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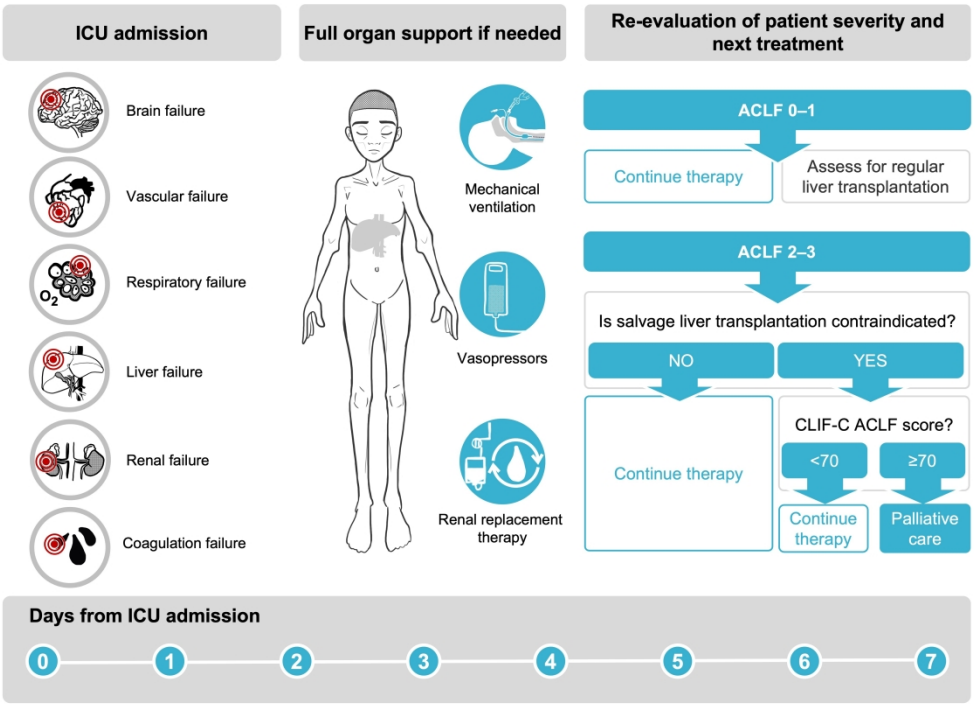

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CRITICAL CARE MANAGEMENT OF ACUTE-ON-CHRONIC LIVER FAILURE: CERTAINTIES AND UNKNOWNS

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ABSTRACT

Intensive care unit (ICU) admission is frequently required in patients with decompensated cirrhosis for organ support. This entity, known as acute-on-chronic liver failure (ACLF), is associated with high short-term mortality. ICU management of ACLF is complex as these patients are prone to develop new organ failures and infectious or bleeding complications. Poor nutritional status, lack of effective liver support systems and shortage of liver donors are also factors that contribute to increase their mortality. ICU therapy parallels that applied in the general ICU population in some complications but has differential characteristics in others. This review describes the current knowledge on critical care management of patients with ACLF including organ support, prognostic assessment, early liver transplantation and futility rules. Certainties and knowledge gaps in this area are also discussed.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a clinical syndrome occurring in patients with decompensated cirrhosis (ascites, hepatic encephalopathy, gastrointestinal hemorrhage) characterized by the presence of new-onset organ failures, intense systemic inflammation, and high short-term mortality[1]. Most cases occur in previously decompensated patients but, in about 40% of cases, ACLF may aggravate the first episode of decompensation[2]. The syndrome is triggered by proinflammatory events, mainly bacterial infections and severe alcoholic hepatitis, severe bleeding, and hepatitis B virus reactivation, among others. ACLF is an extremely dynamic and reversible condition that has a 28-day mortality ranging from 23 to 89% depending on the number of organ failures[2,3]. Early liver transplantation (LT) may be the only option for many patients.

There is no specific treatment for ACLF and management relies on treating the precipitating event, providing organ support, and expediting evaluation for LT[1,4]. Diagnostic criteria vary among European, North American and Asian societies (See Table 1), but all definitions identify a population at high risk of mortality with a distinct pathological phenotype[2,5,6]. Clinical and inflammatory phenotypes of patients with decompensated cirrhosis who will further develop ACLF also differ from those who will not[3]. Among patients with severe alcohol hepatitis or with hepatorenal syndrome, the presence of ACLF is associated with poor treatment response[7,8]. Therefore, ACLF patients are clinically different from simple decompensated cirrhotic patients. Early recognition and referral of these high-risk patients to specialized centers may improve their prognosis. The recognition of ACLF as a distinct syndrome has opened an encouraging research framework for evaluating different therapies and the impact of early LT[9]. ACLF patients often require ICU admission for organ support, which should not be denied as ICU survival in cirrhotic patients has improved in recent years[10,11]. The current manuscript will address certainties and knowledge gaps in critical care of patients with ACLF. Suggested diagnostic work-up and treatment algorithm are shown in Figures 1 and 2, respectively.

MANAGEMENT OF THE MAIN PRECIPITANT EVENTS

1. Infections

Bacterial infections are a frequent complication in patients with ACLF. They can precipitate or complicate the evolution of the syndrome[12,13]. Infections are diagnosed in one third of patients admitted to the hospital with ACLF and complicate its course in around 60% at 28 days[13,14]. Spontaneous bacterial peritonitis, bacteremia and pneumonia are the most common infections and are frequently caused by multidrug resistant organisms. Patients with ACLF and infection present worse clinical course and higher mortality than those without[13,14]. Early diagnosis and appropriate antibiotic therapy are therefore cornerstones of effective management of such patients.

Broad-spectrum antimicrobials adapted to local epidemiological patterns of antibiotic resistance are recommended as empirical treatment of patients with severe infections. Timeliness and optimal administration of antimicrobials are crucial[12]. Any delay in administering adequate antibiotics is associated with an increased mortality, particularly in patients with septic shock[15]. Optimization of antibiotic dosing through prolonged infusions of beta-lactams is also important since it improves clinical efficacy and prevents further antibiotic resistance[16]. These aggressive antibiotic policies must be followed by rapid de-escalation strategies (48-72h), which should rely on the identification of responsible pathogens through rapid or classical microbiological techniques. Epidemiological surveillance data (rectal/nasal swabs) have been suggested to guide the de-escalation process (broad-spectrum antibiotics can be stopped if they are not isolated in the swabs). Finally, reduction in the duration of the antibiotic therapy (up to 7 days for most infections) is also fundamental to prevent new antibiotic resistance[12].

In terms of prevention, it is important to underline that many infections that complicate the course of ACLF are related to the healthcare system[13]. These infections can be prevented through the implementation of adequate hand hygiene programs and of bundles of measures that prevent catheter-related bacteremia and ventilator-associated pneumonia[13]. The administration of granulocyte (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) has been reported to prevent new infections and sepsis in Indian series, finding not confirmed in a recent European

RCT[17,18]. Treatment with GM-CSF also improved the resolution rate of severe infections (SBP and pneumonia) in a single-center RCT[19].

Fungal infections are less frequent than bacterial episodes and usually complicate the course of ACLF (second infection). Invasive candidiasis/candidemia and invasive aspergillosis are the most frequent fungal infections (80% and 20%, respectively) and are associated with very poor prognosis (mortality > 50%) despite adequate therapy[13]. Prompt initiation of empirical antifungal therapy has been suggested in patients with ACLF and prolonged ICU stay who develop shock[20]. Serum 1.3- β-D-glucan is recommended to guide the discontinuation of antifungals.[21].

2. Severe alcoholic hepatitis

Severe alcoholic hepatitis constitutes the second most frequent precipitating event of ACLF in Western countries (40%)[3]. Treatment with corticosteroids in this setting is questionable since treatment efficacy is markedly reduced in patients with severe forms of the syndrome. Consequently, prednisone can be initiated in patients with ACLF-1 or 2 with close clinical monitoring for infection and clinical response (Lille score) but are not recommended in ACLF-3 or in the presence of an uncontrolled infection[22].

3. Hepatitis B virus reactivation

Hepatitis B virus (HBV) reactivation is a common precipitant factor of ACLF in Asian countries[23]. Oral antivirals should be started as soon as possible in these patients since early treatment improves short-term survival. Drugs with potent antiviral effect are recommended in this setting including tenofovir and entecavir[24].

MANAGEMENT OF ORGAN FAILURES

1. Liver, coagulation, and brain failure

Liver, brain, and coagulation failures (See Table 1) are the most inherently associated with advanced/end-stage liver disease. Liver failure is the most relevant organ failure in terms of prognosis in patients with ACLF[25]. Although high bilirubin levels are an easily visible variable of liver dysfunction, INR also accurately reflects liver function. Despite INR being used to categorize coagulation failure, it has a poor correlation with global coagulation status[26]. Coagulation in ACLF patients is complex with viscoelastic tests showing a predominant hypocoagulable state (61% at admission) with prolonged time to initial fibrin formation, clot formation time and reduced clot firmness[27]. Variable fibrinolytic patterns have been described in ACLF and hypofibrinolysis has been associated with sepsis, mortality and organ failure[28]. These disturbances are not correlated with bleeding risk and their prophylactic correction is not indicated prior to an ICU-related procedure (central venous or arterial line catheterization, paracentesis, etc), except for severe disturbances (platelet count <20/µl). If the patient is bleeding, fibrinogen quantification and the use of viscoelastic tests are recommended to better assess coagulative status and guide correction[29].

Brain failure is hard to manage in the ACLF setting since the two essential pathogenic factors, liver dysfunction and portal-systemic shunting, usually coexist with precipitating and worsening factors: infections, hyponatremia, bleeding, etc[30]. Beyond treating precipitating factors, standard medical therapy (lactulose and rifaximin), and minimizing sedation in case of mechanical ventilation, there are no clear options to manage HE in these settings, which in many cases will persist to some degree until LT.

There is no clear role for liver support systems in the treatment of ACLF patients. The systems most studied were based on albumin dialysis (MARS, Prometheus), and were assessed many years ago; despite improving bilirubin and encephalopathy no survival benefit was observed in randomized controlled trials (RCTs)[31]. However, older definitions for ACLF were used and later studies found potential benefits for very short-term survival in ACLF II-III patients (2-3 weeks, bridge to LT)[32]. The complexity and expensiveness of these systems have limited its use and they are being replaced by plasma exchange (PE) which has shown a survival benefit in acute liver failure and shows promising results in ACLF[33–35]. A large ongoing RCT should clarify this point. In the meanwhile, these supportive systems may be considered in ACLF 2-3 patients as a bridge

for LT especially in the setting of high bilirubin levels with cholemic nephropathy, coagulopathy and/or severe HE.

Conflicting results exist regarding the effects of G-CSF in this setting. Initial reports showed that this factor mobilizes progenitor cells to the liver improving hepatic regeneration, liver function and survival[18]. These positive effects of G-CSF on patients with ACLF were not confirmed in a recent European RCT[17], what suggests that only highly selected patients with ACLF benefit from this therapy. Absence of sepsis and extrahepatic failures probably define the target population for this hematopoietic factor.

Modulation of gut microbiota through fecal transplantation has been recently reported as a safe and effective therapy in patients with ACLF and severe alcoholic hepatitis improving liver function and medium-term survival[36].

LT is the clue to definitively correct these failures, especially in ACLF grades 2 or 3 where a mortality of 50% at 3 months is expected. Since these three organ failures are essentially related to end-stage liver failure, their presence must not limit the access to LT but reinforce its indication (see below).

2. Circulatory failure: fluid therapy, vasopressors and hemodynamic targets

Decompensated cirrhosis associates a hyperdynamic circulatory state with high cardiac output (CO) and activation of endogenous vasoactive systems[37]. There is a progressive fall in mean arterial pressure (MAP) as cirrhosis and hydro-saline retention progress to compensate for the effective hypovolemia[38]. Moreover, these patients are at risk of superimposed events further deranging systemic hemodynamics (sepsis and bleeding).

Overall, shock states in patients with cirrhosis are basically related to vasoplegia with high CO. Cirrhotic cardiomyopathy is mainly characterized by diastolic dysfunction with preserved systolic function and high CO[39]. According to current recommendations, a rapid assessment by ecocardiography is advisable in patients with cirrhosis and shock: a vasoplegic pattern is expected in most situations[40]. A low MAP (< 65 mmHg ±lactate

> 2 mM/L) calls for a prompt initiation of vasopressors in cirrhotic patients with or without ACLF, who are more prone to kidney and organ dysfunction than the general septic population[10]. Norepinephrine (NE) is the drug of choice though terlipressin (continuous infusion beginning at 1-2 mg/day) might be an alternative, especially if concomitant variceal bleeding or AKI-HRS are present; attention to acral perfusion must be paid[20]. It is unclear if terlipressin may be a coadjuvant vasopressor for NE instead of vasopressin in ACLF patients with shock (guidelines recommend it when NE goes above 0.25−0.5 μg/kg/min) [20]. Theoretically terlipressin may have additional benefits (splanchnic flow redistribution, lowering portal hypertension)[41–43]However, caution is advised when treating advanced patients (ACLF-3, MELD>35) due to potential ischemic and respiratory side-effects[44].

A target MAP of 65-75 mmHg is reasonable in ACLF patients but specific targets are lacking. This arterial target could be faced to venous pressure to obtain mean perfusion pressure (MPP = MAP – central venous pressure), which has shown a pivotal role for AKI development in septic patients and in cirrhotic patients with ascites receiving β-blockers[45–47]. The optimal MPP has not been established though higher MAPs may be needed in congestive patients (central venous pressure >10-12 mmHg). In patients with tense ascites, a “compartment-like” syndrome has been described leading to altered kidney perfusion pressures. In the presence of tense ascites and high abdominal pressure (≥15 mmHg), decompressive paracentesis (with albumin) usually improves perfusion pressure and kidney function[48,49].

Regarding fluid resuscitation, there is no strong evidence regarding the type and amount of fluid to administer and strategies similar to those used in the general population seem reasonable. Whether ACLF patients should receive fluids to improve CO (fluid responsiveness) is debatable: they have markedly increased CO, and the higher the CO the lower the probability of response[50]. In fact, terlipressin reduces CO while improving kidney function through MAP increases, which again points at vasoplegy as the therapeutic cornerstone[51]. Fluids should be judiciously administered to avoid congestion and ensure perfusion in patients with baseline hydro-saline retention. The use of colloids (albumin) over crystalloids remains unclear in ACLF. Balanced crystalloids, especially Lactated Ringer’s over Plasmalyte®, have shown benefits in general septic

population and should also be preferred in cirrhosis[52]. Albumin could theoretically have additional effects beyond the resuscitation effect: improved refilling, antioxidant, and anti-inflammatory properties[53]. Studies in cirrhosis reported a greater effect of albumin over crystalloids (sodium saline, Plasmalyte®) for initial resuscitation (MAP>65 mmHg prior to vasopressors) with no clear benefit on later survival[54,55]. Additionally, albumin must be cautiously used since it can worsen congestion and precipitate cardiac failure events[44].

3. Respiratory failure

Acute respiratory failure (ARF) is defined by PaO2≤ 60 Torr at room air or PaO2/FIO2 ratio ≤300. Whether invasive or non-invasive methods are used is determined based on the severity of hypoxemia and underlying disease[56]**.** NIV is recommended mostly in the postoperative setting and early phases of ARF, although it should be implemented only for a limited period of time and must not delay intubation and ventilation if the patient does not respond to the initial NIV trial[57].

Invasive mechanical ventilation (MV) is not a specific treatment for ACLF but sometimes needed for either airway protection (AP) (grade 3-4 HE or Glasgow Coma Score < 8), in cases of ARF or a combination of both[44]. The lungs are the least commonly affected organ in ACLF and less than 25% of ACLF patients require MV[45,46]. Nevertheless, cirrhotic and ACLF patients that require MV have increased mortality rates[45,47]. Just over half of MV ACLF patients require intubation for RF, with the remainder requiring AP. MV indicated for ARF is associated with a higher 28-day mortality compared to MV indicated for AP and to non-intubated ACLF patients (72.1% vs. 50.9% vs. 13.8%)[2,45].

There is no consensus on how to ventilate ACLF patients, but it is imperative to apply a protective ventilation strategy, as is done in the general ICU population. Protective volume-controlled ventilation with tidal volumes of 6 ml/kg predicted body weight, positive end-expiratory pressure ≥ 5 cmH_2O, inspiratory plateau pressure <30 cmH_2O with driving pressure < 13-15 cmH_20, and FiO_2 set to target normal PaO_2 (70 to 90 mmHg) should be applied[48]. Prone positioning (≥16 hours/day ±neuromuscular blocking) when PaO2/FIO2 ratio is less than 150 mmHg (i.e. severe acute respiratory distress) should be indicated on a a case-by-case basis in highly selected ACLF patients.

It could probably be applied in ACLF patients up to 3-4 organ failures for a period of 48 to 72 hours (initial treatment); persistence of ≥4 OF after this intervention probably indicates futility. Extracorporeal membrane oxygenation (ECMO) systems, used in the general population with refractory RF, are not indicated in ACLF patients given their poor prognosis. Finally, tracheostomy should be considered in each individual case based on the patient's prognosis.

4. Renal failure

Acute kidney injury (AKI) is a frequent complication of both acute decompensation and ACLF, occurring in up to 50% of hospitalized patients with cirrhosis, and is a strong predictor of poor short and long-term survival[58,59]. The broad heading of AKI encompasses subtypes, conventionally considered as resulting from hepatorenal syndrome (HRS-AKI) and non-HRS-AKI, with the former resulting from the classical functional pathophysiologic mechanisms associated with portal hypertension, splanchnic vasodilation and renal vasoconstriction[60]. HRS-AKI is treated with the combination of vasoconstrictors (first option terlipressin, a vasopressin analogue, followed by norepinephrine) plus intravenous albumin[60]. This treatment reverses the syndrome in about 30-50% of cases but can be associated with an increased incidence of respiratory failure due to pulmonary edema in patients with clinical evidence of intravascular volume overload. These overloaded patients should not receive terlipressin[44,61]. Non-HRS-AKI may result from a multitude of insults ranging from pre-renal insults (hypovolaemia), renal insults (sepsis or drug-induced tubular injury), both of which may be superimposed on underlying intrinsic renal disease[58,62,63].

RRT should be considered in non-responders to pharmacological therapy. Indications for RRT are the same as in the general population, including severe and/or refractory electrolyte or acid-base imbalance, volume overload, and symptomatic azotemia. Extracorporeal RRT can be provided as intermittent hemodialysis (solute predominantly removed by diffusion, 3-7 sessions/week lasting 3-6h, high dialysate and blood flow required) or as continuous renal replacement therapy, which is the preferred option in critically ill and hemodynamic unstable patients. It is designed to last 24 hours

or longer, providing slower removal of fluid and solutes[64,65]. Different solute removal techniques can be applied during continuous RRT: hemofiltration (convective removal), hemodialysis (predominantly diffusive removal of solutes), or hemodiafiltration, which combines diffusion and convection. The optimal strategy remains unclear and a combination of diffusion and convection (hemodiafiltration) is usually applied at a dose of 25 ml/kg/h (effluent flow)[64]. Higher doses (>35 ml/kg/h) did not improve survival[66,67]. The recommendation for intermittent hemodialysis is three sessions per week. Although there is limited data on patients with cirhosis, intensity may be individualized according to the clinical situation[64].

The optimal RRT initiation timing in critically ill patients is controversial; an accelerated strategy for RRT did not result in lower 90-day mortality than standard strategy[68]. In relation to anticoagulation of the circuit, regional anticoagulation with citrate compared with systemic heparin anticoagulation led to a significantly longer filter life and should be used in patients with cirrhosis and moderately preserved liver function (risk of citrate intoxication since being metabolized into bicarbonate by the liver). However, in many ACLF patients the circuit is run without anticoagulation due to severe clinical conditions (platelet count, INR, liver dysfunction, risk of bleeding)[69,70]. RRT is discontinued when kidney function recovers, an ill-defined concept that in clinical practice refers to resumption of diuresis, spontaneous decline in the blood urea nitrogen level, creatinine level, or both.

Prognosis of patients with cirrhosis receiving RRT is poor, especially if they are not candidates for LT, so reassessment after initial intervention is mandatory to define potential futility[71]. More studies are necessary, and a multidisciplinary team (intensive care, nephrologists, hepatologists) is recommended in this setting.

GENERAL MANAGEMENT

1. Nutritional support

Malnutrition is common in cirrhosis due to inadequate intake of macro and micronutrients, impaired absorption and defects in metabolism. This contributes to the

development of frailty and sarcopenia which have been linked to poor ICU outcomes (short-term mortality, increased length of MV and length of stay)[72,73]. Malnutrition increases the mortality risk and hospital length of stay in cirrhosis[74]. A study found that patients with decompensated cirrhosis and TIPS who were sarcopenic had a higher risk of developing ACLF whilst sarcopenia was associated with increased 1-year mortality[75]. Khan et al suggest that this increased mortality may be up to four times higher than in non-sarcopenic patients[76].

ACLF patients should be screened for malnutrition given its high prevalence and actions to ensure an adequate nutritional intake should be undertaken. Royal Free Hospital-Subjective Global Assessment index and mNUTRIC score are well-known scores that assess the nutrition risk and accurately predict poor outcomes and mortality in critically ill patients with cirrhosis[77,78]. Patients unable to improve their oral intake should be considered for enteral nutrition (EN), within 24-48 hours of ICU admission[79,80]. The presence of esophageal varices is not a contraindication for nasogastric tube placement[81]. Gastrointestinal dysmotility might be present leading to feeding intolerance for which the fist-line treatment should be prokinetics[82]**.** Gastrointestinal failure/gut paralysis can be observed in patients with severe forms of ACLF. It has been linked to increased bacterial translocation and systemic inflammation and worsening organ damage[83].

Parenteral nutrition should be considered as a second-line option since it increases the risk of sepsis[79]. In a recent open-label RCT, intravenous omega-3 fatty acid supplementation was safe and effective in reducing systemic inflammation and sepsis in patients with ACLF[84]. There is no evidence regarding the optimal nutritional intake for ACLF patients and therefore we recommend following generic guidelines for critically ill patients, which suggest 20–30 kcal/kg ideal body weight/day and 1.2–2 g of protein/kg ideal body weight/day[80]. In addition to adequate nutritional management, physical exercise and neuromuscular electrical stimulation may be used to prevent excessive muscle mass loss and ought to be specifically considered in ACLF patients[85].

2. Sedation and analgesia

Patients requiring invasive mechanical ventilation should receive a light sedation strategy consisting of short-term sedatives such as propofol and dexmedetomidine and ultra short-acting analgesics such as remifentanil. Benzodiazepines must be avoided given their hepatic metabolism, risk to increase duration of MV, ICU stay and delirium[58,86,87]. Paracetamol at low doses, maximum 2-3 g/day (first line therapy) and opioids (methadone, tramadol) are the analgesics of choice in patients with ACLF. Non-steroidal anti-inflammatory drugs are contraindicated.

3. Prognostic scores and futility rules

Admitting a patient with decompensated cirrhosis for organ support in the ICU was considered futile for many clinicians due to mortality rates between 36-86%, especially if the patient presented with multiorgan failure or required ventilatory support[88,89]. Non eligibility for LT may still limit the access of patients with cirrhosis to the ICU, though their prognosis and management in the ICU has improved in the last decades, as well as their access to LT[90]. Moreover, the recognition of ACLF as a distinct syndrome, the definition of organ failure criteria, and the development of prognostic scoring tools has helped to establish a framework that helps at easing the access of these patients to the ICU. In fact, a recent study showed that the 90-day mortality and length of stay of patients with ACLF admitted to the ICU were similar to a matched ICU population without chronic liver disease and the same degree of critical illness[90]. Therefore, patients with ACLF and no severe comorbid condition should be considered suitable for ICU transfer and full organ support irrespective of their transplantability. It seems reasonable to suspect that an early transfer to a specialized center could improve the outcomes of those patients, although there is no evidence giving support to this statement.

Each of the three main definitions of organ failures in ACLF (Table 1) has its own prognostic score: CLIF-C ACLF, NACSELD and the AARC scores which can be reviewed elsewhere[1,4,6,91]. Classic prognostic scores in decompensated cirrhosis like the Child-Pugh or the Model for End-Stage Liver Disease (MELD) scores perform worse in ACLF because they do not capture the severity of extrahepatic organ failures[92]. Therefore, scores combining the evaluation of hepatic and extrahepatic organ systems are better suited

to prognostication. The CLIF-C ACLF score (EASL-CLIF score: https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf), which is the better balanced score, seems to perform better in prediction of 90-day mortality compared to the NACSELD score which is focused on severe extrahepatic organ failures and may be used to predict short-term mortality[93]. Therefore, the EASL-CLIF score could be a better tool for prioritizing patients for LT. CLIF-C ACLF score predicts mortality significantly better when evaluated at follow-up rather than at diagnosis[92]. However, CLIF-C ACLF score has still some deficiencies including a subjective component in evaluating hepatic encephalopathy, a ceiling effect when evaluating liver, kidney and coagulation functions and, more importantly, it does not include the more recent AKI definition in patients with cirrhosis. The AARC score has also a robust predictive ability, specially at day 7 of ACLF[6].

Futility in ACLF must be considered after some days of intensive care management and no evidence of improvement. Recent evidence suggests that a CLIF-C ACLF score equal or above 70 after 72h of ICU admission may be a good futility cut-off (expected mortality >90%)[94]. An AARC score above 12 has also been demonstrated to predict futility in this setting[6]. The sequential use of these prognosis scores at 3-7 days from admission may help to determine continuity of intensive care or, instead, palliative care if there are no options for early LT (Figure 2).

EARLY LIVER TRANSPLANTATION

The initial course of ACLF is a major determinant of the prognosis of the syndrome. After one week of intensive care management, the probability of 28-day survival in patients with 3 to 6 organ failures (ACLF 3) is only 12.8%. Survival in ACLF-2 patients is also remarkably low (42.9%)[13]. Several studies suggest that early liver transplantation (LT) of selected patients with ACLF 2-3 is associated with a marked improvement in prognosis, with 1-year post-LT survival ranging from 79% to 84%[95–98]. In contrast, other groups have reported poor outcomes for ACLF-3 with 1-year post-LT survival of only 43%, indicating the need of a careful candidate selection[99]. LT in this setting is associated with higher rate of post-LT infections, acute rejection, longer MV, need for dialysis and prolonged ICU and hospital stay[96,100].

The window for LT in patients with ACLF 3 is extremely narrow. These patients are at high risk for second infections (often caused by resistant strains or fungi) and can develop complications that compromise their eligibility for LT[9]. Patients with severe ACLF show higher waitlist mortality than those without[98]. Remarkably, ACLF 3 patients have higher waiting list mortality than patients with acute liver failure (33% vs 20% at 3-weeks, respectively), suggesting they require some kind of prioritization[101]. This finding demonstrate how MELD (and MELD-Na) underestimate ACLF mortality in the waiting list[98,100,101]. CLIF-C ACLF score outperforms the predictive accuracy of these scores in ACLF and could be more adequate in this setting[92]. Finally, an early access to LT for patients with ACLF 2-3 improves post-LT outcomes. The median time from listing to LT in studies reporting good outcomes after transplantation is very short ranging from 5 to 11 days[95,102].

The scarcity of donors and the need for early LT in patients with ACLF 2-3, especially in those with 4-6 organ failures, has led to the use of deceased marginal livers and living donor LT in this population. Marginal organs are associated with decreased 1-year post-LT survival in patients with ACLF-III, but the survival benefit of LT is still retained[98,102]. Reported 1-year post-LDLT survival ranges from 67% to 76% in highly selected patients with ACLF-3[103].

Several futility scores have been developed to predict 1-year post-LT mortality in patients with ACLF-3. The study by Artzner et al. identified four factors independently associated with post-LT mortality: age ≥53 years, pre-LT arterial lactate ≥4 mmol/L, mechanical ventilation with PaO_2/FiO_2 ≤200 and pre-LT WBC ≤10 G/L[97]; the presence of more than 2 factors (TAM score >2) was associated with very low 1-year post-LT survival (8-10%), suggested as a futility rule (too sick for transplantation). Additionally, a consensus document recently elaborated by 35 experts has suggested other limits for LT: severe frailty (clinical frailty scale ≥7), ongoing sepsis, current or recent infection by pandrug resistant bacteria, respiratory failure with PaO_2/FiO_2 ratio <150, circulatory failure requiring a dose of norepinephrine > 1µg/kg/min and arterial lactate > 9 mmol/L[104].

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FIGURE LEGENDS

Figure 1. Suggested diagnostic work-up in patients with ACLF

Diagnostic work-up in ACLF has two main objectives: to identify the potential precipitating events of the syndrome and to assess organ/systems function to determine its severity.

INR: international normalized ratio; PCR: polymerase chain reaction; HAV: hepatitis A virus, HBV: hepatitis B virus; HCV: Hepatitis C virus; HEV: hepatitis E virus.

Figure 2. Therapeutic algorithm in ACLF, time for liver transplantation and futility rules

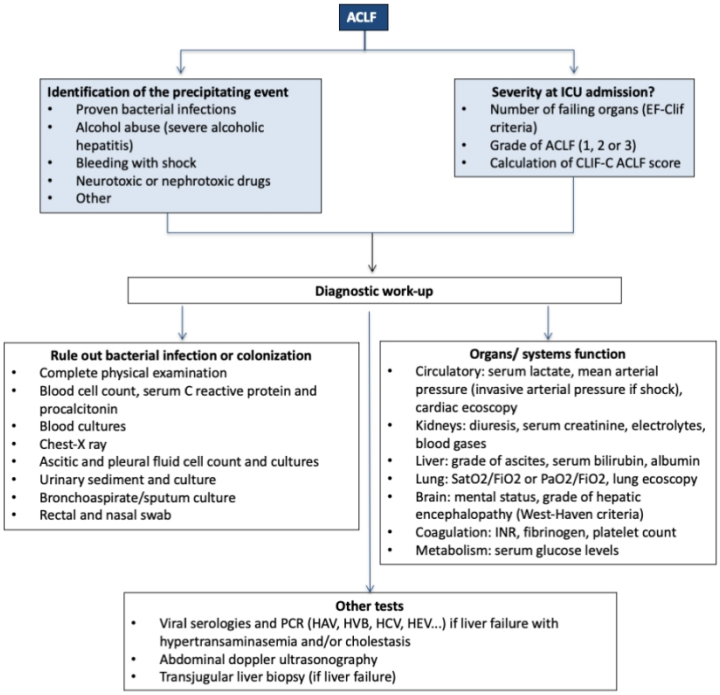
ACLF patients should be admitted to the ICU and receive full critical care and organ support. Recommended treatment of life-threatening complications and of the different organ failures is described. Prognosis should be evaluated after some days of full therapy (at days 3 to 7). Patients with severe forms of the syndrome (ACLF 2-3) should be evaluated for early liver transplantation. Palliative care should be initiated if early liver transplantation is not possible in the presence of a CLIF-C ACLF score ≥ 70 points (90-100% mortality at 28 days).

Hb: hemoglobin levels; HRS-AKI: hepatorenal syndrome-acute kidney injury; ATN: acute tubular necrosis; TIPS: transjugular intrahepatic portosystemic shunt; PK/PD: pharmacokinetic/pharmacodynamic; SAH: severe alcoholic hepatitis, BIPAP: bi-level positive airway pressure; HFNC: high flow nasal cannula

Table 1. Organ failure criteria and ACLF definition and grading according to the three main societies

	EASL-CLIF	NACSELD	AARC
	Bilirubin ≥ 12 mg/dL	-	Bilirubin ≥ 5 mg/dL and INR ≥ 1.5
	Creatinine ≥ 2 mg/dL or RRT	RRT	AKI Network Criteria
	HE grades 3-4	HE grades 3-4	HE grades 3-4
	INR ≥ 2.5	-	INR ≥ 1.5
	Vasopressors	Vasopressors	-
	PaO2/FiO2 ≤ 200 or SpO2/FiO2 ≤214	Mechanical ventilation	-
ACLF	**ACLF 1a**: Single kidney failure **ACLF 1b**: Single OF AND creatinine 1.5-1.9 mg/dL or HE grades 1-2 **ACLF 2**: 2 OF **ACLF 3**: ≥ 3 OF	≥ 2 OF	Liver AND coagulation failure AND ascites or HE in the previous 4 weeks.

EASL: European Association for the Study of the Liver. EF-CLIF: European Foundation for the Study of Chronic Liver Failure. NACSELD: North American Consortium for the Study of End-Stage Liver Disease. APASL: Asian Pacific Association for the Study of the Liver. RRT: Renal Replacement Therapy. AKI: Acute Kidney Injury. HE: Hepatic Encephalopathy. INR: International Normalized Ratio. OF: organ failure



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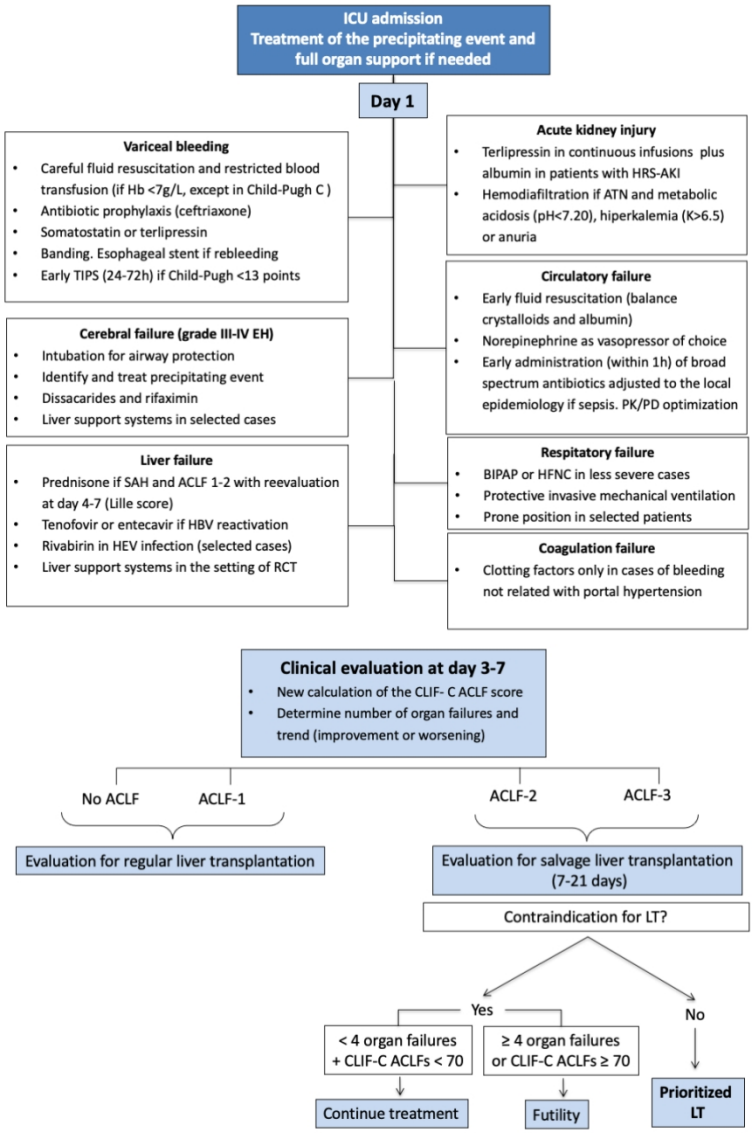

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