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NARRATIVE REVIEW

Intensive care management of acute-on-chronic liver failure

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Abstract

Acute-on-chronic liver failure (ACLF) is a clinical syndrome defined by an acute deterioration of the liver function associated with extrahepatic organ failures requiring intensive care support and associated with a high short-term mortality. ACLF has emerged as a major cause of mortality in patients with cirrhosis and chronic liver disease. ACLF has a unique pathophysiology in which systemic inflammation plays a key role; this provides the basis of novel therapies, several of which are now in clinical trials. Intensive care unit (ICU) therapy parallels that applied in the general ICU population in some organ failures but has peculiar differential characteristics in others. Critical care management strategies and the option of liver transplantation (LT) should be balanced with futility considerations in those with a poor prognosis. Nowadays, LT is the only life-saving treatment that can radically improve the long-term prognosis of patients with ACLF. This narrative review will provide insights on the current understanding of ACLF with emphasis on intensive care management.

Keywords: Cirrhosis, Acute decompensation, Acute on chronic liver failure, Organ failures, Intensive care management, Liver transplantation

Introduction

Traditionally, the course of cirrhosis is characterized by a compensated and a decompensated state, based on the absence or the presence, respectively, of any of the complications, i.e., ascites, hepatic encephalopathy (HE), gastrointestinal hypertensive bleeding, or jaundice [1]. Acute-on-chronic liver failure (ACLF) identifies a subgroup of cirrhotic patients who may either have compensated or decompensated cirrhosis that can progress rapidly following acute decompensation (AD), due to an identified or unidentified acute precipitating event, to develop organ failure(s) (OFs), and high short-term mortality. The present article will provide insights on the current understanding of ACLF with emphasis on intensive care management.

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Clinical characteristics

Definition

More than 13 distinct definitions of ACLF have been proposed [2, 3], largely based on personal experience or consensus agreements. There are currently four widely used definitions of ACLF [4–12] (see Supplementary material: Definition and Supplementary table 1). This article is largely based on the one proposed by the European Association for the Study of the Liver—Chronic Liver Failure (EASL–CLIF) Consortium [11, 12] that defines ACLF as a "*syndrome characterized by AD of cirrhosis, OF(s) and high short-term mortality. AD is defined as development of ascites, HE, gastrointestinal hemorrhage and/or bacterial infections. ACLF may develop in patients with or without a prior history of AD. OFs (liver, kidney, brain, coagulation, respiration, circulation) are defined by the original CLIF-SOFA score (the Sequential Organ Failure*

Assessment Scale adapted for liver patients) [11] *or its simplified version CLIF-C OF score"* [13] (Fig. 1). The definition of high short-term mortality (i.e., ≥ 15% mortality at 28-day) was derived from the mortality rate associated with severe sepsis in the general population.

Diagnostic criteria, ACLF grades and mortality

Patient mortality in the CANONIC study, which was a prospective study specifically designed to develop the diagnostic criteria of ACLF, was related to the presence and number of OFs [11]. Also, renal dysfunction (serum creatinine of 1.5–1.9 mg/dL) and/or cerebral dysfunction (grade 1–2 HE), when associated to single OF, were found to predict risk of 28-day mortality [11]. Based on the presence of OF(s), renal and/or cerebral dysfunction, and short-term mortality rate, three categories of ACLF were defined (Fig. 1 and Table 1). On the contrary, patients experiencing AD without ACLF may follow 3 different trajectories: (a) stable decompensated cirrhosis (DC) sub-phenotype (no further hospital readmission at 90 days); (b) unstable DC sub-phenotype (≥ 1 hospital readmission at 90 days, unrelated with ACLF); and (c) pre-ACLF sub-phenotype (development of ACLF within 90-day follow-up period) [14, 15].

Among the different organ and system failures in ACLF, the most frequently affected organs or systems were the kidneys (56% of patients), followed by the liver (44% of patients), coagulation (28% of patients), the brain (24% of patients), circulation (17% of patients) and the lungs (9% of patients). Renal failure is the most common OF in ACLF grade 1. Liver failure is the most common OF in ACLF grade 2. For ACLF grade 3, the prevalence of all OFs is high.

The 28-day mortality of patients with ACLF according to the EASL-CLIF Consortium definition ranges between 20 and 75% and correlates closely with the number of OFs (Table 1) [11].

Take-home message

Acute-on-chronic liver failure (ACLF) is a clinical syndrome defined by an acute deterioration of the liver function associated with extrahepatic organ failures requiring intensive care support and associated with a high short-term mortality. ACLF has emerged as a major cause of mortality in patients with cirrhosis and chronic liver disease. Critical care management strategies and the option of liver transplantation should be balanced with futility considerations in those with a poor prognosis. This article provide insights on the current understanding of ACLF with emphasis on intensive care management.

Clinical course

ACLF has a dynamic course and potential for reversibility [16]. Indeed, in the CANONIC study, 50% of patients experienced improvement or resolution, while approximately one third experienced a steady course, whereas 20% worsened. Unsurprisingly, the trajectory was mainly related to the initial ACLF state, with high rate of resolution in those with initial ACLF-1. It is worth emphasizing that the majority of ACLF 1–2 were not in intensive care unit (ICU). The reported

Organ/system	Subscore = 1	Subscore = 2	Subscore = 3
Liver	Bilirubin <6 mg/dL	Bilirubin ≥6 mg/dL and <12 mg/dL	Bilirubin ≥12 mg/dL
Kidney	Creatinine <2 mg/dL	Creatinine ≥2 mg/dL and <3.5 mg/dL	Creatinine ≥3.5 mg/dL or renal replacement
Brain (West-Haven grade for HE)	Grade 0	Grade 1-2	Grade 3-4*
Coagulation	INR <2	INR ≥2.0 and <2.5	INR ≥2.5
Circulatory	MAP ≥70 mmHg	MAP <70 mmHg	Use of vasopressors
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	 >300 or >357	 >200 and ≤300 or >214 and ≤357	 ≤200# or ≤214#

Adapted from Reference [13]
The framed area describes criteria for diagnosing organ failures.
Abbreviations: HE, hepatic encephalopathy; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.
*Patients submitted to Mechanical Ventilation (MV) due to HE and not due to a respiratory failure were considered as presenting a cerebral failure (cerebral subscore = 3).
#Other patients enrolled in the study with MV were considered as presenting a respiratory failure (respiratory subscore = 3).

Fig. 1 The CLIF-organ failure (CLIF-OF) scoring system [13]

Table 1 ACLF grades and mortality without liver transplantation [11]

Category	Definition	28-day mortality without LT (%)	90-day mortality without LT (%)
No ACLF	No OF or a single non-renal OF without renal dysfunction and cerebral dysfunction	1.9	10
ACLF (total)		33	51
ACLF grade 1	Includes one of the following: renal failure, single non-renal OF which is associated with renal and/or cerebral dysfunction	23	41
ACLF grade 2	Two OFs of any combination	31	55
ACLF grade 3	Three or more OFs of any combination	74	78

Adapted from Ref. [11]

ACLF acute-on-chronic liver failure; *LT* liver transplantation; *OF* organ failure

28-day transplant-free mortality rate was 6% in those with ACLF resolution, 18% in those with final ACLF-1, 42% in those with final ACLF-2, and 92% in those with final ACLF-3, regardless of the initial ACLF grade.

The clinical trajectory could have been predicted at days 3–7 in most patients (81%). The estimated survival at 28 days was high in patients with no ACLF (89.6%) and ACLF-1 (78.7%) at 3–7 days, and lower in patients with ACLF-2 (42.9%) and ACLF-3 (12.8%) at 3–7 days. Taken together, these data suggest that ACLF has a potential for reversibility and that the increasing grades of ACLF may be associated with limited capacity for liver regeneration and hence ongoing extra-hepatic OFs.

Prognostic scores

Several prognostic tools to support clinical practice are available (see Supplementary material: Supplementary table 2). The CLIF-C ACLF score enables dynamic risk stratification of patients in a critical care setting and proved to be useful for consideration and listing of patients for liver transplantation (LT), early hospital discharge or determination of futility of ongoing ICU supportive care in the absence of liver transplantation [13]. Compared with the CLIF-C ACLF score, the model for end-stage liver disease (MELD) score underestimated the risk of death of patients by 20–30%, suggesting that organ allocation for LT using the MELD score seriously disadvantages the patient with ACLF. The ACLF grading system and the CLIF-C ACLF score allow a stepwise algorithm for a rational management of patients with ACLF [13, 16, 17]. An online calculator is available: https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf. The APASL ACLF Research Consortium (AARC) score [18] is based on the APASL definition of ACLF which may underestimate the diagnosis of this condition. The North American Consortium for the Study of End Stage Liver Disease (NACSELD) score includes criteria which are representative of advanced circulatory, renal, brain and ventilatory failure. This score may be best used to address consideration of futility of aggressive intensive care [19]. The Chinese Group on the Study of Severe Hepatitis B (COSSH) ACLF score includes specific risk factors for mortality in patients with ACLF related to Hepatitis B virus (HBV) infection [20], and its application should not be extended to non-HBV population. None of these scores have reached a c-statistic of ≥ 0.8, which indicates an excellent prognostic model. Thus, all models can only be considered to be clinically useful, but they require additional modelling and refinement using objective, verifiable and continuous variables.

Pathophysiological considerations

Cirrhosis-associated immune dysfunction: towards a new paradigm of ACLF

Immune deficiency and systemic inflammation are two key components of cirrhosis-associated immune dysfunction (CAID) [21, 22], and they are both present in patients with ACLF [23]. The immune deficiency [24] affects both the innate and acquired immune responses and contributes to increased risk of infections [24]. Systemic inflammation is considered a major driver of single or multiple OFs in ACLF [11, 14, 25] through two different mechanisms: immunopathology, i.e., direct damage to tissues, and immunometabolism, i.e., an energetic imbalance [26, 27]. A key component of the systemic inflammation is the disruption of the gut–liver axis, defined by a combination of dysbiosis, a damaged intestinal barrier, and increased bacterial translocation [28]. Systemic

inflammation acts along with organ-specific mechanisms (e.g., portal hypertension (PH), effective arterial blood volume, and hyperammonemia) [25] through a massive release of cytokines, the activation of immunogenic forms of cell death, the exacerbation of oxidative stress, and the greater recruitment and activation of immune effector cells [29] a similar picture to severe sepsis.

Importance of infections in ACLF (Fig. 2)

Bacterial infections (BIs) are a common cause of AD in cirrhotic patients and is over represented as a precipitating event in the patients with ACLF [7, 8, 11, 14, 30]. In the CANONIC study [11], BIs triggered ACLF in one third of the cases; a lower rate (17–24%) was reported in the NACSELD studies [7, 8]. The analysis of 1175 patients with DC and with BI on admission or nosocomial infection, from 6 geographic regions worldwide, reported an overall rate of BI related-ACLF of 48% [30]. Spontaneous bacterial peritonitis (SBP) and pneumonia more frequently precipitated ACLF [30]. Of note, BIs were more frequently nosocomial in patients who subsequently developed ACLF [30]. BIs are not only a frequent trigger of ACLF but also an extremely common complication. Approximately half of non-infected patients with ACLF develop BIs within 4 weeks after diagnosis [31].

BIs caused by multidrug-resistant (MDR) bacteria are more frequently associated with ACLF development [30–33]. The prevalence of multidrug-resistant organisms (MDROs) varies widely among countries and centers and over time [32, 33]. MDROs are more frequently isolated in the ICU, in nosocomial episodes, and in patients with a recent hospitalization (< 3 months) [32, 33]. BIs caused by MDROs are associated with lower resolution rates, higher incidence of septic shock and ACLF and higher short-term mortality compared to those caused by susceptible strains, especially if treated with inadequate empirical antibiotic strategies [30–33]. Rectal colonization by MDRO is a relevant issue in ICU cirrhotic patients, with potential risk of sepsis in the short term [34]. A timely diagnosis and treatment of infection is of paramount importance [14, 31–33].

Invasive fungal infections (IFIs), most commonly invasive candidiasis (70–90%) and aspergillosis (10–20%), can

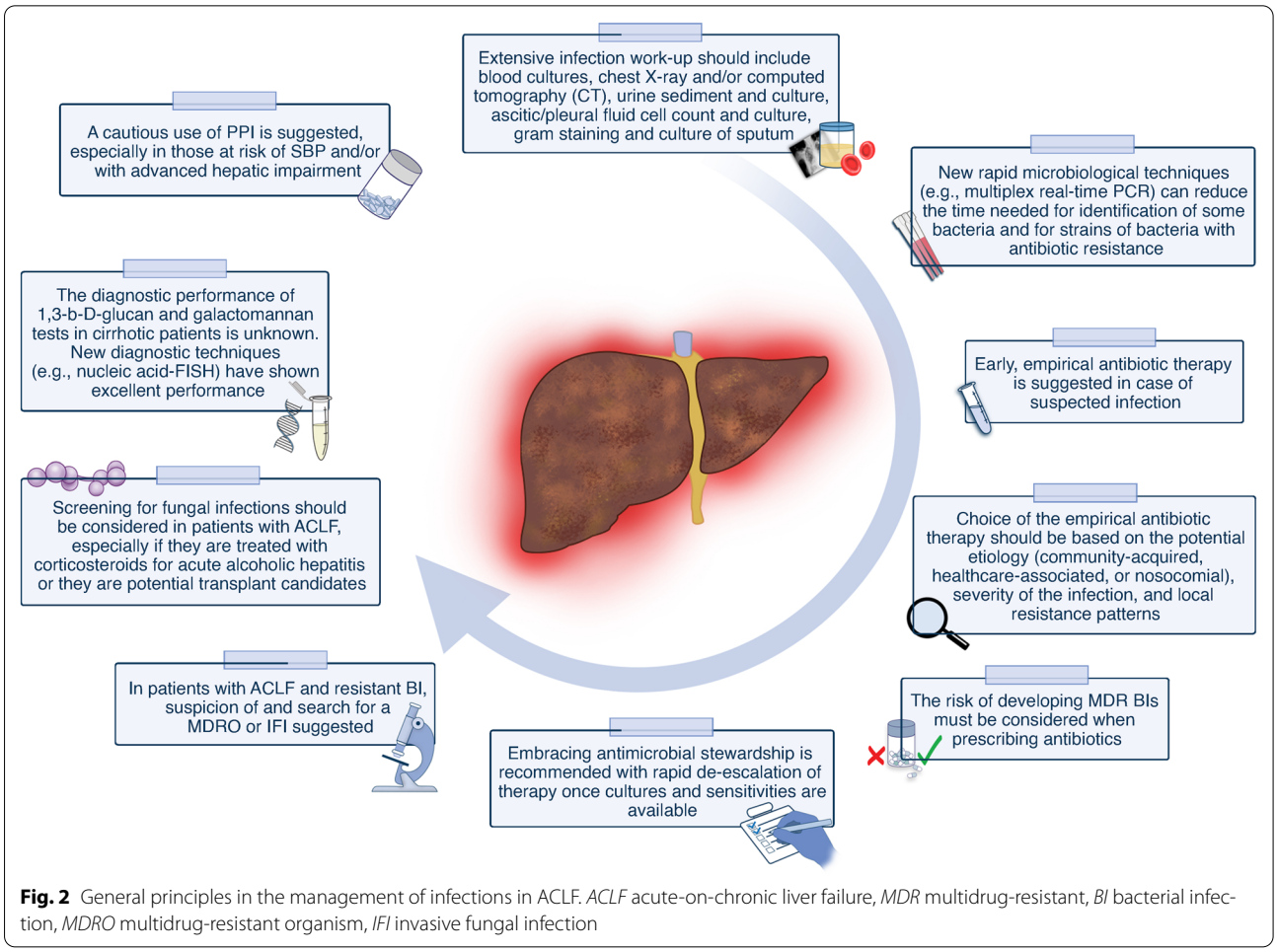

Fig. 2 General principles in the management of infections in ACLF. *ACLF* acute-on-chronic liver failure, *MDR* multidrug-resistant, *BI* bacterial infection, *MDRO* multidrug-resistant organism, *IFI* invasive fungal infection

complicate the course of ACLF (3–7% of culture-positive infections in cirrhosis) [31–33], and result in a high 28-day mortality rate (>45%) [31, 33, 35].

Proton pump inhibitors (PPIs) have been associated with a higher risk of BI (i.e., SBP) and adverse short-term outcomes in patients with SBP, especially for those taking a high daily dose, HE, and acute kidney injury (AKI) [9, 36].

Management of individual organ dysfunction in liver disease patients (Fig. 3)

Liver

Clinical context

The liver plays a central role in the metabolic homeostasis, regulated by hormones secreted by the pancreas, thyroid, and adrenal glands. Therefore, ACLF may cause several metabolic and endocrine disturbances complicating the clinical course.

Evidence

Glycemic control

Cirrhotic patients are often insulin-resistant [37]. Patients developing ACLF can suffer hyperglycemia that can be deleterious on the disease course. Unlike acute liver failure (ALF), hypoglycemia is less common possibly due to concomitant hyperglucagonemia. Consequently, it is of utmost importance to target a serum blood glucose of 110–180 mg/dL, although there are no studies exploring the best target of blood glucose levels in patients with ACLF. There is no evidence to support a very tight glucose control (80–109 mg/dL), which in turns may increase the risk of hypoglycemia [38].

Nutrition

Sarcopenia and frailty might confer an increased risk of morbidity and mortality in ACLF patients with PH [39]. The accelerated starvation typical of cirrhosis is aggravated by PH which contributes to impaired gut motility, ascites, decreased absorption of nutrients, protein-losing enteropathy, inappropriate dietary protein restriction, hospitalization, HE and gastrointestinal bleeding [40]. Direct measurement of resting energy expenditure by indirect calorimetry is advisable in these patients whenever possible [40]. With the lack of robust data in ACLF, it is recommended to follow the guidelines on nutritional support in critically ill patients with cirrhosis [40–42].

Oral feeding or enteral nutrition should be introduced at an early stage, though caution is advised in those at high risk of aspiration, e.g., those with grade III/IV HE, or micro-aspiration, e.g., those with grade II HE. Insertion of a nasogastric tube for enteral feeding in patients with (not bleeding) esophageal varices is not contraindicated and is associated with a low risk of bleeding [43]. Whereas, after acute gastrointestinal bleeding, it is recommend withholding enteral nutrition for 48–72 hours [44].

Parenteral nutrition must be introduced in those who cannot meet their nutritional needs by mouth or in those with an unprotected airway, such as in patients with grade 3–4 HE. Of note, late initiation of parenteral nutrition after ICU admission in patients without cirrhosis is associated with faster recovery and fewer complications as compared with early initiation [45]. Oral branched-chain amino acids (BCAA) have shown a beneficial effect on HE in non-critically ill cirrhotic patients, although with no effect on mortality, quality of life, or nutritional parameters [46]. Their role in ACLF is unclear. The target of nutritional support is the supply of 20–30 kcal/kg body weight/day, increasing over the course of illness from acute to recovery phases, and 1.2–1.5 g of protein/kg ideal body weight/day [40, 47]. The use of actual body weight, corrected for ascites, is considered safe.

Coagulation

Clinical context

Critically ill cirrhotic patients have a fragile, continuum rebalancing between ineffective hemostasis and excessive coagulation, i.e., a rebalanced hemostasis [48–50]. These patients have an impairment of primary hemostasis, secondary hemostasis, and fibrinolysis, with reduction of circulating levels of both pro- and anti-coagulant factors, which results in a net increased risk for both bleeding and thrombotic complications [48–50]. No randomized controlled trials (RCT) investigating the therapeutic interventions to correct the hemostasis in ACLF patients are available [51].

Evidence

While patients with AD have exaggerated thrombin generation (TG), ACLF patients may have TG similar to healthy controls, that may be complicated by simultaneous dynamic changes in fibrinolysis [52]. ACLF patients with sepsis and/or any OF have longer clot lysis times compared to AD patients and this may be the operative mechanism behind formation of intraorgan microthrombi that can worsen OFs [53].

Bleeding in critically ill patients with ACLF mostly results from PH, and the treatment aim should be lowering portal pressure rather than correcting coagulation parameters [54]. Conventional coagulation tests (prothrombin time, PT, INR and activated partial thromboplastin time, aPTT) do not accurately reflect the hemostatic status of ACLF patients [54, 55], and they do not correlate with post-procedural bleeding in cirrhotic patients undergoing invasive procedure [55–57].

Viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are point-of-care test that give a much better estimate of hemostatic balance than other clotting parameters. These are sensitive to decreased levels of both pro- and anti-coagulants and the interaction with platelets and other blood cells, although they are insensitive for von Willebrand factor (VWF) and protein C system (which requires the thrombomodulin) and therefore likely underestimate hemostatic competency. Their use may be reserved in guiding transfusion in patients who are actively bleeding and in whom hemostatic failure likely contributes to the bleeding. They have also shown to reduce the need of blood products transfusion in those undergoing invasive procedures [56, 58].

Procedure-related bleeding in ACLF patients is not common, and its risk is mainly based on the intrinsic risk of the procedure and the operator experience [59]. Transfusion with fresh frozen plasma (FFP) might have a negligible effect on thrombin production, despite improvements in INR, whereas expansion of circulating volume may increase portal hypertensive bleeding risk and fluid overload [60]. Therefore, the protocol use of FFP in ACLF patients with no signs of bleeding should be avoided [55]. Prothrombin complex concentrates (PCCs) including factor II, VII, IX, X, may be preferable to FFP for emergency anticoagulant reversal, in case of bleeding from a non-portal hypertensive cause. This requires accurate monitoring using a TEG- or ROTEM-guided algorithm to monitor the risk of thrombosis and requires sufficient serum levels of fibrinogen [55, 61].

Thrombocytopenia is common in cirrhosis, although platelet adhesion in vitro is preserved by increased levels of VWF [49, 62]. Platelet count exceeding 50×10^9/L is associated with adequate thrombin formation (using thrombin production as a surrogate for clot formation), making this in vitro finding a practical clinical target in the setting of active bleeding or as prophylaxis prior

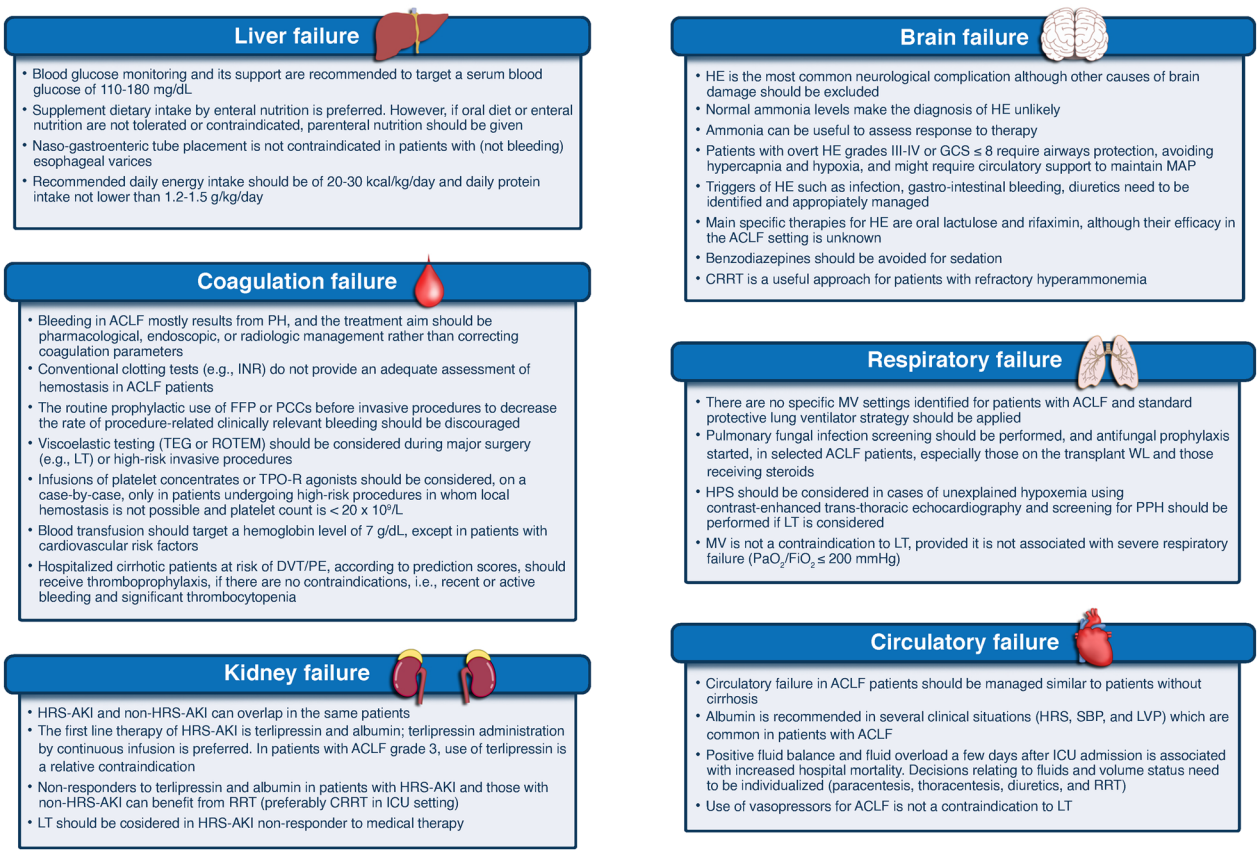

Fig. 3 Tips and tricks of intensive care interventions in ACLF. *ACLF* acute-on-chronic liver failure, *FFP* fresh frozen plasma, *PCCs* prothrombin complex concentrates, *TEG* thromboelastography, *ROTEM* rotational thromboelastometry, *LT* liver transplantation, *TPO-R* thrombopoietin receptor, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *AKI* acute kidney injury, *HRS* hepatorenal syndrome, *RRT* renal replacement therapy, *CRRT* continuous renal replacement therapy, *ICU* intensive care unit, *HE* hepatic encephalopathy, *GCS* Glasgow coma scale, *MAP* mean arterial pressure, *MV* mechanical ventilation, *WL* waiting list, *HPS* hepato-pulmonary syndrome, *PPH* porto-pulmonary hypertension, PaO_2 partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, *SBP* spontaneous bacterial peritonitis, *LVP* large-volume paracentesis, *OF* organ failure

to procedures [63]. The European Association for the study of the liver (EASL) guidelines [55], not specific for ACLF patients, are "against the infusion of platelet concentrates or use of thrombopoietin receptor (TPO-R) agonists prior invasive procedures when platelet count is $>50\times10^9$/L or when bleeding can be treated by local hemostasis. In patients undergoing high-risk procedures, infusion of platelet concentrates or TPO-R agonists may be considered on a case-by-case basis if local hemostasis is not possible and platelet count is between 20×10^9/L and 50×10^9/L, and should be considered on a case-by-case basis if local hemostasis is not possible and platelet count is $<20\times10^9$/L.

In patients with cirrhosis undergoing invasive procedures, routine correction of fibrinogen deficiency or the use of tranexamic acid to decrease the rate of procedure-related clinically relevant bleeding is discouraged [55].

In case of bleeding, inferring from the approach in patients with cirrhosis [64], a restrictive transfusion policy (hemoglobin target of 7 g/dL) to avoid increase in PH, can be applied in patients with ACLF, except in patients with cardiovascular risk factors [9].

Last, the risk of developing deep vein thrombosis (DVT)/pulmonary embolism (PE) is high in patients with cirrhosis, and this might be increased in acutely ill ACLF patients. Therefore, thromboprophylaxis with low-molecular-weight heparin is suggested in patients at risk of DVT/PE (according to clinical prediction scores) without contraindications such as recent or active bleeding and significant thrombocytopenia [9, 55].

Kidney

Clinical context

AKI is observed in more than half of the ACLF patients. Moreover, a significant number of cirrhotic patients also have chronic kidney disease (CKD) (i.e., IgA nephropathy, diabetic or hypertensive kidney disease), which adds another layer of complexity. AKI is associated with higher morbidity and mortality and an increased incidence of CKD after LT. The major cause of AKI in cirrhotic patients is hypoperfusion due to hypovolemia (~50%), followed by intrinsic renal causes (e.g., acute tubular necrosis, ~30%), and hepatorenal syndrome (HRS, ~20%), which is a unique cause of AKI in cirrhotic patients, secondary to renal hypoperfusion along with intense systemic inflammatory reaction. Less than 1% of cases are secondary to post-renal obstruction [65, 66].

Evidence

Definitions

AKI, according to the most recent definition [67], is "an increase in the serum creatinine (sCr) level $\geq$0.3 mg/dL ($\geq$26.5 µmol/L) within 48 h or as an increase in the sCr level that is at least 1.5 times the baseline level and that is known or presumed to have occurred within the previous 7 days". A value of sCr from the previous 3 months (the closest to the admission), if available, can be used as baseline sCr (Fig. 4) [67]. Before 2012, HRS was defined as "a syndrome that occurred in patients with cirrhosis and PH and was characterized by impaired kidney function (sCr > 1.5 mg/dL [132.6 µmol/L]) in the absence of underlying kidney disease". From a clinical perspective, HRS was divided into type 1 (HRS-1), defined by an increase in sCr > 2.5 mg/dL [221 µmol/dL] in < 2 weeks, and type 2 (HRS-2), with a more chronic deterioration in the renal function.

The new definition of HRS replaced the cut off value for the sCr (1.5 mg/dL), with the increase of sCr $\geq$0.3 mg/dL within 48 hours or $\geq$1.5 times baseline level or urinary output $\leq$0.5 mL/kg/h for $\geq$6 h. This allows an earlier recognition and management in those with normal sCr levels but reduced kidney filtrate [67, 68], such as women, old patients, and patients with sarcopenia, very common in cirrhosis. The HRS-1 has been renamed HRS-AKI to distinguish it from the chronic type, HRS-2, now renamed HRS-CKD (Fig. 4) [68, 69].

Terlipressin and albumin

In case of HRS-AKI the first-line therapy is based on the use of albumin (20% human albumin, 20–40 g/day) and vasoconstrictors (terlipressin, or norepinephrine, or midodrine and octreotide) [70, 71]. Terlipressin has shown superiority to norepinephrine on survival in ACLF patients with HRS-AKI [72]. The continuous infusion of terlipressin has been associated with less side effects compared to boluses. Response is defined as complete (return of sCr to a level within 0.3 mg/dL of baseline level) or partial (regression of AKI stage, with reduction of sCr to $\geq$0.3 mg/dL above baseline level). Complete HRS-AKI reversal with terlipressin is observed in 33–81% of patients, with lower rates for more severe ACLF [71, 73, 74]. Patients with partial response should continue receiving terlipressin until there is a complete response or to a maximum duration of 14 days. Recurrence of HRS-AKI once treatment is discontinued can occur in up to 20% cases and retreatment is usually effective [73]. The most worrying adverse effects of terlipressin include ischemic events (e.g., digital infarction, gut ischemia, cerebral ischemia), respiratory failure and pulmonary edema [71]. Therefore, terlipressin should be avoided in case of ACLF grade 3, baseline oxygen saturation < 90%, peripheral, coronary or mesenteric ischemia. Evaluation of cardiac function is suggested prior to starting terlipressin. Notably, as the development of ischemic events or respiratory failure might make potential or listed patients ineligible for LT, the benefits of terlipressin

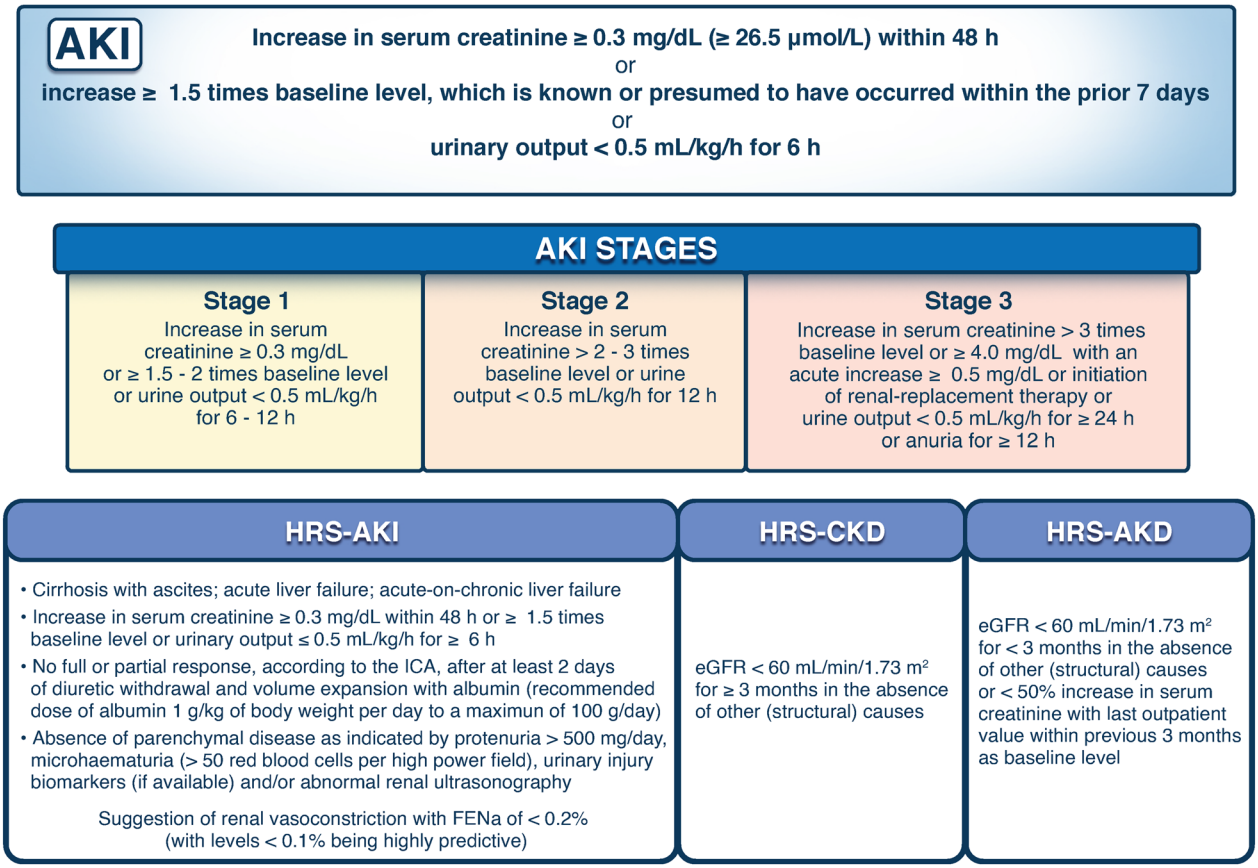

Fig. 4 Definition of AKI, AKI stages, HRS-AKI, HRS-CKD, HRS-AKD [65–69]. Adapted from Refs. [65–69]

Baseline serum creatinine level: serum creatinine measured in previous 3 months; in patients with > 1 value within previous 3 months, the value closest to time of hospital admission should be used; in patients without a previous serum creatinine value, the value on admission should be used baseline

AKI acute kidney injury, *HRS* hepato-renal syndrome, *ICA* international club of ascites, *CKD* chronic kidney disease, *AKD* acute kidney disease, *FENa* fractional excretion of sodium, *eGFR* estimated glomerular filtration rate

should not outweigh its risks in patients with high priority for LT (e.g., MELD ≥ 35) [70].

Renal replacement therapy

Timing of institution of renal replacement therapy (RRT) remains controversial, although the composite of acidosis and other metabolic drivers (fluid overload, sodium imbalance and HE) may bring forward the initiation of RRT. RRT can represent a bridge to LT in those with reversible precipitant of their multiple OFs, or in case of non-HRS-AKI [75]. However, the distinction of HRS-AKI and non-HRS-AKI is not always straightforward.

Due to the common hemodynamic challenges in this patients, continuous modes of RRT (CRRT) (continuous veno-venous hemodiafiltration [CVVHDF] or sustained low efficiency dialysis [SLED]) are suggested. Anticoagulation may be achieved with a variety of agents according to the patients clinical and physiological status (heparin, epoprostenol or citrate). In ACLF patients demonstrating hypercoagulability and filter clotting, the use of citrate seemed to be safe, provided acid–base balance and electrolytes are monitored closely [76, 77].

Liver transplantation

EASL guidelines recommend that LT should be considered in case of HRS-AKI not responding to therapy [75].

Brain

Clinical context

HE is the most common neurological complication in ACLF. This most likely arises secondary to hyperammonemia in the setting of a systemic inflammatory response. Exclusion of intra-cranial hemorrhage and

stroke, decompensated diabetes, psychiatric issues, and alcohol-related dementia is necessary [78, 79]. Elevated ammonia levels are common in HE, though many patients with elevated ammonia will not have HE; on the other hand, normal ammonia levels is incompatible with the diagnosis of HE. HE grades III-IV (West Haven classification) [80] is associated with higher in-hospital mortality compared to lower HE grades [81]. Treatment of HE in ACLF is derived from the chronic setting.

Evidence

Airways, breathing, circulation, electrolytes, glycemia and ammonia

Endotracheal intubation is suggested to mitigate the risk of aspiration in case of Glasgow coma scale (GCS) ≤ 8 (or HE grade III-IV). Benzodiazepines should be avoided for sedation. Hypoglycemia and hyponatremia should be monitored and corrected. Reduction in ammonia levels reflects response to therapy [82], although clinical improvement often lags significantly behind changes in ammonia.

Treatment of precipitating factors

Infection screen and start of empirical antibiotics start should be urgent since BI is a common trigger for HE [83]. Diuretics should be stopped, intravascular volume depletion corrected and search for gastro-intestinal bleed and abuse of recreational or therapeutic drugs, e.g., benzodiazepines, haloperidol and alcohol, performed [78].

Specific therapies

Ammonia targeting drugs

Lactulose is currently the mainstay for treating HE in cirrhotic patients [84], as it reduces the absorption of the ammonia by converting it to ammonium in the colon. Its administration by enema may be clinically effective, whereas via nasogastric (NG) tube in ventilated patients with ileus may be poorly tolerated. Enteral poly-ethylene glycol could be an alternative [85]. The use of rifaximin, a non-absorbable antibiotic, ornithine phenylacetate, L-ornithine-L-aspartate and glycerol phenylbutyrate has not been tested in the ACLF setting [86–92]. In refractory hyperammonemia, CRRT may be useful as shown in patients with ALF [93].

Albumin, albumin dialysis and hemadsorption techniques

Albumin infusion can be beneficial, particularly in patients with diuretic-induced HE [94], though there is no clear evidence in ACLF [95]. The use of extracorporeal albumin dialysis (ECAD) using the molecular adsorbent recirculating system (MARS) can improve refractory HE in patients with ACLF with no clear gain in survival [96, 97]. No data exist on the use of the cytokine adsorber Cytosorb® in the ACLF setting although data in patients with ALF are not promising [98].

Lung

Clinical context

Critically ill patients with cirrhosis are at risk of developing respiratory failure for a variety of reasons that may or may not be due directly to cirrhosis and ACLF. These include microbial and/or aspiration pneumonia, overload-related and/or due to hepatic hydrothrorax and hepatopulmonary syndrome (HPS). Porto-pulmonary hypertension (PPH) does not cause respiratory failure but may result in right ventricle failure.

Evidence

Mechanical ventilation

The prognosis of cirrhotic patients requiring mechanical ventilation (MV) for respiratory failure in the ICU is poor, with a reported one-year mortality of 89% [99]. No studies on ventilation strategies and settings have been specifically conducted for patients with ACLF, therefore general ICU guidelines should be applied [100].

Hepatic hydrothorax

Hepatic hydrothorax may be infected in a manner similar to SBP and cultures should be taken. Drainage of ascites may result in concurrent drainage of the pleural fluid. Consideration may be given to LT [75] but not to trans-jugular intrahepatic portosystemic shunt (TIPS) [75, 100], especially in patients with severe ACLF. Drainage with an intercostal drain may be required but can be hazardous with intercostal varices to consider [117], risk of infection and ongoing large volume loss when the drain is removed [118]. However, drainage of the pleural fluid is often crucial to maintain gas exchange and should therefore be undertaken with ultrasound guidance and specialist support.

Microbial and/or aspiration pneumonia

Mortality due to sepsis is increased in patients with cirrhosis, especially in the case of bacterial pneumonia [101–105]. In addition, cirrhosis is associated with immune system dysfunction [21, 22], which can lead to *Pneumocystis jirovecii* pneumonia [106, 107] and fungal pulmonary infections [33, 35].

Hepatopulmonary syndrome and porto-pulmonary hypertension

Hepatopulmonary syndrome (HPS) and PPH are specific, cirrhosis-induced causes of pulmonary and/or cardiac dysfunction with distinct pathophysiological causes and clinical consequences. HPS should be sought in cases of

unexplained hypoxemia in critically ill cirrhotic patients [108, 109]. It is associated with vascular shunting through the lung parenchyma and results in abnormal arterial oxygenation (defined by an elevated alveolar-arterial oxygen gradient ≥ 15 mmHg, or ≥ 20 mmHg if age >64 years, while breathing room air in the sitting position at rest), worse when upright and diagnosed with contrast-enhanced trans-thoracic echocardiography (late identification of microbubbles in the left atrium or ventricle ≥ 3 cardiac cycles after injection of 10 mL agitated saline in a peripheral arm vein) [108]. Platypnea (worsening of dyspnea moving supine to upright position) and orthodeoxia (drop in $PaO_2 > 5\%$ or >4 mmHg when standing) are common in this syndrome (one quarter of HPS patients) [108, 109].

PPH is the pulmonary arterial hypertension (PAH) in the setting of PH [110], which should be sought in any cirrhotic patient with elevated right sides pressures and can constitute a contraindication to liver transplantation. The confirmatory diagnosis requires right heart catheterization (RHC) [110, 111], which shows an increase in mean pulmonary artery pressure (mPAP) >25 mmHg (secondary to the increase in pulmonary vascular resistance (PVR) >3 wood units [240 dynes/s per cm^{-5}]) in the setting of a normal PA wedge pressure (PAWP, <15 mmHg) [107, 108]. Other causes of pulmonary hypertension in cirrhotic patients include high flow state, intravascular central blood, diastolic dysfunction, obstructive/restrictive lung disease, sleep disordered breathing [109]. There is no evidence available concerning the management of these situations in the specific context of ACLF, but general practical guidelines are available for diagnosis and management of these conditions [109]. PPH and HPS can coexist [111].

Safe and successful LT can be accomplished in the setting of an mPAP >35 mmHg and normal PVR (<240 dyn-s/cm^{-5}) [111]. Multicenter RCTs and open-label clinical trials of PAH-targeted therapies in PPH have recently demonstrated safety and efficacy [112].

Respiratory failure and liver transplantation for patients with ACLF

Large-scale transplant registry studies have reported that pre-LT MV is associated with poorer post-LT prognosis in patients with ACLF [113, 114]. A small granular study has shown that MV should not constitute a contraindication to LT per se, provided there is no active infection, $FiO_2 \leq 40\%$ and positive end-expiratory pressure ≤ 10 cmH_2O [115]. By contrast, patients requiring pre-transplant MV with low PaO_2/FiO_2 (≤ 200 mmHg) have been reported to have higher post-LT mortality [116].

Circulation

Clinical context

Hemodynamic assessment and management of patients with cirrhosis and PH raises specific challenges. Splanchnic vasodilation can result in central intravascular hypovolemia, leading to renal vasoconstriction and sodium and water retention in patients who often already have ascites, pleural effusion, and extravascular fluid overload. In addition, patients may have both systolic and diastolic cardiac dysfunction and, as noted previously, may also have pulmonary venous or arterial hypertension. Cirrhotic cardiomyopathy (CCM) defines cardiac dysfunction in patients with end-stage liver disease in the absence of prior heart disease. CCM represents a causative or contributory factor in the pathogenesis of OF(s), and morbidity and mortality following surgery, transplantation, and infection [119, 120]. The role of markers of myocardial injury (e.g., brain natriuretic peptide [BNP], propeptide N-terminal prohormone [NT-proBNP], and cardiac troponins [either T or I]), advanced cardiac imaging, submaximal exercise testing, contractile reserve on myocardial stress imaging, markers of right ventricular dysfunction, and electrocardiography (ECG) abnormalities to improve evaluation of CCM has not been proved yet [121]. Cardiomyopathies may be seen specific to some disease states (e.g., alcohol or haemochromatosis) or congenital (e.g., Alagille syndrome) and might contribute to OF(s) (e.g., HRS-AKI) and poor outcomes before and after LT [119, 120].

Evidence

Fluid therapy

Crystalloid solutions are the recommended as the initial fluid of choice for patients who have hypovolemia [100, 122, 123]. Albumin, recommended in HRS-AKI, SBP and large-volume paracentesis (LVP), may also be considered for fluid resuscitation [100, 123–125]. Notably, higher positive fluid balance and fluid overload at day 7 in ICU might increase in-hospital mortality [126].

Vasopressors

Norepinephrine is the first-line vasopressor in patients with ACLF [100, 122, 123]. Adding terlipressin or vasopressin to norepinephrine as second line agents for persistent hypotension has been suggested [100, 123], but only with very little evidence in cirrhotic patients [127].

Since cirrhotic patients tend to have splanchnic vasodilation, which makes them chronically hypotensive, a median arterial pressure (MAP) target of 60–65 mmHg can be acceptable, although their management should be personalized [100, 123]. Non-invasive and invasive methods to assess organ perfusion and cardiac function should

be introduced at an early stage to guide fluid replacement and inotrope support [77, 100].

Steroids

Relative adrenal insufficiency (RAI) is common in critically ill patients (51–82%) [128–130]. This should be suspected in case of refractory hypotension, unexplained and/or severe hyponatremia, or unexplained and/or persistent hypotension relative to baseline [130]. Diagnosis is based on adrenocorticotropic hormone (ACTH) stimulation testing with cortisol levels (delta cortisol rather than peak cortisol) [130]. A trial of hydrocortisone doses of 200–300 mg/day for patients with increasing vasopressor requirements is cautiously suggested [100, 129–132].

Serum lactate

Elevated serum lactate levels in patients with severe ACLF can be due to tissue hypoperfusion, to decreased lactate liver clearance, and increased glycolytic production [133, 134]. Persistently elevated serum lactate levels are predictive of inpatient mortality for patients hospitalized with chronic liver disease [135], patients hospitalized with ACLF [136] and patients with cirrhosis in the ICU [137].

Circulatory failure and LT

Among patients with ACLF-3, pre-LT circulatory failure was not associated with higher post-LT mortality in a granular multicenter study [138]. However, pre-LT elevated lactate levels were independently associated with post-LT mortality in two multicenter studies [116, 139].

Pre-transplantation cardiac risk evaluation

General consensus recommendations are available concerning cardiovascular risk assessment in LT [140, 141], but there are currently no guidelines concerning pre-transplant evaluation for patient presenting with ACLF. When patients are potential candidates for LT but have not been listed prior to developing ACLF, they require urgent pre-transplant workup. Non-invasive assessment of heart function, heart valves, and CCM, and RHC if there are concerns of PPH, should be performed. Evaluation of coronary artery disease (CAD) is suggested by coronary artery calcium scoring via computed tomography angiography or directly with coronary angiography. Angiography can be performed safely in LT candidates even with renal dysfunction and elevated bleeding risk and the trans-radial approach should be preferred for the patients [140, 141]. If coronary artery imaging is not available and the patient is in shock (as expression of cardiac failure in the context of ACLF), monitoring of serum troponin level and/or ECG could constitute a simplified "stress test" for LT clearance.

Critical care management

Clinical context

Individual OF management is described in each OF section above (Fig. 5) and recent guidelines have reviewed the literature on this topic in great detail [9, 100, 122, 142]. While the number of patients with cirrhosis admitted in the ICU has increased and their prognosis has improved over time [143–145], short- and long-term survival remains poor for this category of patients [105, 146, 147]. There is nevertheless no consensus over criteria that should guide the admission of these patients in the ICU, but there is growing agreement that cirrhosis should not, in and of itself, constitute a contraindication to admitting a patient with multiorgan failure in the ICU. Admitting patients for a trial of ICU care is reasonable given that the clinical course and prognosis of patients with severe ACLF is easier to evaluate 2–7 days after ICU management [16, 148, 149]. In patients for whom LT is not an option, determining the potential futility or inappropriate levels of care within an ICU environment should be considered after having a few days' hindsight and response to interventions [150, 151]. A detailed discussion of various prognostic scores that can be used in this context is available in a recent review [122]. In general, a CLIF-C ACLF score >70, 3–7 days after initiation of intensive care support, should guide discussions regarding potential futility of ongoing ICU support [151]. However, it should always be considered that prognostic scores can, in themselves, only provide a partial help guiding as to whether ongoing treatment is appropriate for an individual patient. Other elements, such as frailty and the clinical course of the patient during the ICU stay, should be taken into account.

Evaluation for potential LT should be at the heart of ICU management

LT is the only life-saving treatment that can radically improve the long-term prognosis of patients with ACLF [152–154]. The limits of this therapeutic strategy are outside the scope of this narrative review and, given donor organ shortage, LT will only be available to a minority of patients with severe ACLF. However, early identification of patients who are eligible candidates for LT is crucial since it can radically change their prognosis. A European study focusing on the epidemiology of LT for critically ill patients with cirrhosis has shown that there are variabilities in LT practice in this indication [155]. These variabilities translate into inequity of access to a life-saving treatment. One of the factors that limits access to LT is the capacity to perform the pre-LT work-up in ICUs. Indeed, most patients transplanted with ACLF-3 in the European study were listed while they had ACLF-3 [154, 155]. This implies that intensivists need to collaborate with transplant specialists

to quickly conduct the pre-LT work-up in the ICU. This also holds true outside LT centers, where intensivists need to be aware that LT can be an option for severe ACLF patients, including when the patient is not on the transplant waitlist at the time of ACLF diagnosis (Fig. 5). Physicians in secondary care centers need to know that such patients should be referred to LT centers for potential urgent LT [154, 156]. In this respect, conducting a thorough anamnesis as early as possible is crucial, especially when the patient is at risk of severe HE or of requiring sedation for MV. Obtaining the patient's complete medical history and conducting an in-depth psychological/psychiatric evaluation, directly by the patient and/or with the help of family members or close people, especially in the context of alcohol-related liver disease, is a necessary precursor to taking the decision to carry out a pre-LT work-up. This can all too easily be overlooked and undervalued in ICU academic medical literature and clinical practice. Neither biomarkers nor prognostic scores nor ICU care, with the ICU's emphasis on complex, costly invasive care and machine-driven organ support, should overshadow the importance of this undertaking.

Interventions other than LT or specific organ support

Several artificial and bioartificial extracorporeal liver support systems have been tested in ACLF [157–159]. Examples of artificial extracorporeal liver support systems are MARS, single-pass albumin dialysis, and fractionated plasma separation and adsorption (Prometheus) liver support system. MARS device may be considered, where available, in patients with HE refractory to 24–48 hours of standart medical treatment (SMT) although no survival benefit has been shown; the decision to stop or to continue extracorporeal therapy after a minimum of three sessions should be based on a careful individual clinical assessment of efficacy and safety. A novel liver dialysis device specifically developed for ACLF patients (DIALIVE) has recently been tested in a small RCT, that shows that the device is safe and its use is associated with significant reduction in

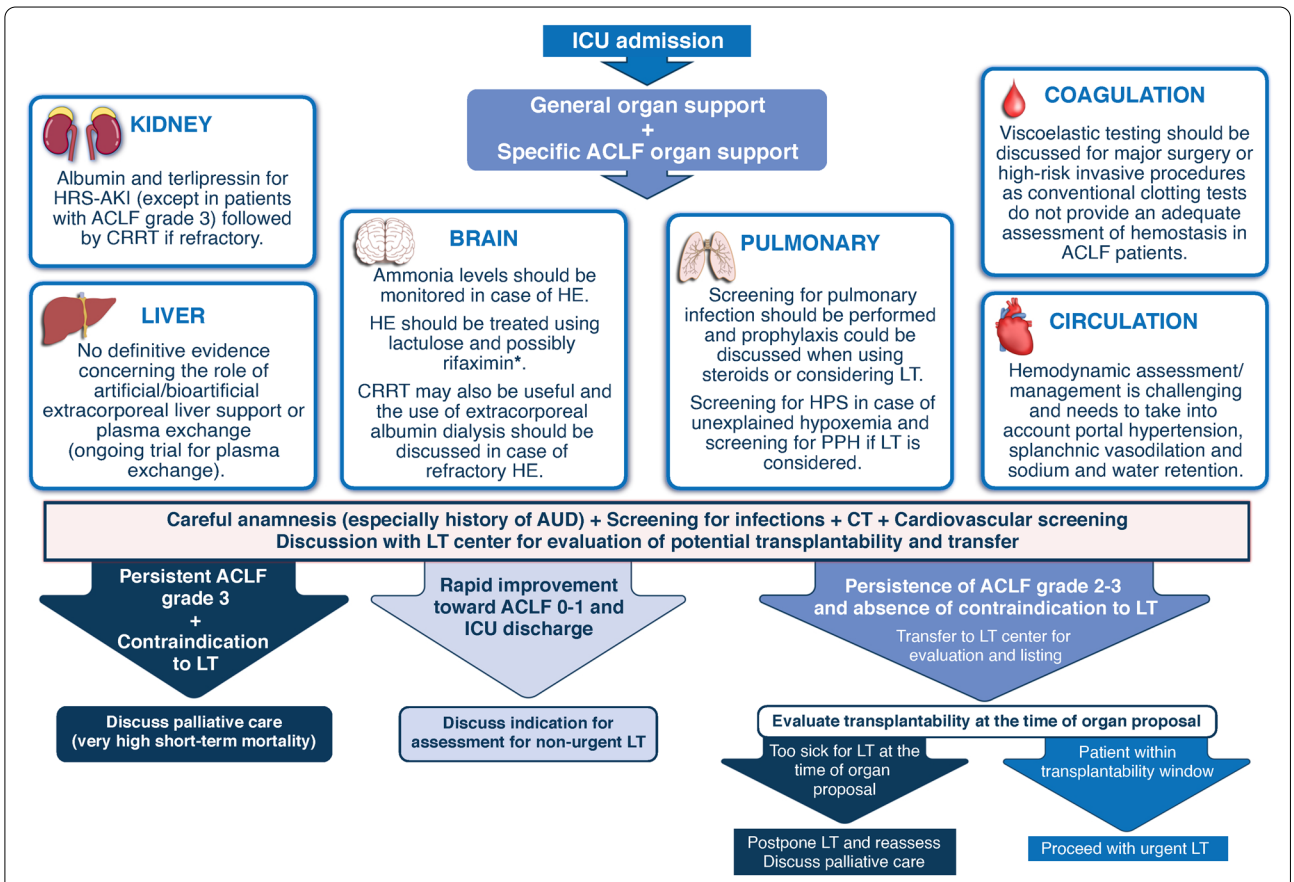

Fig. 5 Specificities of management of patients with ACLF in ICU. *Scant data to inform their use in ICU setting. *ICU* intensive care unit, *PE* plasma exchange, *ACLF* acute-on-chronic liver failure, *LT* liver transplantation, *HPS* hepato-pulmonary syndrome, *HRS-AKI* hepato-real syndrome-acute kidney injury, *PPH* porto-pulmonary hypertension, *HE* hepatic encephalopathy, *GCS* Glasgow come score, *CRRT* continuous renal replacement therapy, *AUD* alcohol use disorder, *CT* computed tomography

time to resolution of ACLF and pathophysiological biomarkers [160]. These artificial extra-corporeal liver support systems can only perform the detoxifying functions of the liver. The bioartificial extracorporeal liver support systems, by contrast, can provide synthetic and detoxifying functions of the liver but has not been shown to improve survival [157–159]. The latter requires a source of hepatocytes (human or porcine), the technology is complex, and raises concern for xeno-transmission [157]. The role of plasma exchange in the treatment of patients with ACLF in under investigation. The ongoing APACHE phase III trial will provide pivotal results on the efficacy and safety of plasma exchange as a treatment to improve survival in ACLF [161].

Liver transplantation

LT is an effective therapeutic option for patients with ACLF. Recent data have shown a clear survival benefit, even in those with ACLF-3 [113, 139, 162], although the path to LT is very challenging. Many patients with ACLF are not listed for LT on the assumption that they are too ill to survive LT [156]. Patients with ACLF listed for LT have a high mortality rate on the waiting list (WL). There could also be a significant delay in listing patients for logistical reasons or because of indecisiveness about the utility or futility of LT in such a situation. Moreover, there may be center specific differences in listing for LT in the presence of multiple OFs. These factors introduce a dimension of selection bias in the studies published to date [155, 156].

Because a large proportion of patients with ACLF die on the WL, a better rule for organ allocation is probably needed for this group. ACLF grade and the specific score for ACLF (CLIF-C ACLF score) [13] are more accurate for prediction of short-term outcomes than the MELD score. Indeed, an analysis of the United Network for Organ Sharing (UNOS) database clearly showed that deaths on the WL of patients with MELD scores < 25 was high if they had ACLF grade 3 [114]. In fact, a pilot program has been introduced in the United Kingdom where patients with ACLF grade 3 are allocated organs on a special tier such that they can get access to organs rapidly. Wider implementation of these scores could decrease the mortality on the WL, but they need further evaluation and validation.

The limits defining when a patient should be considered too sick for transplantation and LT should be considered

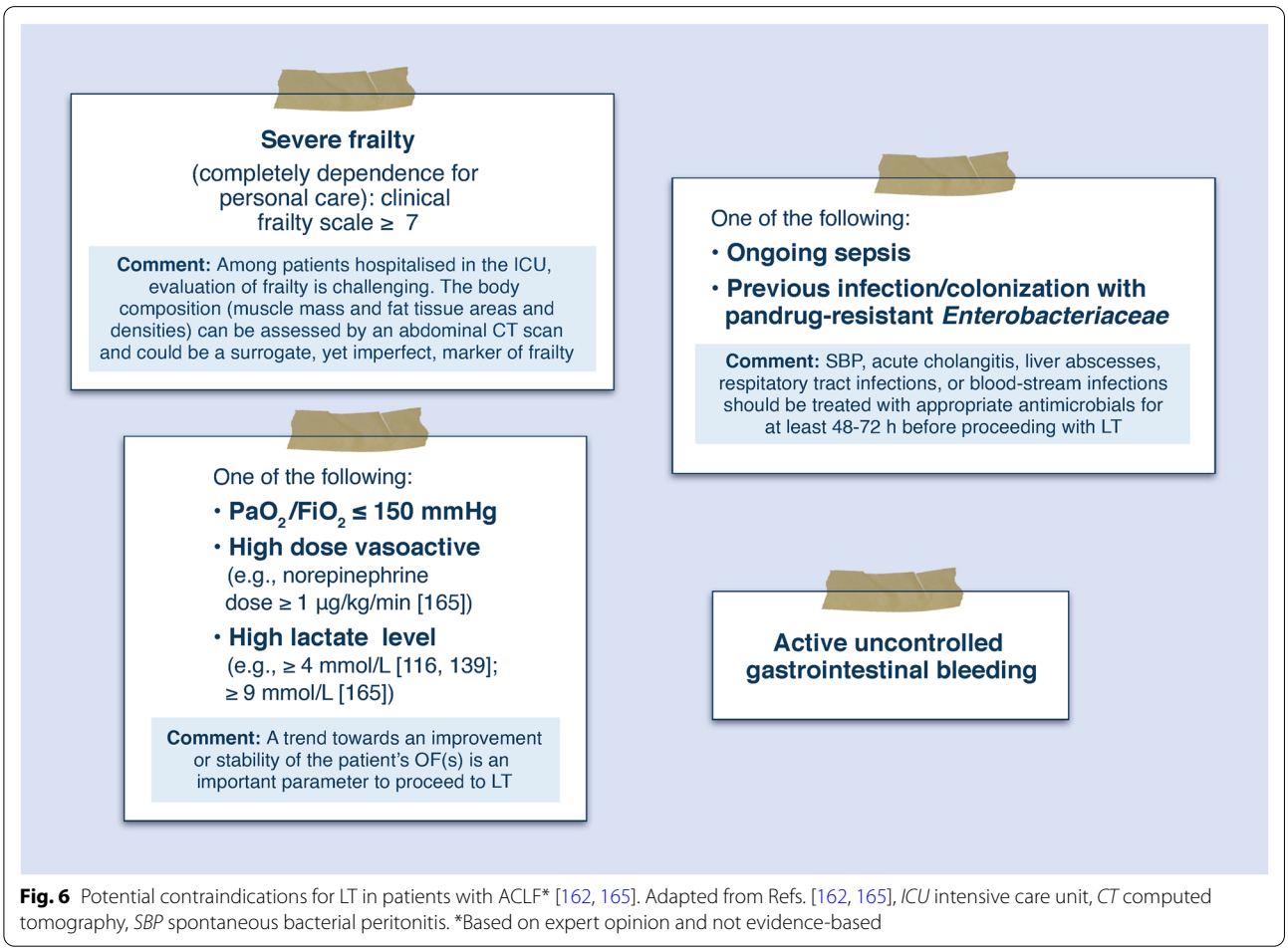

Fig. 6 Potential contraindications for LT in patients with ACLF* [162, 165]. Adapted from Refs. [162, 165], *ICU* intensive care unit, *CT* computed tomography, *SBP* spontaneous bacterial peritonitis. *Based on expert opinion and not evidence-based

futile are currently not completely known [154, 162–165]. In addition to general considerations such as advanced age, portal vein thrombosis, extra-hepatic cancer, and severe co-morbid illnesses, there are several potential contraindications for LT (Fig. 6) [162, 164, 165]. Of note, many of these contraindications are based on expert opinion [165]; in addition, none of these parameters taken solely can discriminate outcomes following LT [164]. Using a combination of baseline characteristics and ICU-specific variables, two prognostic models have been developed and need further validation [116, 166]. Transplantation for ACLF-3 model (TAM) score was developed in Europe to define the risk of death following transplantation of patients with ACLF-3. Independent predictors of mortality were age > 53 years, arterial lactate > 4 mmol/L, a PaO_2/FiO_2 ratio < 200 mmHg and need for MV, and a white cell count $< 10 \times 10^9$/L (https://www.chru-strasbourg.fr/transplantation-for-aclf-3-patients-model-tam-score/). This is a categorical score with a score ≥ 2 defining a high risk of post-LT mortality [116]. The Sundaram acute on chronic liver failure liver transplantation model (SALT model) (https://vocal.shinyapps.io/MODEL/) was developed in the United States of America and validated in Europe. It includes age, use of two inotropes, respiratory failure, diabetes mellitus and body mass index, all risk factors for post-LT death in ACLF grades 2 and 3 [166].

However, the decision to offer or not a LT is often complex and requires multidisciplinary expertise; selection of very sick patients with extrahepatic OFs for LT is more art than science and dependent upon a combination of different variables. The ongoing global CHANCE study [NCT04613921] aims to address several unanswered questions on better defining the role of LT for patients with ACLF [167].

It is important to integrate principles of palliative care early in ACLF for both patient/caregiver comfort. In the lack of established guidelines, future research should assess the effect on wait-list mortality and quality of life in patients with ACLF regardless of listing status [168].

Box 1. Liver transplantation for ACLF

- One-year post-LT survival of patients with ACLF, who are known to have a high risk of short-term mortality, can be > 80%, providing evidence of transplant benefit
- Current organ allocation systems underestimate the risk of death of patients with ACLF grade 3
- Severe frailty, ongoing sepsis, < 48–72 h of appropriate antimicrobial therapy in case of infections, or active uncontrolled bleeding should be considered reasons to delay LT
- The thresholds of severity of OFs that could be associated with high risk of post-LT mortality are a PaO_2/FiO_2 < 150 mmHg, a high norepinephrine dose > 1 µg/kg/min, and/or a serum lactate level ≥ 4 mmol/L and should be considered potential contraindications

LT liver transplantation, *ACLF* acute on chronic liver failure, *OF* organ failure, PaO_2 partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen

Perspectives and conclusions

The recognition of ACLF as a distinct clinical entity from DC and the validation of its diagnostic and prognostic criteria has changed our understanding of the trajectory of cirrhosis. It provides the framework for early identification of patients at high risk of mortality and in need of intensive care, defining the futility of ongoing intensive care in those unlikely to survive, prioritizing patients for LT and identifying those unlikely to survive with a LT. The recognition that ACLF has a unique pathophysiology in which systemic inflammation plays a key role, provides the basis of novel therapies, several of which are now in clinical trials. These new developments are already impacting on the clinical care, public policy and healthcare costs.

Supplementary Information

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Declarations

Conflicts of interest

GP, TA, EDM, JW and MC do not have conflicts of interest related to this manuscript. RJ is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Discovery, Hepyx Limited (spin out companies from University College London), and Cyberliver. He has research collaborations with Yaqrit Discovery.

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