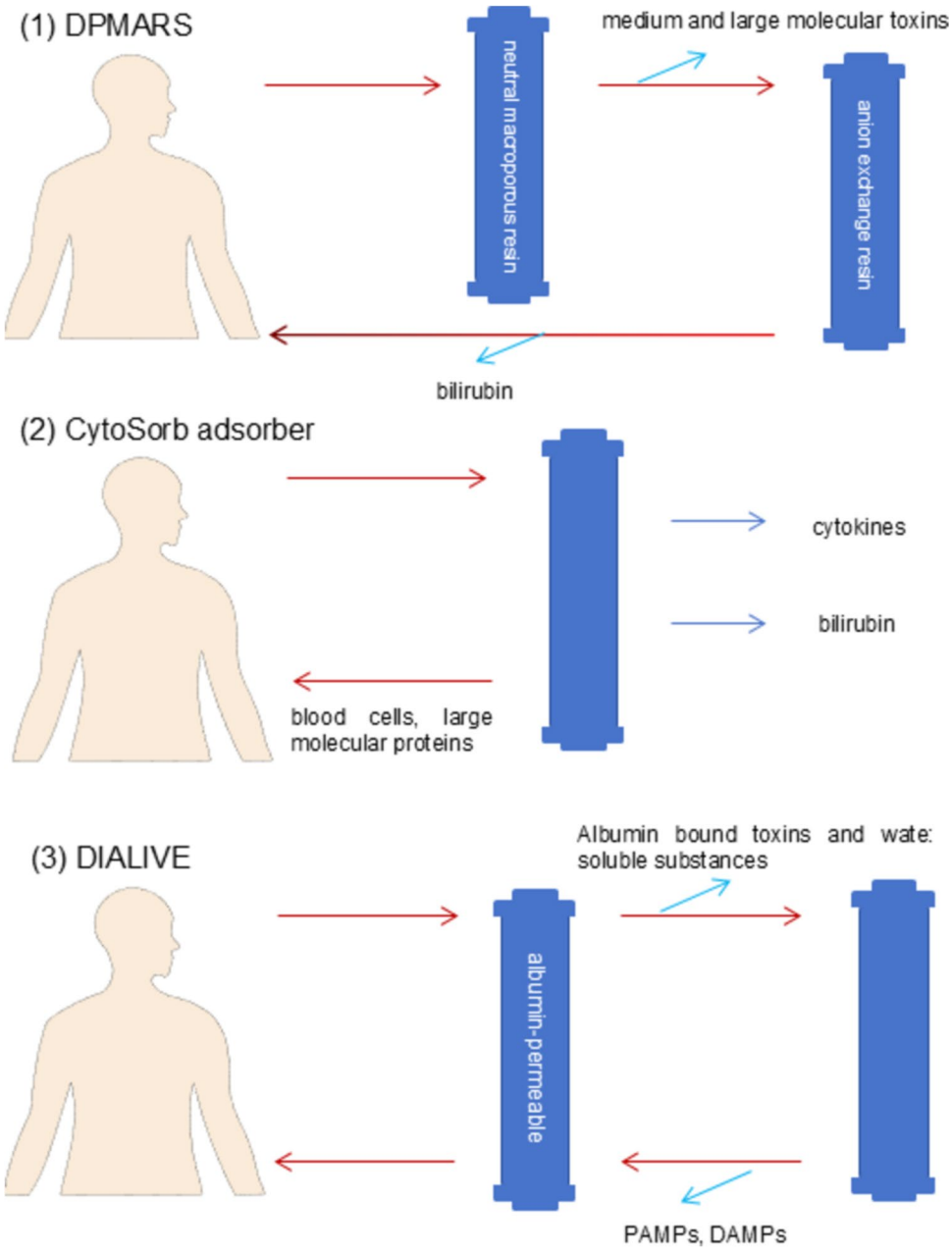

Fig. 3 Different filters in adsorption therapy for ACLF. DPMAS, double plasma molecular adsorption system; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular pattern

potentially improving efficiency but risking excessive loss of blood components [162].

Close monitoring of physiological indicators and treatment response is mandatory to adjust the plan timely [132, 163].

Position statement

72. The choice of filter is crucial, as different materials and designs significantly impact therapeutic outcomes. (LoE—high; recommendation—strong).

ALSS in ACLF—the good, the bad, and the ugly?

The role of ALSS in ACLF is complex and multifaceted [156]. Studies show that compared to standard medical therapy alone, ALSS can improve prognosis and extend survival [154, 164]. By removing toxins and inflammatory mediators, ALSS can alleviate complications like hyperbilirubinemia and endotoxemia, and improve intestinal microbiota dysbiosis. For transplant candidates, ALSS can serve as a vital bridge, maintaining liver function while awaiting a donor [132, 165].

Table 2 Selection of adsorption therapy filters in ACLF

Studies	ACLF definition	Filter	Adsorbate	Control	Type of study	Outcome
Sekandarzad et al. 2024 [161]	Undefined	CytoSorb adsorber	Cytokines, bilirubin, and myoglobin	CRRT without hemoadsorption, no CRRT	RCT	No difference in reducing serum bilirubin
Zhang et al. 2024 [219]	Multiple	DPMAS	Medium and large molecular toxins	PE	Meta-analysis	Improved bilirubin reduction
Xu et al. 2023220	TBIL ≥ 10 ULN; PTA ≤ 30% and > 20%, or PT-INR ≥ 1.9 and < 2.6	DPMAS + LPE	Medium and large molecular toxins	SMT	RCT	Improved 12-week survival
Wu et al. 2023221	APASL	DPMAS + LPE	Medium and large molecular toxins	SMT	Prospective study	Improved TBIL, AST, and Cr reduction; improved 28-day effectiveness and 90-day survival
Agarwal et al. 2023222	EASL	DIALIVE	PAMPs, DAMPs	SOC	RCT	Acceptable performance for albumin exchange and reduction in endotoxin; improved prognostic scores

CRRT, continuous renal replacement therapy; RCT, randomized controlled trial; DPMAS, double plasma molecular adsorption system; PE, plasma exchange; LPE, low-volume plasma exchange; TBIL, total bilirubin; ULN, upper limit of normal; PT-INR, prothrombin time-international normalized ratio; SMT, standardized medical treatment; APASL, the Asian Pacific Association for the Study of the Liver; AST, aspartate aminotransferase; Cr, creatinine; EASL, the European Association for the Study of the Liver; SOC, standard of care; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular pattern

However, ALSS implementation demands specialized equipment and skilled personnel, increasing costs and limiting accessibility in resource-limited settings [165]. While generally safe, complications like bleeding, infection, and thrombosis can occur, with risks heightened in patients with coagulopathy. Efficacy varies, and benefits may be limited in extremely severe cases [166]. For end-stage patients, ALSS may not reverse the disease, raising ethical questions about high-cost, low-benefit treatments [167]. Despite short-term improvements, the long-term prognosis for some patients remains poor, with high 28-day mortality rates persisting, for instance, in ACLF patients with AKI [42].

Position statements

73. ALSS (PP + PE, DPMAS + PE) may improve hyperbilirubinemia, endotoxemia, and encephalopathy and may be used as a bridge to transplantation in selected cases. (LoE—moderate; recommendation—weak).
74. ALSS (PP + PE, DPMAS + PE) requires significant resources and skilled personnel, is associated with potential complications, and has variable efficacy depending on the patient's condition and etiology. (LoE—high; recommendation—strong).
75. ALSS (PP + PE, DPMAS + PE) can mask true disease progression, raise ethical concerns regarding high-cost treatments with limited benefit, and may not improve long-term prognosis. (LoE—low; recommendation—weak).

Nutritional assessment and planning in obese ACLF patients

Obesity is a significant risk factor for ACLF, contributing to increased morbidity and mortality through systemic inflammation, metabolic dysfunction, and sarcopenia [168]. Patients with a body mass index (BMI) > 40 kg/m^2 have a higher risk of ACLF at LT [45, 49, 169]. Sarcopenic obesity, the co-existence of sarcopenia and obesity, is associated with higher mortality and worse metabolic and physical function than either condition alone [170] and is present in up to a third of cirrhosis patients [171].

Nutritional assessment and targeted interventions are critical. A structured approach includes early enteral nutrition, precise energy calculation, and tailored macronutrient/micronutrient supply. Indirect calorimetry, particularly with handheld devices, provides an accurate method for assessing

resting energy expenditure (REE) [172, 173]. Structured assessment using tools like the Royal Free Hospital Nutrition Prioritizing Tool is essential. Sarcopenic obesity can be accessed via CT/MRI (L3 muscle area), dual-energy X-ray absorptiometry (DEXA), or bioelectrical impedance analysis (BIA) in the absence of fluid retention [174].

For patients with or at risk of sarcopenic obesity, a moderate energy deficit (200–750 kcal) is recommended [175], when restricting energy, high biological quality protein intake (up to 1.5 g/kg of ideal body weight) should be maintained to mitigate muscle catabolism, assuming adequate renal function [174, 176, 177]. Early enteral nutrition is recommended to reduce mortality and infections. Essential micronutrients should be optimized, while sodium and fluid intake should be restricted to prevent complications [58, 178].

Position statements

76. Obesity and related metabolic dysfunction should be recognized as important comorbid factors in ACLF and should be considered in risk assessment, nutritional evaluation, and transplantation planning. (LoE—high; recommendation—strong).
77. Nutritional assessment with the Royal Free Hospital Nutrition Prioritizing Tool is helpful in ACLF. (LoE—moderate; recommendation—strong).
78. Critically ill ACLF patients should receive at least 30–35 kcal/kg/BW/day, with protein intake ranging from 1.2 to 1.5 g/kg/day to prevent sarcopenia. Carbohydrates should constitute 45–50% of daily intake, with the remainder from lipids. (LoE—high; recommendation—strong).
79. Enteral nutrition is recommended to reduce mortality and infectious morbidity in ACLF patients. In patients with HE who are unable to maintain adequate oral intake, nasogastric feeding may be considered with appropriate aspiration precautions, including head-up positioning and close monitoring. (LoE—moderate; recommendation—strong).

Prognostic impact of sarcopenia in ICU and post-transplant outcome

Sarcopenia is highly prevalent (37.5%) in cirrhosis, linked to alcohol etiology, male gender, and Child C status, and associated with an adjusted mortality hazard ratio of 2.3 [179]. Sarcopenia is a significant predictor of ACLF development and mortality. Studies have shown that sarcopenia is associated with a higher risk of EASL-defined ACLF and mortality after procedures like TIPS [180] and is an independent predictor of ACLF development in patients awaiting LT [181, 182]. While most studies link sarcopenia to increased mortality in ACLF [183–185], some have not found this association [186, 187].

Sarcopenia also impacts post-transplant outcomes [188, 189]. A prospective study found sarcopenia was associated with increased postoperative sepsis, neurological complications, and higher 90-day mortality, despite comparable 90-day mortality rates in that specific cohort [190].

Position statements

80. Sarcopenia is common and associated with poorer long-term outcomes and may guide a decision-making in the management of patients with ACLF. (LoE—moderate; recommendation—strong).
81. Sarcopenia in cirrhosis is a risk factor for ACLF development in patients on the waiting list for LT. (LoE—low; recommendation—weak).
82. Sarcopenia is associated with high mortality, infection, and longer hospital stay among hospitalized ACLF patients and post-LT patients. (LoE—moderate; recommendation—strong).

Gut failure in ACLF—approach and management

Emerging evidence highlights the gut–liver axis's pivotal role in ACLF pathophysiology, with gut barrier dysfunction and dysbiosis often preceding systemic inflammation and extrahepatic organ failure [191]. The clinical approach begins with early recognition of GI symptoms like bloating, diarrhea, or unexplained sepsis. Biomarkers like elevated zonulin and serum calprotectin, along with stool microbiome analysis, may help identify gut dysfunction, though they are not yet routine [192, 193].

Rifaximin, a non-absorbable antibiotic, is widely used for recurrent HE and has demonstrated clinical efficacy [194]. Long-term use was associated with a reduced risk of portal hypertension-related complications and improved survival in one study [195], though its impact on disease progression was unclear [196]. Evidence for probiotics remains inconclusive [197]. Prompt recognition and management of infections are crucial. Quinolones are often used for SBP prophylaxis, linked to improved survival [198], but long-term use raises concerns about MDRO emergence.

FMT has shown promise with comparable efficacy and safety [199], demonstrating sustained improvements in microbial diversity, cognition, and reduced hospitalizations in HE patients. However, its safety in patients with ACLF requires particular caution. Because ACLF patients are often profoundly immunocompromised and have marked disruption of gut barrier integrity, they may be at increased risk

of FMT-related infectious complications. Safety concerns have been highlighted by reports of severe infection, including fatal ESBL *E. coli* bacteremia following FMT [200], as well as by U.S. Food and Drug Administration (FDA) safety communications regarding the risk of transmission of multidrug-resistant and other pathogenic organisms [201, 202]. Therefore, at present, FMT in ACLF should be considered only in carefully selected settings, preferably within clinical trials or specialized centers, with rigorous donor screening and close safety monitoring.

Position statements

83. Gut dysfunction should be systematically evaluated in patients with ACLF and considered in high-risk patients with decompensated cirrhosis, given its potential role in systemic inflammation and extrahepatic organ failure. (LoE—high; recommendation—strong).
84. Restoration of gut microbiota balance is a key therapeutic target, with current interventions such as rifaximin, probiotics, and FMT representing promising therapeutic options but requiring cautious application due to inconsistent evidence and potential risks. Further validation studies are needed. (LoE—low; recommendation—weak).
85. Long-term antibiotic prophylaxis and microbial modulation strategies must be carefully balanced against the risk of AMR, emphasizing the need for patient-specific approaches. (LoE—high; recommendation—strong).

Selecting an ACLF grade III for liver transplant

LT is often the only curative option for ACLF, but selecting candidates with ACLF Grade III is particularly complex, as these patients can rapidly become too sick for transplant. These patients exhibit severe hepatic dysfunction and multiple organ failures. The AARC score is a key tool for evaluating severity and transplant urgency, with a high score generally indicating higher priority [203]. Evidence from both European and North American cohorts indicates that carefully selected patients with severe ACLF may achieve meaningful post-transplant survival, supporting the role of dynamic transplant assessment [6, 204].

The patient's overall medical condition is critical. Comorbidities like cardiovascular disease, active infections, and malignancies significantly impact transplant success and require thorough assessment and pre-transplant optimization if possible [203]. Donor liver availability is a major challenge. The urgency of ACLF Grade III often means patients cannot wait for an ideal match, forcing the transplant team to weigh the risks of a suboptimal donor against the risk of further patient deterioration. Psychological and social factors are also important; the patient's mental health, ability to adhere to post-transplant care, and social support network are crucial considerations for long-term success [205].

Position statements

86. In ACLF Grade III, the decision to transplant depends on the extent and reversibility of organ failure, the severity of ALI/ARDS, the dynamic changes in AARC score, the number and dose of vasopressors, and the presence or absence of sepsis. (LoE—high; recommendation—strong).
87. Given the urgency of ACLF Grade III patients' conditions, the transplant team must weigh the risks and benefits of proceeding with a less-than-perfect donor liver against the risk of further deterioration of the patient's condition. (LoE—high; recommendation—strong).
88. The patient's psychological status, adherence to post-transplant care, and social support system are also important considerations, as these factors can significantly impact the patient's postoperative recovery and quality of life. (LoE—high; recommendation—strong).

ACLF due to alcohol and transplant decision—when to say no?

The decision for transplantation in alcohol-related ACLF Grade III is especially complex. A comprehensive evaluation beyond the MELD score is essential. The presence of severe, treatment-unresponsive complications like HE and refractory ascites indicates an urgent need. However, severe, unmanageable comorbidities like active infections or cardiovascular disease may render a patient unable to withstand the transplant procedure [203, 204, 206].

The global donor liver shortage adds another layer. If only a marginal graft (e.g., with hepatic steatosis) is available, it may affect post-transplant function and increase complication risks [207]. A critical factor is pre-transplant alcohol abstinence. Patients who cannot abstain pre-transplant have a high risk of relapse post-transplant, which can damage the new graft and lead to poor outcomes, potentially accelerating death [208].

Living donor liver transplantation (LDLT) is increasingly considered a viable option for select ACLF patients, offering comparable survival to chronic liver disease patients without ACLF when performed timely [209–211]. This underscores the need for rapid evaluation and stringent selection.

The patient's psychological state and adherence are crucial. Patients with active alcohol dependence often have

co-existing anxiety or depression and lack insight, which can impair recovery and quality of life. Those lacking family support or the ability to follow long-term medical regimens face an increased risk of transplant failure [205]. Clear contraindications for transplantation include an inability to achieve alcohol abstinence pre-transplant without engagement in treatment. Transplantation with limited abstinence should be approached with extreme caution. Patients with poor psychosocial support and an inability to comply with post-transplant care should generally be declined until these issues are adequately addressed.

Position statements

89. For alcohol-related ACLF grade III patients, a comprehensive evaluation is required. Severe comorbidities such as uncontrollable infections or severe cardiovascular diseases make transplantation too risky, necessitating a refusal. (LoE—high; recommendation—strong).
90. The shortage of donor livers and the poor quality of available donors can complicate decisions. If patients cannot quit alcohol before transplantation and have a high risk of relapse post-transplantation, warranting a refusal need to be fully considered. (LoE—high; recommendation—strong).
91. Poor psychological status, lack of family support, and inability to adhere to postoperative care requirements are critical considerations. If these factors are present, they significantly increase the risk of transplant failure, leading to a decision to refuse transplantation. (LoE—moderate; recommendation—strong).
92. LDLT if indicated and feasible should be considered for patients with ACLF. (LoE—low; recommendation—weak).
93. ACLF in the setting of AH should be differentiated and managed differently than ACLF in patients with underlying alcohol-associated cirrhosis without AH. (LoE—moderate; recommendation—strong).
94. Liver transplant for ACLF in the setting of alcohol-associated cirrhosis should not proceed in the setting of prior history of hepatic decompensation due to alcohol-use disorder, multiple failed rehabilitation attempts, impaired mental status precluding assessment of commitment to sobriety, lack of social support, polysubstance abuse, and severe sarcopenia. (LoE—moderate; recommendation—strong).
95. Liver transplant for ACLF in the setting of AH may not proceed in the setting of an advanced stage of ACLF until stabilized. (LoE—moderate; recommendation—strong).

Pre-LT optimization for favorable post-transplant recovery

ACLF patients are fragile and dynamic, and can deteriorate on the waiting list. They should ideally be transplanted within 30 days of listing [212]. Prioritization on waitlists is crucial. With the advent of ex vivo machine perfusion, the use of marginal grafts can be considered depending on local expertise [213]. International cohort data suggest that careful pre-transplant optimization and dynamic reassessment are critical to achieving favorable outcomes in ACLF candidates, particularly in those with multi-organ dysfunction awaiting urgent transplantation [6, 204].

Regular re-evaluation for transplant suitability may be abbreviated, focusing on the most pertinent investigations to optimize the risk–benefit ratio without delay [214]. The cause of AKI should be identified and addressed pre-transplant to optimize renal recovery [215]. Patients non-responsive to AKI treatment should have a low threshold for initiating RRT as a bridge. Those requiring prolonged RRT should be evaluated for simultaneous liver–kidney transplantation [216].

ALSS can be used to bridge patients, prolonging their transplant suitability while awaiting a donor [147]. ACLF patients are at high risk of infections and should be closely monitored [217, 218]. There should be a low threshold for evaluation with blood tests, fluid analysis, and imaging. Empiric broad-spectrum antimicrobials should be initiated until a pathogen is identified, and antibiotics often need to be continued post-transplant.

Position statements

96. Patients should ideally be transplanted within 30 days of listing or assessment of suitability for transplantation. (LoE—moderate; recommendation—strong).
97. Patients with ACLF should be prioritized on waitlists to ensure early access to liver grafts. (LoE—low; recommendation—weak).
98. Marginal grafts can be considered for use with machine perfusion depending on local expertise. (LoE—low; recommendation—weak).
99. An abbreviated process of evaluation for transplant suitability can be applied for critically ill patients under emergency transplantation, with limited examinations. (LoE—low; recommendation—strong).
100. Patients with non-response to treatment of AKI should have a low threshold for initiation of RRT as a bridge to transplant. (LoE—moderate; recommendation—strong).

101. Patients requiring prolonged RRT can be considered for simultaneous liver and kidney transplants. (LoE—moderate; recommendation—weak).
102. ALSS can be used to bridge patients to liver transplant, to prolong the time that they are suitable for transplant while awaiting a suitable donor. (LoE—moderate; recommendation—strong).
103. There should be a low threshold to evaluate for infections with routine examination of blood, body fluids, and imaging. These should be treated with empiric broad-spectrum antimicrobials till identification of the responsible species. (LoE—moderate; recommendation—strong).
104. Antibiotics should be initiated 24 h before and continued until 24–72 h post-transplantation. (LoE—moderate; recommendation—strong).

Limitations

Several limitations of the present consensus should be acknowledged. First, although this document was developed through a global expert collaboration, a few recommendations are supported predominantly by regional evidences and should therefore be interpreted with local contexts. Second, some of the cited literature originates from members of the consensus panel. Although the recommendations were developed through collective review, discussion, and revision by the full expert panel rather than by individual authors alone, the possibility of panel-related citation bias cannot be completely excluded. In addition, patient or public involvement was not incorporated into the present consensus development process, which should also be recognized as a limitation. Inclusion of patient and public perspectives may further strengthen the relevance and applicability of future updates of this work.

Conclusion

This global consensus provides a crucial framework and practical guidance for standardizing the management of ACLF through comprehensive, multidisciplinary recommendations developed by leading international experts using a rigorous methodology (Fig. 4). Its key strengths lie in the extensive collaboration, the systematic application of the GRADE framework, and the practical coverage of all clinical facets from diagnosis and organ support to transplantation. However, limitations persist, as part of recommendations are necessarily based on moderate-quality evidence and expert opinion rather than high-level data from RCT, reflecting the inherent challenges of conducting research in this critically ill and heterogeneous population. Future perspectives must prioritize the validation of these

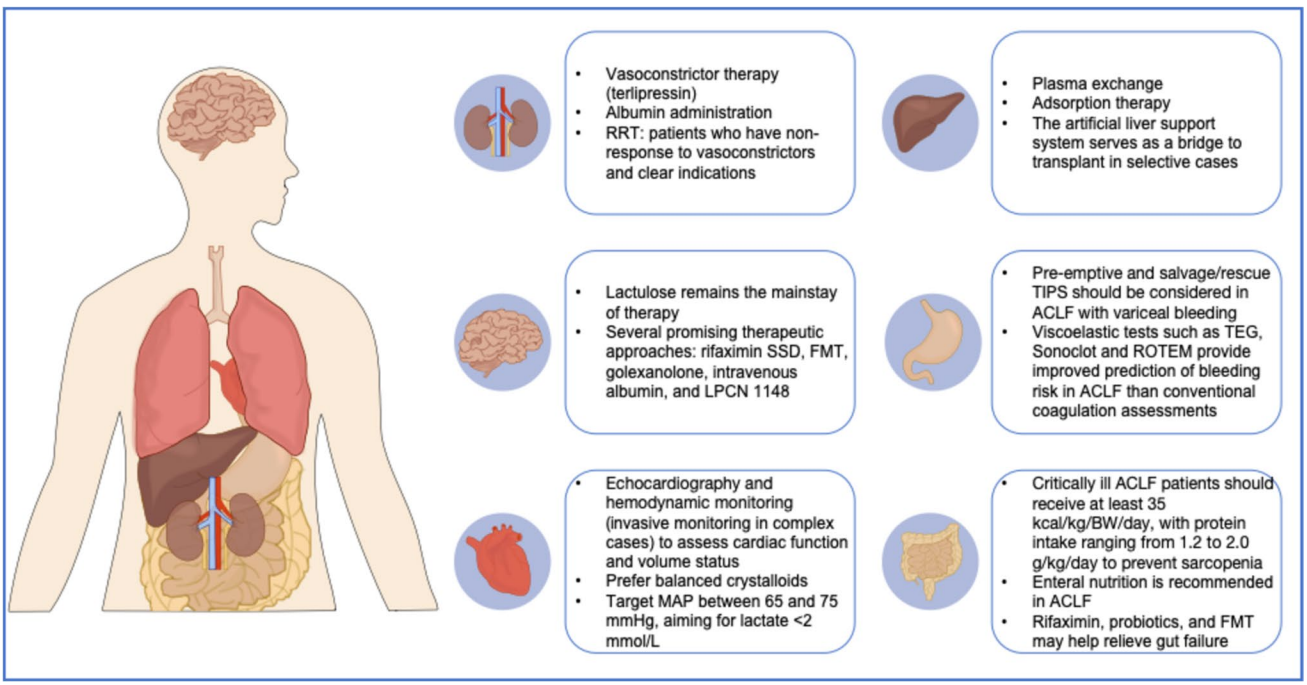

Fig. 4 Comprehensive managements for ACLF. RRT, renal replacement therapy; SSD, soluble solid dispersion; FMT, fecal microbiota transplantation; MAP, mean arterial pressure; TIPS, transjugular intrahepatic portosystemic shunt; ACLF, acute-on-chronic liver failure; TEG, thromboelastography; ROTEM, rotational thromboelastometry; BW, body weight

guidelines through prospective implementation studies, the development of novel biomarkers for early disease detection and prognostication, and the advancement of targeted therapies that address the underlying immunopathology and multi-organ dysfunction characteristic of ACLF. The establishment of this consensus represents a significant step toward improving patient outcomes globally, while simultaneously highlighting the urgent and ongoing need for more robust clinical evidence and personalized treatment approaches in the care of this vulnerable patient population.

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Author contributions Corresponding authors: Qin Ning, Shiv Kumar Sarin, and Paul Y. Kwo proposed, designed and supervised the overall project, assigned manuscript writing, organized face-to-face discussions and meetings, took charge of manuscript submission and response to reviewers' comments. Advisors: Qin Ning, Shiv Kumar Sarin, Paul Y. Kwo, Lai Wei, Daniel Q Huang, Juan Pablo Arab, Yoon Jun Kim, Manal Hamdy El-Sayed, Masao Omata, and Necati Ormeci served as advisors to the working group and provided overall strategic and scientific guidance for the development of the consensus. Working group chairs: Qin Ning, Shiv Kumar Sarin, Paul Y. Kwo, Zaigham Abbas, Ashwani K. Singal, George K. Lau, Sunil Taneja, James Fung, Diana Alcantara Payawal, Madunil A. Niriella, Vincent Wai-Sun Wong, and Mohamed Rela led topic coordination, expert discussion, and integration of recommendations across the working groups. Expert panel members: Tao Chen, Xiaojing Wang, Tatsuo Kanda, Charles Panackel, Kessarin Thanapirom, Khin Maung Win, Gupse Adali, Rahul Kumar, Anil Arora, Jinlin Hou, Jidong Jia, Nipun Verma, Amna Subhan Butt, Ashish Goel, Arun Valsan, Madhumita Premkumar, Akash Roy, Imelda Maria Loho, Shalimar, Saeed Hamid, Suprabhat Giri, Sunil Dadhich, Akash Shukla, Santhosh E. Kumar, C. E. Eapen, Soek Siam Tan, Narendra Singh Choudhary, Albert C. Y. Chan, Mamatha Bhat, and Sanjiv Saigal participated in expert review, panel discussion, and consensus voting. Drafting committee: Tao Chen, Ashok Choudhury, Wei Liu, Meng Zhang, Wenhui Wu, Huiling Xiang, Ramazan Idilman, Hai Li, Paolo Angeli, Debbie L. Shawcross, Elliot B. Tapper, Jonel Trebicka, Aleksander Krag, Jinhua Hu, Haibin Su, Javier Fernandez, Dong Joon Kim, Sakkarin Chirapongsathorn, Rakhi Maiwall, Jasmohan Bajaj, Constantine J. Karvellas, Sanjaya K. Satapathy, Sumeet Asrani, Manoj K Sharma, Ruben Hernaez, Ruveena Bhawani Rajaram, Jun Li, Rajiv Jalan, Ming Lung Yu, Gamal E. Shiha, Prashant Bhangui, Ramon Bataller, and Mark Dhinesh Muthiah contributed to drafting, scientific review, statement refinement, and critical revision of the manuscript. Evidence review group: Tao Chen, Wei Liu, Meng Zhang, Wenhui Wu, Huiling Xiang, Xiaojing Wang, Kemal Fariz Kalista, Rosmawati Binti Mohamed, Mohamed Elbasiony, Hasitha S. Wijewantha, Ananta Shrestha, Abdul Kadir Dokmeci, Anand V. Kulkarni, Tawesak Tanwandee, Mamun-Al-Mahtab, Cosmas Rinaldi A. Lesmana, Gokhan Kabacam, Wasim Jafri, R. K. Dhiman, Cesar Yaghi, Barjesh Chander Sharma, Lubna Kamani, Igor G. Bakulin, Hasmik Ghazinian, Zhongping Duan, Atsushi Tanaka, Vinod Arora, Mohd Golam Azam, Ashish Kumar, Shahinul Alam, Yogesh K. Chawla, Ajay Duseja, Francois Durand, Paul Y Kwo, and Nadim Mahmud contributed to evidence review, evaluation of supporting literature, and refinement of the scientific basis for the consensus statements. Scientific assistants: Wei Liu, Meng Zhang, Wenhui Wu, and Huiling Xiang coordinated the literature collation, manuscript preparation, administrative organization, and communication across the working groups. All contributors participated in the development of the consensus statements. All the authors critically reviewed the manuscript and approved the final version for submission.

Declarations

Conflict of the interest All the authors declare no competing interests for this manuscript.

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