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Bridging the critically ill acute on chronic liver failure patient through liver transplantation

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Abstract:	Liver transplantation (LT) has emerged as an effective therapy for severe forms of acute on Chronic Liver Failure (ACLF), an entity characterized by the development of multiorgan failure and high short-term mortality. The aim of critical care management of ACLF patients is to rapidly treat precipitating events and aggressively support failing organs to ensure that patients may successfully undergo LT or, less frequently, recover. Malnutrition and sarcopenia are frequently present adversely impacting the prognosis of these patients. Management of critical care ACLF patients is complex and requires the participation of different specialties. Once the patient is stabilized, a rapid evaluation for salvage LT should be performed, since the window for LT is often narrow. The development of sepsis and prolonged organ support may preclude LT or diminish its chances of success. The current review describes strategies to bridge severe ACLF patients to LT, highlights the minimal evaluation required for listing, and describe different aspects of management during the perioperative and early post-transplant period.
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Editor and Reviewer comments:

Editor 1: Only comment is that "In summary" is used twice toward the end of the paper - not sure if this was meant but it is redundant

Modified, thanks

Editor 2: My concerns have been adequately addressed, thorugh a few language changes are suggested:

P5 L51 'lo' to 'to' (sp).

Modified, thanks

P9 L59 'solves' to 'resolves'

Modified, thanks

P12 L25 'never' a bit strong. Very occasionally one encounters a CLD patient with very severe hyperammonaemia and cerebral edema and very short term protein restriction may be warranted until ammonia levels are controlled.

Done

P13 L25 'Deepness' to 'depth' Not all use BIS so this could be toned down

Modified, thanks

P13 L42 replace 'as the' with 'as a'

Minor changes have been done. Thanks a lot

Reviewer comment: Thank you for addressing all the comments and the high quality review

Thanks for your positive consideration on ou review

Bridging the critically ill acute on chronic liver failure patient through liver transplantation

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Abbreviations: LT: liver transplantation; ACLF: acute-on-chronic liver failure; AKI: acute kidney injury: ICU: intensive care unit; HBV: hepatitis B virus; DNA: deoxyribonucleic acid; HE: hepatic encephalopathy; TIPS: transjugular intrahepatic portosystemic shunt; NE: norepinephrine; MV: mechanical ventilation; HRS-AKI: hepatorenal syndrome- acute kidney injury; ATN: acute tubular necrosis: RRT: renal replacement therapy; GFR: glomerular filtration rate; VET: viscoelastic tests;

MARS: molecular adsorbent recirculating system; RCT: randomized controlled trial; NUTRIC: nutrition risk in the critically ill; CVP: central venous pressure; PAC: pulmonary artery catheter; TEE: transesophageal echocardiography; PRS: post-reperfusion syndrome; IRI: ischemia reperfusion injury; MELD: model for end stage liver disease; NIPPV: non-invasive positive pressure ventilation; HFNC: high-flow nasal cannula; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; CIN: calcineurin inhibitor; MMF: mycophenolate mofetil; MDR multidrug resistant; ESBL-PE: extended spectrum beta-lactamase producing *Enterobacteriaceae;* CLIF-C: chronic liver failure consortium; IFI: invasive fungal infection; ERAS: enhanced recovery after surgery;

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ABSTRACT

Liver transplantation (LT) has emerged as an effective therapy for severe forms of acute on Chronic Liver Failure (ACLF), an entity characterized by the development of multiorgan failure and high short-term mortality. The aim of critical care management of ACLF patients is to rapidly treat precipitating events and aggressively support failing organs to ensure that patients may successfully undergo LT or, less frequently, recover. Malnutrition and sarcopenia are frequently present adversely impacting the prognosis of these patients. Management of critical care ACLF patients is complex and requires the participation of different specialties. Once the patient is stabilized, a rapid evaluation for salvage LT should be performed, since time window for LT is often narrow. The development of sepsis and prolonged organ support may preclude LT or diminish its chances of success. The current review describes strategies to bridge severe ACLF patients to LT, highlights the minimal evaluation required for listing and the currently suggested contraindications to proceed with LT and addresses different aspects of management during the perioperative and early post-transplant period.

INTRODUCTION

Patients with decompensated cirrhosis frequently require ICU admission for the treatment of life-threatening complications. Septic shock, variceal bleeding, severe hepatic encephalopathy (HE) and stage 3 acute kidney injury (AKI) usually occur in the setting of ACLF, an entity characterized by the presence of organ failure(s) and high short-term mortality [1, 2]. Support of failing organs and early and adequate treatment of the precipitating event(s) are key in the management of these patients [3]. Early improvement of ACLF is associated with acceptable mid-term prognosis while the persistence of $\geq$3 organ failures despite adequate therapy translates into very poor prognosis at short-term in the absence of LT [4]. Several studies suggest that early LT improves survival in ACLF-3: 1-year post-LT survival is around 80% compared to only 13% in non-transplant candidates. The window of opportunity for LT in these patients is very short ranging from days to few weeks [5]. The higher the severity of ACLF, the shorter the time available to proceed with LT [6-9].

STABILIZING THE PATIENT PRIOR TO LIVER TRANSPLANTATION

Prior to listing for LT, critically ill patients with multiorgan failure must first be stabilized which involves treating the precipitating event and providing the required organ support [10, 11]. After a period of therapy and provided there is a clear clinical improvement, patients should be rapidly evaluated for LT. Management of these complex patients should be multidisciplinary. Table 1 and Figure 1 summarize critical care management in ACLF.

1. Management of the precipitating event

Infections

Bacterial infections frequently cause and complicate the evolution of patients with ACLF and are the most frequent cause of delisting and death in liver transplant candidates with ACLF. Therefore, a comprehensive workup for the presence of bacterial infections is mandatory at the time of ACLF diagnosis and whenever the patient clinically deteriorates. The risk of infection is especially high in patients with ACLF-3 ($\geq$ 3 organ failures). Spontaneous bacterial peritonitis, bacteremia and pneumonia are the most common infections [12-14]. As multidrug resistant organisms (MDROs) are frequently responsible for these infections, broad-spectrum antimicrobial therapy adapted to local resistance patterns covering all potential pathogens are recommended in their empirical treatment. Antibiotics should be administered early and consider the most effective way which may include pharmacokinetic optimization (continuous infusions of beta-lactams in the first 48h if available). Rapid de-escalation strategies should be applied (48-72h). De-escalation relies on the identification of the responsible pathogen in clinical samples by rapid or classical techniques and on epidemiological surveillance data [3]. Once the evolution of the infection is adequate, patient can be activated/reactivated in the waiting list and transplanted under peri-transplant antibiotic therapy. This strategy appears to be sure, although infection prior to LT is associated with an increased incidence of infectious complications after surgery [15]. Criteria for activation of infected patients with ACLF for LT are poorly described in the literature. Resolution of bacterial infection is generally not required. Table 2 describes considerations on the management of infected patients in the pre-transplant period [16-18].

Invasive fungal infections (IFI) are less frequent than bacterial episodes in ACLF and usually complicate the course of the syndrome. Invasive candidiasis/candidemia and aspergillosis are the most frequent [12, 13]. Two cell-wall biomarkers, serum 1,3 β-D glucan (BDG) and galactomannan antigen (GM) are used in the diagnosis of IFI. BDG is a pan-fungal marker with good sensitivity but a more variable specificity for the diagnosis of IFI, having many sources for false positivity. It has very good negative predictive value being used to rule out an IFI. Empirical antifungal therapy can be discontinued in the presence of two consecutive negative determinations. GM is produced by *Aspergillus* spp, but not by Candida. It can be detected in bronchoalveolar lavage (BAL) and serum samples in patients with invasive aspergillosis. Values >0.5 ng/ml have a specificity of 87-97% for the diagnosis of probable IA. Sensitivity of this biomarker is higher in BAL samples [19, 20]. Prompt initiation of echinocandins is recommended in patients with ACLF and prolonged ICU stay who develop shock under the suspicion of invasive candidiasis [21]. If fungemia is confirmed, patients must receive a complete course of therapy (2 weeks of antifungals after obtaining the first negative blood cultures) and secondary sources, mainly catheter infection, must be excluded before activation for LT occurs [16, 22]. Invasive aspergillosis in the pre-transplant period is considered an absolute contraindication for LT [23].

Severe alcoholic hepatitis

Early LT is emerging as a rescue therapy in patients with severe alcoholic hepatitis refractory to steroids or in whom they are contraindicated [24, 25]. Whereas prednisone can be initiated in patients with ACLF-1 or 2, they are not recommended in ACLF-3 due to low efficacy and high risk of infections [26]. If prednisone is initiated, close clinical monitoring for infections is

recommended including periodical surveillance cultures and GM determinations [12]. Steroids must be stopped in non-responders by day 4-7 according to the Lille model. [27, 28]

Hepatitis B virus reactivation

Hepatitis B virus (HBV) reactivation is a common precipitant of ACLF in Asia [29]. Early treatment with potent antivirals (tenofovir or entecavir) should be started as soon as possible with the aim to reduce viral load and hepatocyte death [30]. A reduction of 2 log in HBV DNA levels at week 2 improves prognosis. Patients who do not stabilize with antiviral therapy should undergo rapid evaluation for LT. Entecavir should be avoided in patients with poor renal or liver function due to the risk of lactic acidosis [31]. Combination of hepatitis B immunoglobulin (HBIG) and antiviral therapy is recommended after LT to reduce graft infection. HBIG prophylaxis must be initiated in the anhepatic phase. The duration of this combination depends on the grade of viral replication. In low-risk patients (undetectable HBV DNA at transplantation) short course or even free HBIg free regimens can be considered [32, 33].

Severe variceal bleeding

Acute variceal bleeding can cause or complicate the evolution of ACLF [34]. Initial management consists of careful fluid resuscitation/transfusion, the administration of splanchnic vasoconstrictors (somatostatin/octreotide or terlipressin), prophylactic antibiotics and early endoscopic treatment [35]. Intubation for airway protection prior to endoscopy is recommended in patients with overt HE, respiratory insufficiency, or important hematemesis. In the event of failed endoscopic therapy, a self-expandable, covered, esophageal stent may be placed in patients with esophageal varices [36] and a balloon tamponade tube in those with gastric varices.

Pre-emptive TIPS (within first 72h after first bleed) decreases treatment failure and mortality [37] in patients with ACLF 1-2 [38]. A case-by-case evaluation is required in patients with ACLF 3. TIPS is usually contraindicated in patients with poor liver function (Child>13 points) unless the patient is already listed for LT [35].

2. Organ support

Circulatory failure

Sepsis and bleeding are the main causes of shock in ACLF. In this setting, volume status and cardiac function should be evaluated by echocardiography at patient's bedside, thereby monitoring fluid administration to avoid congestion. The use of colloids (albumin) over balanced crystalloids remains unclear in critical care [3, 39].

Patients who do not respond to fluid therapy should be started promptly on vasopressors. Norepinephrine (NE) is the vasopressor of choice. Continuous infusion of terlipressin or vasopressin should be initiated when high doses of NE are required (>0.25−0.5 μg/kg/min)[21]. Terlipressin should be used with caution in patients with ACLF-3 given its possible ischemic and respiratory side-effects [40]. Patients with refractory shock could benefit from the administration of stress dose steroids [3].

Patients responding to therapy will experience a marked reduction in vasopressor requirements and a progressive improvement of arterial lactate levels. Improvement in both parameters should be present to consider the activation for LT. However, threshold criteria vary greatly among centers. Most groups don't activate patients with NE >0.5g/kg/min, increasing requirements of vasopressors or high arterial lactate levels. NE requirements >1 g/kg/min or

arterial lactates >9 mmol/L are considered an absolute contraindication for LT, Table 3 [3, 17, 41-43].

Respiratory failure

Endotracheal intubation and mechanical ventilation (MV) are often required for either airway protection in patients with severe HE (Glasgow score ≤ 8) and/or in the presence of acute respiratory failure (RF; PaO2/FIO2 ratio ≤200). Multiple factors can cause RF in ACLF including uncontrolled sepsis (acute respiratory distress syndrome), aspiration, massive hydrothorax, and tense ascites. Decompressive paracentesis improves RF in patients with tense ascites and high abdominal pressure (≥15 mmHg)[44].

In patients requiring invasive mechanical ventilation, lung protective ventilation strategies should be applied. Volume-controlled ventilation with tidal volumes of 6 ml/kg predicted body weight, inspiratory plateau pressure <30 cmH_2O and driving pressure <15 cmH_20 should be implemented. Prone positioning should be indicated on a case-by-case basis in highly selected patients with ACLF when PaO2/FIO2 ratio is <150 mmHg [3, 45].

ACLF patients under MV have increased mortality [46]. MV is also a well-known risk factor for postoperative mortality in LT. Therefore, low ventilation requirements: Fi02 <50% and PaO2/FIO2 ratio > 150-200 mmHg are usually required for proceeding to LT [3, 8, 17, 41, 42].

Renal failure

AKI is extremely frequent in ACLF and is a strong predictor of short-term mortality [47]. Twenty to thirty percent of patients experience volume-responsive AKI that resolves with hydration and

discontinuation of diuretics [48]. Among volume non-responders the two main phenotypes are hepatorenal syndrome AKI (HRS-AKI) and structural AKI The former is consequence of functional mechanisms associated with portal hypertension. HRS-AKI is treated with vasoconstrictors (terlipressin or NE) and albumin [47]. Pharmacological treatment reverses the syndrome in about 50% of cases, although response is much lower in ACLF-3 [49]. Reversion of HRS-AKI before LT is associated with excellent renal outcomes after transplantation [50]. Patients with severe fluid overload should not receive terlipressin nor albumin**.** Structural AKI, mainly acute tubular necrosis (ATN), result from renal insults (sepsis, hypoperfusion, nephrotoxic drugs) [51]. Renal replacement therapy (RRT) should be considered in patients with HRS-AKI not responding to pharmacological therapy and in those with ATN and persistent metabolic acidosis (pH $\leq$ 7.20) or refractory/severe hyperkalemia ($\geq$6.0-6.5 mmol/l), therapy-resistant volume overload, RF (PaO2/FIO2 ratio is <200 mmHg), and symptomatic azotemia. Patients with severe hypervolemic hyponatremia may also require the initiation of RRT. Optimal timing of initiation of dialysis in ACLF patients is unknown. However, early initiation of renal support is not associated with better outcomes in the general population [52].

Hemodynamic unstable patients should receive continuous RRT at standard doses (25-30 ml/kg/h) [53]. RRT should bridge patients with renal failure to LT in adequate metabolic and fluid balance state. RRT can be considered during the perioperative period in oliguric/metabolically deranged patients. Patients with prolonged AKI, with either GFR < 25 ml/min or RRT for > 6 weeks should be considered for combined liver-kidney transplant [54].

Coagulation failure

Coagulation alterations are complex in ACLF patients with viscoelastic tests (VET) showing a predominant hypocoagulable state and variable fibrinolytic patterns. Coagulation disturbances should not be corrected in the absence of bleeding except for platelet count <20/µl in invasive procedures. In the presence of bleeding, VET can guide coagulation correction [3, 55, 56].

Brain failure

Patients with brain failure require endotracheal intubation for airway protection. Sedation and analgesia with short-acting medications (propofol/dexmedetomidine and remifentanil) is recommended in the presence of respiratory failure. Hepatic encephalopathy is the main cause of coma in patients with ACLF. Brain imaging and/or lumbar puncture should be performed in the presence of neurological focality or seizures. Treatment of hepatic encephalopathy is based on the identification and control of the precipitating factor (infections, hyponatremia, bleeding and sedative drugs) together with the administration of lactulose and possibly rifaximin. Polyethylene glycol is an alternative to lactulose in patients with ACLF at risk of ileus [57, 58].

Liver failure and liver support systems

Liver failure impacts prognosis in ACLF [4]. Current guidelines do not recommend the routine use of liver support systems in the treatment of ACLF patients outside research trials. Albumin dialysis (MARS, Prometheus) improve bilirubin levels and encephalopathy without improving survival [3, 18, 59]. Recent studies suggest potential benefits in short-term survival in ACLF 2-3 patients treated with MARS (bridge to LT) [60, 61]. Moreover, several uncontrolled studies show promising results of plasma exchange (PE) in ACLF [62-64]. An ongoing RCT should clarify the

impact of PE on short-term survival in this setting. In the meanwhile, these supportive systems could be considered in ACLF-3 patients as a bridge for LT in the setting of high bilirubin levels, cholemic nephropathy, coagulopathy and/or severe HE.

3. Nutritional support and physiotherapy

Malnutrition and sarcopenia are very common in ACLF and linked to poor outcomes. ACLF patients should always be screened for malnutrition (Royal Free Hospital-Subjective Global Assessment index or mNUTRIC score) and adequate nutritional intake should be ensured. Protein administration should not be restricted, even in patients with brain failure. Short-term protein limitation could be needed in patients with severe hyperammonemia and brain edema, an exceptional clinical picture. Patients unable to improve their oral intake should receive enteral nutrition within 24 hours of ICU admission. Parenteral nutrition is always a second-line option due to the risk of sepsis [65]. The optimal nutritional support for ACLF patients is that recommended in other critically ill patients [66-68] (Table 1). In addition to an adequate nutritional support, intense passive and active physiotherapy should be used in this setting to prevent muscle mass loss and critically ill myopathy [3, 10]. Active physiotherapy should be avoided until clinical stabilization.

4. Urgent evaluation and contraindications for LT

After initial stabilization and adequate control of infection patients with severe ACLF should have a quick assessment for LT. A standard evaluation is not feasible in this setting. Some tests are impracticable,

and others would delay LT. Recommended investigations are described in Table 4 [3, 8, 42, 69, 70].

Suggested contraindications for LT in ACLF-3 are described in Table 3. [3, 17, 41-43, 71].

INTRAOPERATIVE SUPPORT

1. Hemodynamic monitoring

Intraoperative monitorization of ACLF patients undergoing LT require invasive arterial blood pressure (peripheral and central) and central venous pressure (CVP) assessment and the insertion of, at least, a high flow cannula [72]. Pulmonary artery catheter (PAC) and/or transesophageal echocardiography (TEE) monitoring is strongly recommended. Although PAC remains the gold-standard monitoring method in many centers, advantages of TEE include its ability for real-time assessment of cardiac function, fluid responsiveness and rapid diagnosis of life-threatening cardiac events[73-75]. Depth of anesthesia is usually controlled by bispectral index monitoring.

2. Fluid management

Intraoperative fluid policy impacts the hemodynamic and hemostatic systems and the risk of bleeding. Restrictive fluid administration (low cardiac filling pressures) during the pre-anhepatic and anhepatic phases reduce blood losses. Both, albumin and balanced crystalloids, are used for volume replacement [76] in LT. Balanced solutions are recommended in recipients with severe hyponatremia [77] due to the risk of osmotic demyelination.

2. Hemodynamic management

Maintenance of hemodynamic stability during surgery in patients with ACLF is challenging. The use of NE during LT is almost universal. Patients with severe ACLF can present systolic or diastolic cardiac dysfunction and decreased sensitivity to vasoconstrictors [78], alterations that may compromise tissue perfusion. The most critical hemodynamic phase of surgery is liver reperfusion, traditionally after portal vein clamp removal [79-82]. Post-reperfusion syndrome (PRS), defined as a significant fall in arterial pressure with low vascular resistances, remains a major concern. Its incidence in ACLF is unknown but is presumably higher than that observed in other liver recipients. Ischemia reperfusion injury (IRI) plays a major role [83, 84] in PRS and therefore graft selection and modality of liver preservation are of paramount relevance. Graft selection is extremely relevant in recipients with a short window of opportunity. Many of these patients cannot wait for an optimal graft and may require the acceptance of marginal livers. Recent advances in organ preservation using dynamic oxygenated machine perfusion have allowed the use of suboptimal organs with outcomes comparable to standard grafts. Hypothermic or normothermic machine perfusion have the potential to diminish IRI and early allograft dysfunction, and potentially PRS [85-87]. Adequate surgical technique [88-93] and preemptive use of additional vasopressors (epinephrine, phenylephrine) or of methylene blue may contribute to reduce the prevalence and severity of PRS in ACLF patients [94, 95].

3. Coagulation management

VET frequently shows hypocoagulable features with prolonged time to initial fibrin formation and clot formation time, reducing clot firmness [55]. Mixed fibrinolytic phenotypes have been also reported in patients with ACLF with baseline hypofibrinolysis associated with worse outcome

[96]. Prophylactic administration of antifibrinolytics is not systematically recommended in LT in ACLF.

Bleeding during surgery is mostly of hemodynamic origin. The most effective homeostatic strategy is to maintain low splanchnic pressures. Despite the derangement of the standard coagulation tests, their prophylactic correction is not recommended. VET should be used to monitor coagulation and transfusion during LT [97, 98]. VET reduces the transfusion of fresh frozen plasma and platelet units compared to conventional coagulation tests in ACLF patients with active bleeding. Fibrinogen [99] should only be administered in patients with levels <1 g/L or with clot firmness in FIBTEM test <8 mm for treating active bleeding or before high-risk invasive procedures [100].

POST-TRANSPLANT PERIOD

Recovery after LT for ACLF can be challenging as it is well established that these patients are at higher risk of developing surgical and infectious complications post-LT [101]. Similar to other surgical populations, balanced anesthetic techniques with short-acting neuromuscular blockade and minimal narcotics and benzodiazepines expedite liberation from MV [102]. Traditionally clearance of aminotransferase elevation during the first 36 hours has been used to identify persistent preservation injury. While there has been investigation into the potential role of n-acetyl cysteine to mitigate IRI, no evidence supports its use in clinical practice [103, 104]. Vascular patency is routinely assessed with early Doppler ultrasonography, with computed tomography/angiography considered in patients with sonographic abnormalities/unexplained aminotransferase elevation.

In patients without ACLF, hyperdynamic circulation and humoral abnormalities (activation of vasoconstrictor systems) reverse within 2-4 weeks after LT, although vasopressors can be rapidly stopped after surgery [105]. Time to hemodynamic normalization in ACLF is probably longer, feature that could explain the longer times of vasopressor support that these patients may require [6].

1. Weaning from mechanical ventilation

While rapid post-operative liberation from MV is the aim in the post-LT setting, this can be challenging in ACLF patients. Risk factors for failed extubation/prolonged MV include high MELD score (> 25), high transfusion requirements (> 1600 ml of packed red blood cells) and vasopressor use [106]. Spontaneous breathing modes can be implemented with recovery from anesthesia and patients should be extubated when protecting their airway, hemodynamically stable and return to operating room is not imminent. Prolonged times of MV are expected in these sick patients. The higher the severity of ACLF at LT, the longer the time of respiratory support. Strategies to avoid reintubation include the use of non-invasive positive pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC) [107, 108]. Factors that limit the use of NIPPV include altered mental status, shock, multi-organ failure, and extreme frailty where HFNC is preferable[108]. Acute respiratory failure following LT may be due causes associated with cirrhosis (i.e. hepatopulmonary syndrome, capillary leak/non-cardiogenic pulmonary edema, portopulmonary hypertension) along with those that are unrelated (pneumonia, atelectasis, pulmonary embolism). Risk factors for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) post-LT patients include massive transfusion, fluid overload, sepsis, and aspiration which

have a high prevalence in ACLF patients [109, 110]. ALI/ARDS post-LT is associated with up to a 2-fold increase in 1-year mortality [110]. The treatment of ALI/ARDS in post-LT is similar to treatment for general critical care patients with a lung protective strategy [45, 111, 112]. In the ACLF patient, post-LT high PEEP strategy (> 10 cm H_2O) is not recommended as it can impede venous return and cardiac preload [113, 114]. Different PEEP levels (0, 5, and 10 cm H_2O), did not impact flow velocities in the hepatic artery, portal vein, or hepatic veins and hence hepatic perfusion was not impaired by PEEP < 10 cmH2O [115]. In patients who require protracted ventilator support, consider early percutaneous tracheostomy [116].

2. Immunosuppression in ACLF

Improved graft and patient survival in LT recipients have been attributed to decreased rates of acute cellular rejection with improved immunosuppression regimens. The use of these agents can be associated with potential increasing toxicities in LT recipients with ACLF. AKI is the most frequent organ failure in ACLF. Calcineurin inhibitor (CNI) -based regimens are associated with a decrease of renal function ranging from 13% to 33% according to whether the CNI is administered alone or in combination with antimetabolite or induction therapy [117]. Lower target tacrolimus trough concentrations should therefore be considered in patients with ACLF to prevent AKI [118]. Furthermore, according to two large RCT, induction therapy with an anti-interleukine-2 receptor in combination to mycophenolate mofetil (MMF) and corticosteroids, and reduced/delayed initiation of CNI is associated with superior renal function and decreased need for RRT than early initiation of standard dosing of CNI [119, 120].

ACLF patients undergoing LT are immunocompromised and potentially more susceptible to infections/sepsis due to numerous immune alterations. There is no consensus on the management of immunosuppressive regimen in ACLF patients' post-LT at-risk of sepsis or with sepsis. It has been proposed to hold immunosuppression temporarily to improve sepsis recovery [121]. However, this strategy may increase the risk of allograft rejection. Maintenance of CNI in association with MMF with a rapid withdrawal of steroids may be proposed.

3. Perioperative antimicrobial prophylaxis

Patients with ACLF are at increased risk of post-LT infection, especially MDR pathogens [122]. Extended spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-PE) are become more prevalent with an incidence that has increased almost tenfold from 2001 to 2010 [123]. Patients with ACLF often have several risk factors for ESBL-E infections including high severity of illness, recent hospitalization and recent antimicrobial therapy [124]. A rectal swab is a screening tool to evaluate the risk of ESBL-PE or other MDRO infection after LT. In a recent study, 45% of patients with a preoperative rectal ESBL-E rectal carriage developed an ESBL-E infection within the first 90 days whereas post-LT ESBL-E infection occurred in only 3.5% of the non-carriers. In the same study, the authors evaluated the efficacy of a directed prophylaxis regimen against ESBL-PE in LT recipients. Incidence of ESBL-PE related infections following LT was lower in patients that received a perioperative antimicrobial prophylaxis targeting the colonizing ESBL-PE [124]. No studies have addressed the best surgical prophylaxis regimen among patient colonized with *carbapenem resistant Enterobacteriaceae*. Nevertheless, specific prophylactic regimens should be considered in these patients. Nasopharyngeal swab for *Staphylococcus aureus* testing is also

recommended in patients with ACLF at the time of transplantation. Colonized patients, mainly those carrying the methicillin-resistant strain, should be decolonized [125].

Patients transplanted for ACLF are prone to IFI after LT and frequently have risk factors (ie. MELD>30, AKI, RRT, previous broad-spectrum antimicrobial therapy) [126]. Some studies have shown that antifungal prophylaxis may reduce the incidence of IFI and its associated mortality [127]. The risk of IFI should be carefully evaluated in every ACLF patient at the time of LT. In high risk patients, prophylaxis using echinocandins as first-line therapy should be considered until risk factor disappearance.

4. Nutritional support

Malnutrition in ACLF may complicate recovery after LT. A multi-disciplinary approach including nutritionists/dietitians is associated with improved outcomes and reduced readmissions [66, 128-131]. An objective assessment of the patient's nutrition status should be performed on all patients prior to and post-LT. The Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition guidelines recommend the use of the Nutrition Risk in the Critically Ill (NUTRIC) score to identify patients that benefit most from nutrition support [132, 133]. Energy and protein requirements for nutrition support are calculated by predictive equation initially, using ideal body weight [66]. There is considerable inter-individual variability in patients with ACLF, and indirect calorimetry to measure resting energy expenditure should be used if available for more accurate assessment. Based on recent guidelines from the European Society for Clinical Nutrition and Metabolism [134], the European Association for the Study of Liver [135] and a recent position paper by the Enhanced Recovery after Liver Transplantation

(ERAS4OLT.org) Working Group [136], there is global agreement to screen for malnutrition and sarcopenia in all cirrhosis/ACLF patients listed for LT. While treating sarcopenia prior to LT is associated with improvement in body protein status and clinical outcomes, this is often not feasible in ACLF. Preoperatively, a total energy intake of 20-35 kcal/kg/d and a protein intake of 1.2-2 g/kg/d should be aimed for. Enhanced recovery after surgery (ERAS) protocols are the illustration of multipronged approaches and have been associated with improved short-term complications after LT and should be considered particularly in those patients with standard reconstructions (end to end, duct to duct) [137] . These protocols especially include preoperative carbohydrate loading and post-transplant enteral nutrition. Administration of micronutrients and vitamins are recommended to treat confirmed or clinically suspected deficiency. Enteral nutrition is preferred over parenteral nutrition [138, 139]. This should be started as soon as possible after transplantation is complete and the patient is not requiring high-dose vasopressors, though the exact vasopressor level is not known. Standard enteral formulas are indicated [133].

5. Physiotherapy

Severe deconditioning with muscle wasting in ACLF patients complicates recovery from LT. While prehabilitation in patients awaiting LT appears to improve aerobic capacity, and seems feasible and safe, it is often not feasible in ACLF [140]. Patients should be mobilized early in the postoperative period even if mechanical ventilation, continuous RRT, or low to moderate-dose vasopressor support is on-going [141].

6. Outcomes after LT

While several studies have demonstrated comparable post-LT survival outcomes in cirrhosis patients with and without ACLF [142], most investigations have demonstrated that ACLF patients have higher rates of post-LT complications and are more likely to be readmitted to hospital/ICU post-LT [143]. A recent meta-analysis comparing 22,238 patients with vs. 30,791 without ACLF, post LT survival in those with ACLF was lower as compared to other indications (e.g. 1 and 5 year 86.0% vs 91.9%, 66.9% vs 80.7, $p<0.01$) and associated with increased resource utilization (ICU and hospital stay) and higher post-transplant complications (including infectious complications) (74.4% vs 55.5%) [144]. In ACLF patients with AKI pre or post-LT, calcineurin inhibitors (i.e. tacrolimus) often may need to be avoided in the early post-transplant period (in favor of sirolumus based therapies) but may be re-evaluated when renal function has recovered. In summary, transplant in ACLF is resource intensive and requires multidisciplinary transplant and critical care teams that can provide significant physiological levels of care after LT. Careful consideration of post-operative protocols need to be individualized for the ACLF patient given their unique risk profile (i.e. infectious risk, AKI risk etc.) as recovery for ACLF patients post-LT can be protracted.

CURRENT GAPS AND FUTURE DIRECTIONS

Multiorgan failure was considered for many years a contraindication for LT in patients with advanced cirrhosis. Recent retrospective data suggest, on the contrary, that LT is feasible in this context and associated with improvement in short and long-term survival even in the most severe patients, those with 3 to 6 organ failures. Two main reasons could explain these positive results: 1) Accurate selection of patients to be transplanted; 2) Early transplantation: short window for

LT. Prospective studies should confirm these results and clarify an extremely important point: which are the independent predictive factors of death within 1 year after LT in ACLF 3 to design futility criteria for LT. Rate, time and determinants of extrahepatic organ recovery (organ support requirements), resources utilization and post-LT quality of life should also be investigated. Finally, type of grafts to be transplanted (i.e. donor type, use of preservation systems in suboptimal organs) and organ allocation policy should be redefined. An ongoing prospective investigation, the Chance study (https://www.clifresearch.com/chance/Home.aspx), will hopefully clarify some of these questions.

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Table 1. ICU management of ACLF

Management of septic shock

- Early antibiotic therapy (within the first hour) adjusted to local epidemiology.
- Continuous IV infusion of ß-lactams in the first 48-72 h.
- Early de-escalation based on fast microbiological tests and colonization data.
- Balanced crystalloids as first line fluids.
- Human albumin if substantial amounts of fluids are required.
- Administration of fluids guided by dynamic parameters (mainly bedside echocardiography)
- Goals of resuscitation: MAP>65 mm Hg and normalization of arterial lactates
- Norepinephrine as vasopressor of choice
- Continuous infusion of terlipressin/vasopressin when moderate/high doses of norepinephrine are required.
- Empirical antifungal therapy in patients with nosocomial septic shock and additional risk factors for fungal infection.[a]

Fluid therapy for other conditions

- Transfusion of blood products guided by VTE in bleeding patients.
- 20% albumin in patients with spontaneous bacterial peritonitis, HRS-AKI and in those requiring large volume paracentesis.

Respiratory support

- Non-invasive ventilation: high flow nasal cannula in moderate hypoxemic respiratory failure and non-invasive mechanical ventilation in patients with hypercapnia
- Invasive mechanical ventilation: apply protective strategies with low tidal volumes (6 ml/kg) and low plateau (<30 cm H_2O) and driving pressures (<15 cm H_2O).
- Early prone position in highly selected ACLF patients with refractory hypoxemia ($PaO2/FiO_2$ <150).
- Slight sedation using short half-life drugs (propofol/dexmedetomidine and fentanyl or remifentanil)

Management of kidney failure

- Fluid challenge in patients with infection induced AKI, no clear cause of AKI or signs of low preload (pre-renal AKI). Albumin as fluid of choice (1g/kg/day for 2 days)
- Terlipressin or norepinephrine plus albumin in patients with HRS-AKI
- Continuous RRT at standard doses (25-30 ml/kg/h) in patients with AKI and persistent hyperkalemia ($\geq$6-6.5 mmol/l), persistent metabolic acidosis (pH $\leq$7.2) or therapy-resistant fluid overload

Prevention of second infections

- Apply measures to prevent catheter-related infections[b] and ventilator-associated pneumonia[c]
- Patients at high risk for invasive aspergillosis[d] can benefit from the periodic determination of galactomannan antigen and from antifungal prophylaxis (nebulized amphotericin or echinocandins).

Nutritional support and physiotherapy

- Early enteral nutrition: 20-35 Kcal/Kg/day with 1.2-2 g of proteins ideal body weight/day
- Daily passive mobilization. Avoid active physiotherapy until clinical stabilization

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MAP: mean arterial pressure; Hb hemoglobin, VET: viscoelastic tests; HRS-AKI hepatorenal syndrome-acute kidney injury, RRT renal replacement therapy,

[a] Multiple colonization, parenteral nutrition, renal replacement therapy, steroids, long ICU stay
[b] Hand hygiene, use of alcohol/chlorhexidine-containing skin antiseptics with sterile dressing, sterile barrier precautions, catheter insertion site selection (subclavian > jugular > femoral), timely central line removal
[c] Elevation of the head of bed (>30º), chlorhexidine mouthwash, subglottic suctioning;
[d] Severe alcoholic hepatitis, poor liver function and prolonged steroid therapy

Table 2. Criteria for activation in the waiting list for LT of patients with ACLF and common bacterial or fungal infections

	LLAA consensus[15]	ILTS consensus[16]	AASLD guidelines[17]
Bacterial infections			
UTI without bacteremia	Not a contraindication	Not a contraindication	Not a contraindication
SBP	Clinical improvement and control tap showing a decrease in ascitic fluid PMN count (>25%) ≥ 48h after initiation of antibiotics	Appropriate antibiotic treatment for >72h.	Decrease in ascitic fluid PMN count >25% ≥ 48h after initiation of antibiotics
Pneumonia	Seven days of antibiotic therapy with clinical improvement achieving oxygen levels above "local standards."	Appropriate antibiotic treatment for >72h.	Seven days of appropriate antibiotic therapy with clinical improvement
Bacteremia	Documented clinical improvement with negative control cultures for ≥ 48h (activation on day 4-5)	-	Reactivation at ≥ 5 days of antibiotics with clinical improvement and negative repeat blood cultures for at least 48h
CDI	Therapy for at least 7 days with clinical improvement and normalization of WBC.	-	Therapy for at least 7 days with clinical improvement and normalization of WBC. Earlier if sigmoidoscopy shows mucosal healing. Consider prophylactic treatment peri-transplant
Skin and soft tissue infections			Reactivation at resolution or after 5 days of antibiotics with clinical improvement
Fungal infections			
Candidemia	Complete course of adequate antifungal therapy (2 weeks after obtaining negative blood cultures)	-	Negative blood cultures off therapy

Table 3. Suggested contraindications to proceed with LT in patients with ACLF-3

Definitive contraindications

- Elderly patients
- Severe frailty: clinical frailty scale ≥7
- Portal vein thrombosis
- Significant comorbidities
- Infection by pan-drug resistant bacteria

Temporal contraindications

- Ongoing sepsis with worsening clinical course
- Respiratory failure with PaO_2/FiO_2 ratio ≤200-150
- Circulatory failure requiring a dose of norepinephrine >0.5-1µg/kg/min
- Arterial lactate >4-9 mmol/L
- Transplantation for ACLF-3 Model, TAM score >2*

* [TAM]: age ≥53 years, pre-transplant arterial lactate ≥4 mmol/L, mechanical ventilation with PaO_2/FiO_2 ratio ≤200 and pre-transplant leucocyte ≤10 G/L

Table 4. Tests included in the fast-track evaluation for LT in patients with ACLF-3

Evaluation of relevant comorbidities
Echocardiography
CT scan of thorax, including coronary arteries, and abdomen
Direct coronarography in high-risk patients (i.e., MAFLD)*
Psychological and psychiatric history
Alcohol/other drugs dependency history
Social environment evaluation
Nutritional status
Frailty (before ICU)

*Significant lesions requiring stenting and double antiplatelet therapy temporarily contraindicate LT

Figure legend. Management of ACLF-3 patients in the ICU. From stabilization to liver transplantation. Patients are first stabilized. Clinical response is evaluated some days later. Patients still with ACLF-3 are considered for potential salvage liver transplantation (LT) and rapidly evaluated. In the absence of general contraindications, the patient is listed. The liver recipient is re-evaluated when a graft is offered. In the presence of clinical stability, LT is performed.

Figure

ACLF-3

ICU admission: clinical stabilization

- Treatment of the precipitating event
- Organ support: vasopressors, mechanical ventilation, renal replacement therapy
- Early nutritional support and physiotherapy

Assess clinical evolution at day 3-7

- New calculation of the CLIF- C ACLF score
- Determine number of organ failures and trend (improvement/steady/worsening)

No ACLF / ACLF-1

ICU discharge
Evaluation for regular LT

ACLF-2 / ACLF-3

Rapid evaluation for early LT

General contraindications?

- Elderly patients
- Severe frailty/severe sarcopenia
- Relevant comorbidities including cardiac, psychosocial or psychiatric disorders

Yes

< 4 organ failures + CLIF-C ACLFs < 70

Continue treatment

≥ 4 organ failures or CLIF-C ACLFs ≥ 70

Consider goals of care
Case by case decision

No

Inclusion in the waiting list

Organ offert

Graft selection

- High quality organs
- Machine perfusion systems if marginal organs

Transplantability at organ proposal?

- Adequate control of infection
- Norepinephrine < 0.5-1 µg/kg/min
- PaO_2/FiO_2 ratio >150-200
- Arterial lactate levels < 4-9 mmol/L

No

Postpone LT
Reassess

Transplantability at new organ offer?

Yes

Salvage LT

- Possible prolonged organ support
- Higher rate of complications
- Need for intense physiotherapy
- Early nutritional support post-surgery

Bridging the critically ill acute on chronic liver failure patient through liver transplantation

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Abbreviations: LT: liver transplantation; ACLF: acute-on-chronic liver failure; AKI: acute kidney injury: ICU: intensive care unit; HBV: hepatitis B virus; DNA: deoxyribonucleic acid; HE: hepatic encephalopathy; TIPS: transjugular intrahepatic portosystemic shunt; NE: norepinephrine; MV: mechanical ventilation; HRS-AKI: hepatorenal syndrome- acute kidney injury; ATN: acute tubular necrosis: RRT: renal replacement therapy; GFR: glomerular filtration rate; VET: viscoelastic tests;

MARS: molecular adsorbent recirculating system; RCT: randomized controlled trial; NUTRIC: nutrition risk in the critically ill; CVP: central venous pressure; PAC: pulmonary artery catheter; TEE: transesophageal echocardiography; PRS: post-reperfusion syndrome; IRI: ischemia reperfusion injury; MELD: model for end stage liver disease; NIPPV: non-invasive positive pressure ventilation; HFNC: high-flow nasal cannula; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; CIN: calcineurin inhibitor; MMF: mycophenolate mofetil; MDR multidrug resistant; ESBL-PE: extended spectrum beta-lactamase producing *Enterobacteriaceae;* CLIF-C: chronic liver failure consortium; IFI: invasive fungal infection; ERAS: enhanced recovery after surgery;

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ABSTRACT

Liver transplantation (LT) has emerged as an effective therapy for severe forms of acute on Chronic Liver Failure (ACLF), an entity characterized by the development of multiorgan failure and high short-term mortality. The aim of critical care management of ACLF patients is to rapidly treat precipitating events and aggressively support failing organs to ensure that patients may successfully undergo LT or, less frequently, recover. Malnutrition and sarcopenia are frequently present adversely impacting the prognosis of these patients. Management of critical care ACLF patients is complex and requires the participation of different specialties. Once the patient is stabilized, a rapid evaluation for salvage LT should be performed, since time window for LT is often narrow. The development of sepsis and prolonged organ support may preclude LT or diminish its chances of success. The current review describes strategies to bridge severe ACLF patients to LT, highlights the minimal evaluation required for listing and the currently suggested contraindications to proceed with LT and addresses different aspects of management during the perioperative and early post-transplant period.

INTRODUCTION

Patients with decompensated cirrhosis frequently require ICU admission for the treatment of life-threatening complications. Septic shock, variceal bleeding, severe hepatic encephalopathy (HE) and stage 3 acute kidney injury (AKI) usually occur in the setting of ACLF, an entity characterized by the presence of organ failure(s) and high short-term mortality [1, 2]. Support of failing organs and early and adequate treatment of the precipitating event(s) are key in the management of these patients [3]. Early improvement of ACLF is associated with acceptable mid-term prognosis while the persistence of $\geq$3 organ failures despite adequate therapy translates into very poor prognosis at short-term in the absence of LT [4]. Several studies suggest that early LT improves survival in ACLF-3: 1-year post-LT survival is around 80% compared to only 13% in non-transplant candidates. The window of opportunity for LT in these patients is very short ranging from days to few weeks [5]. The higher the severity of ACLF, the shorter the time available to proceed with LT [6-9].

STABILIZING THE PATIENT PRIOR TO LIVER TRANSPLANTATION

Prior to listing for LT, critically ill patients with multiorgan failure must first be stabilized which involves treating the precipitating event and providing the required organ support [10, 11]. After a period of therapy and provided there is a clear clinical improvement, patients should be rapidly evaluated for LT. Management of these complex patients should be multidisciplinary. Table 1 and Figure 1 summarize critical care management in ACLF.

1. Management of the precipitating event

Infections

Bacterial infections frequently cause and complicate the evolution of patients with ACLF and are the most frequent cause of delisting and death in liver transplant candidates with ACLF. Therefore, a comprehensive workup for the presence of bacterial infections is mandatory at the time of ACLF diagnosis and whenever the patient clinically deteriorates. The risk of infection is especially high in patients with ACLF-3 ($\geq$ 3 organ failures). Spontaneous bacterial peritonitis, bacteremia and pneumonia are the most common infections [12-14]. As multidrug resistant organisms (MDROs) are frequently responsible for these infections, broad-spectrum antimicrobial therapy adapted to local resistance patterns covering all potential pathogens are recommended in their empirical treatment. Antibiotics should be administered early and consider the most effective way which may include pharmacokinetic optimization (continuous infusions of beta-lactams in the first 48h if available). Rapid de-escalation strategies should be applied (48-72h). De-escalation relies on the identification of the responsible pathogen in clinical samples by rapid or classical techniques and on epidemiological surveillance data [3]. Once the evolution of the infection is adequate, patient can be activated/reactivated in the waiting list and transplanted under peri-transplant antibiotic therapy. This strategy appears to be sure, although infection prior to LT is associated with an increased incidence of infectious complications after surgery [15]. Criteria for activation of infected patients with ACLF for LT are poorly described in the literature. Resolution of bacterial infection is generally not required. Table 2 describes considerations on the management of infected patients in the pre-transplant period [16-18].

Invasive fungal infections (IFI) are less frequent than bacterial episodes in ACLF and usually complicate the course of the syndrome. Invasive candidiasis/candidemia and aspergillosis are the most frequent [12, 13]. Two cell-wall biomarkers, serum 1,3 β-D glucan (BDG) and galactomannan antigen (GM) are used in the diagnosis of IFI. BDG is a pan-fungal marker with good sensitivity but a more variable specificity for the diagnosis of IFI, having many sources for false positivity. It has very good negative predictive value being used to rule out an IFI. Empirical antifungal therapy can be discontinued in the presence of two consecutive negative determinations. GM is produced by *Aspergillus* spp, but not by Candida. It can be detected in bronchoalveolar lavage (BAL) and serum samples in patients with invasive aspergillosis. Values >0.5 ng/ml have a specificity of 87-97% for the diagnosis of probable IA. Sensitivity of this biomarker is higher in BAL samples [19, 20]. Prompt initiation of echinocandins is recommended in patients with ACLF and prolonged ICU stay who develop shock under the suspicion of invasive candidiasis [21]. If fungemia is confirmed, patients must receive a complete course of therapy (2 weeks of antifungals after obtaining the first negative blood cultures) and secondary sources, mainly catheter infection, must be excluded before activation for LT occurs [16, 22]. Invasive aspergillosis in the pre-transplant period is considered an absolute contraindication for LT [23].

Severe alcoholic hepatitis

Early LT is emerging as a rescue therapy in patients with severe alcoholic hepatitis refractory to steroids or in whom they are contraindicated [24, 25]. Whereas prednisone can be initiated in patients with ACLF-1 or 2, they are not recommended in ACLF-3 due to low efficacy and high risk of infections [26]. If prednisone is initiated, close clinical monitoring for infections is

recommended including periodical surveillance cultures and GM determinations [12]. Steroids must be stopped in non-responders by day 4-7 according to the Lille model. [27, 28]

Hepatitis B virus reactivation

Hepatitis B virus (HBV) reactivation is a common precipitant of ACLF in Asia [29]. Early treatment with potent antivirals (tenofovir or entecavir) should be started as soon as possible with the aim to reduce viral load and hepatocyte death [30]. A reduction of 2 log in HBV DNA levels at week 2 improves prognosis. Patients who do not stabilize with antiviral therapy should undergo rapid evaluation for LT. Entecavir should be avoided in patients with poor renal or liver function due to the risk of lactic acidosis [31]. Combination of hepatitis B immunoglobulin (HBIG) and antiviral therapy is recommended after LT to reduce graft infection. HBIG prophylaxis must be initiated in the anhepatic phase. The duration of this combination depends on the grade of viral replication. In low-risk patients (undetectable HBV DNA at transplantation) short course or even free HBIg free regimens can be considered [32, 33].

Severe variceal bleeding

Acute variceal bleeding can cause or complicate the evolution of ACLF [34]. Initial management consists of careful fluid resuscitation/transfusion, the administration of splanchnic vasoconstrictors (somatostatin/octreotide or terlipressin), prophylactic antibiotics and early endoscopic treatment [35]. Intubation for airway protection prior to endoscopy is recommended in patients with overt HE, respiratory insufficiency, or important hematemesis. In the event of failed endoscopic therapy, a self-expandable, covered, esophageal stent may be placed in patients with esophageal varices [36] and a balloon tamponade tube in those with gastric varices.

Pre-emptive TIPS (within first 72h after first bleed) decreases treatment failure and mortality [37] in patients with ACLF 1-2 [38]. A case-by-case evaluation is required in patients with ACLF 3. TIPS is usually contraindicated in patients with poor liver function (Child>13 points) unless the patient is already listed for LT [35].

2. Organ support

Circulatory failure

Sepsis and bleeding are the main causes of shock in ACLF. In this setting, volume status and cardiac function should be evaluated by echocardiography at patient's bedside, thereby monitoring fluid administration to avoid congestion. The use of colloids (albumin) over balanced crystalloids remains unclear in critical care [3, 39].

Patients who do not respond to fluid therapy should be started promptly on vasopressors. Norepinephrine (NE) is the vasopressor of choice. Continuous infusion of terlipressin or vasopressin should be initiated when high doses of NE are required (>0.25−0.5 μg/kg/min)[21]. Terlipressin should be used with caution in patients with ACLF-3 given its possible ischemic and respiratory side-effects [40]. Patients with refractory shock could benefit from the administration of stress dose steroids [3].

Patients responding to therapy will experience a marked reduction in vasopressor requirements and a progressive improvement of arterial lactate levels. Improvement in both parameters should be present to consider the activation for LT. However, threshold criteria vary greatly among centers. Most groups don't activate patients with NE >0.5g/kg/min, increasing requirements of vasopressors or high arterial lactate levels. NE requirements >1 g/kg/min or

arterial lactates >9 mmol/L are considered an absolute contraindication for LT, Table 3 [3, 17, 41-43].

Respiratory failure

Endotracheal intubation and mechanical ventilation (MV) are often required for either airway protection in patients with severe HE (Glasgow score ≤ 8) and/or in the presence of acute respiratory failure (RF; PaO2/FIO2 ratio ≤200). Multiple factors can cause RF in ACLF including uncontrolled sepsis (acute respiratory distress syndrome), aspiration, massive hydrothorax, and tense ascites. Decompressive paracentesis improves RF in patients with tense ascites and high abdominal pressure (≥15 mmHg)[44].

In patients requiring invasive mechanical ventilation, lung protective ventilation strategies should be applied. Volume-controlled ventilation with tidal volumes of 6 ml/kg predicted body weight, inspiratory plateau pressure <30 cmH_2O and driving pressure <15 cmH_20 should be implemented. Prone positioning should be indicated on a case-by-case basis in highly selected patients with ACLF when PaO2/FIO2 ratio is <150 mmHg [3, 45].

ACLF patients under MV have increased mortality [46]. MV is also a well-known risk factor for postoperative mortality in LT. Therefore, low ventilation requirements: Fi02 <50% and PaO2/FIO2 ratio > 150-200 mmHg are usually required for proceeding to LT [3, 8, 17, 41, 42].

Renal failure

AKI is extremely frequent in ACLF and is a strong predictor of short-term mortality [47]. Twenty to thirty percent of patients experience volume-responsive AKI that resolves with hydration and

discontinuation of diuretics [48]. Among volume non-responders the two main phenotypes are hepatorenal syndrome AKI (HRS-AKI) and structural AKI The former is consequence of functional mechanisms associated with portal hypertension. HRS-AKI is treated with vasoconstrictors (terlipressin or NE) and albumin [47]. Pharmacological treatment reverses the syndrome in about 50% of cases, although response is much lower in ACLF-3 [49]. Reversion of HRS-AKI before LT is associated with excellent renal outcomes after transplantation [50]. Patients with severe fluid overload should not receive terlipressin nor albumin**.** Structural AKI, mainly acute tubular necrosis (ATN), result from renal insults (sepsis, hypoperfusion, nephrotoxic drugs) [51]. Renal replacement therapy (RRT) should be considered in patients with HRS-AKI not responding to pharmacological therapy and in those with ATN and persistent metabolic acidosis (pH $\leq$ 7.20) or refractory/severe hyperkalemia ($\geq$6.0-6.5 mmol/l), therapy-resistant volume overload, RF (PaO2/FIO2 ratio is <200 mmHg), and symptomatic azotemia. Patients with severe hypervolemic hyponatremia may also require the initiation of RRT. Optimal timing of initiation of dialysis in ACLF patients is unknown. However, early initiation of renal support is not associated with better outcomes in the general population [52].

Hemodynamic unstable patients should receive continuous RRT at standard doses (25-30 ml/kg/h) [53]. RRT should bridge patients with renal failure to LT in adequate metabolic and fluid balance state. RRT can be considered during the perioperative period in oliguric/metabolically deranged patients. Patients with prolonged AKI, with either GFR < 25 ml/min or RRT for > 6 weeks should be considered for combined liver-kidney transplant [54].

Coagulation failure

Coagulation alterations are complex in ACLF patients with viscoelastic tests (VET) showing a predominant hypocoagulable state and variable fibrinolytic patterns. Coagulation disturbances should not be corrected in the absence of bleeding except for platelet count <20/µl in invasive procedures. In the presence of bleeding, VET can guide coagulation correction [3, 55, 56].

Brain failure

Patients with brain failure require endotracheal intubation for airway protection. Sedation and analgesia with short-acting medications (propofol/dexmedetomidine and remifentanil) is recommended in the presence of respiratory failure. Hepatic encephalopathy is the main cause of coma in patients with ACLF. Brain imaging and/or lumbar puncture should be performed in the presence of neurological focality or seizures. Treatment of hepatic encephalopathy is based on the identification and control of the precipitating factor (infections, hyponatremia, bleeding and sedative drugs) together with the administration of lactulose and possibly rifaximin. Polyethylene glycol is an alternative to lactulose in patients with ACLF at risk of ileus [57, 58].

Liver failure and liver support systems

Liver failure impacts prognosis in ACLF [4]. Current guidelines do not recommend the routine use of liver support systems in the treatment of ACLF patients outside research trials. Albumin dialysis (MARS, Prometheus) improve bilirubin levels and encephalopathy without improving survival [3, 18, 59]. Recent studies suggest potential benefits in short-term survival in ACLF 2-3 patients treated with MARS (bridge to LT) [60, 61]. Moreover, several uncontrolled studies show promising results of plasma exchange (PE) in ACLF [62-64]. An ongoing RCT should clarify the

impact of PE on short-term survival in this setting. In the meanwhile, these supportive systems could be considered in ACLF-3 patients as a bridge for LT in the setting of high bilirubin levels, cholemic nephropathy, coagulopathy and/or severe HE.

3. Nutritional support and physiotherapy

Malnutrition and sarcopenia are very common in ACLF and linked to poor outcomes. ACLF patients should always be screened for malnutrition (Royal Free Hospital-Subjective Global Assessment index or mNUTRIC score) and adequate nutritional intake should be ensured. Protein administration should not be restricted, even in patients with brain failure. Short-term protein limitation could be needed in patients with severe hyperammonemia and brain edema, an exceptional clinical picture. Patients unable to improve their oral intake should receive enteral nutrition within 24 hours of ICU admission. Parenteral nutrition is always a second-line option due to the risk of sepsis [65]. The optimal nutritional support for ACLF patients is that recommended in other critically ill patients [66-68] (Table 1). In addition to an adequate nutritional support, intense passive and active physiotherapy should be used in this setting to prevent muscle mass loss and critically ill myopathy [3, 10]. Active physiotherapy should be avoided until clinical stabilization.

4. Urgent evaluation and contraindications for LT

After initial stabilization and adequate control of infection patients with severe ACLF should have a quick assessment for LT. A standard evaluation is not feasible in this setting. Some tests are impracticable,

and others would delay LT. Recommended investigations are described in Table 4 [3, 8, 42, 69, 70].

Suggested contraindications for LT in ACLF-3 are described in Table 3. [3, 17, 41-43, 71].

INTRAOPERATIVE SUPPORT

1. Hemodynamic monitoring

Intraoperative monitorization of ACLF patients undergoing LT require invasive arterial blood pressure (peripheral and central) and central venous pressure (CVP) assessment and the insertion of, at least, a high flow cannula [72]. Pulmonary artery catheter (PAC) and/or transesophageal echocardiography (TEE) monitoring is strongly recommended. Although PAC remains the gold-standard monitoring method in many centers, advantages of TEE include its ability for real-time assessment of cardiac function, fluid responsiveness and rapid diagnosis of life-threatening cardiac events[73-75]. Depth of anesthesia is usually controlled by bispectral index monitoring.

2. Fluid management

Intraoperative fluid policy impacts the hemodynamic and hemostatic systems and the risk of bleeding. Restrictive fluid administration (low cardiac filling pressures) during the pre-anhepatic and anhepatic phases reduce blood losses. Both, albumin and balanced crystalloids, are used for volume replacement [76] in LT. Balanced solutions are recommended in recipients with severe hyponatremia [77] due to the risk of osmotic demyelination.

2. **Hemodynamic management**

Maintenance of hemodynamic stability during surgery in patients with ACLF is challenging. The use of NE during LT is almost universal. Patients with severe ACLF can present systolic or diastolic cardiac dysfunction and decreased sensitivity to vasoconstrictors [78], alterations that may compromise tissue perfusion. The most critical hemodynamic phase of surgery is liver reperfusion, traditionally after portal vein clamp removal [79-82]. Post-reperfusion syndrome (PRS), defined as a significant fall in arterial pressure with low vascular resistances, remains a major concern. Its incidence in ACLF is unknown but is presumably higher than that observed in other liver recipients. Ischemia reperfusion injury (IRI) plays a major role [83, 84] in PRS and therefore graft selection and modality of liver preservation are of paramount relevance. Graft selection is extremely relevant in recipients with a short window of opportunity. Many of these patients cannot wait for an optimal graft and may require the acceptance of marginal livers. Recent advances in organ preservation using dynamic oxygenated machine perfusion have allowed the use of suboptimal organs with outcomes comparable to standard grafts. Hypothermic or normothermic machine perfusion have the potential to diminish IRI and early allograft dysfunction, and potentially PRS [85-87]. Adequate surgical technique [88-93] and preemptive use of additional vasopressors (epinephrine, phenylephrine) or of methylene blue may contribute to reduce the prevalence and severity of PRS in ACLF patients [94, 95].

3. Coagulation management

VET frequently shows hypocoagulable features with prolonged time to initial fibrin formation and clot formation time, reducing clot firmness [55]. Mixed fibrinolytic phenotypes have been also reported in patients with ACLF with baseline hypofibrinolysis associated with worse outcome

[96]. Prophylactic administration of antifibrinolytics is not systematically recommended in LT in ACLF.

Bleeding during surgery is mostly of hemodynamic origin. The most effective homeostatic strategy is to maintain low splanchnic pressures. Despite the derangement of the standard coagulation tests, their prophylactic correction is not recommended. VET should be used to monitor coagulation and transfusion during LT [97, 98]. VET reduces the transfusion of fresh frozen plasma and platelet units compared to conventional coagulation tests in ACLF patients with active bleeding. Fibrinogen [99] should only be administered in patients with levels <1 g/L or with clot firmness in FIBTEM test <8 mm for treating active bleeding or before high-risk invasive procedures [100].

POST-TRANSPLANT PERIOD

Recovery after LT for ACLF can be challenging as it is well established that these patients are at higher risk of developing surgical and infectious complications post-LT [101]. Similar to other surgical populations, balanced anesthetic techniques with short-acting neuromuscular blockade and minimal narcotics and benzodiazepines expedite liberation from MV [102]. Traditionally clearance of aminotransferase elevation during the first 36 hours has been used to identify persistent preservation injury. While there has been investigation into the potential role of n-acetyl cysteine to mitigate IRI, no evidence supports its use in clinical practice [103, 104]. Vascular patency is routinely assessed with early Doppler ultrasonography, with computed tomography/angiography considered in patients with sonographic abnormalities/unexplained aminotransferase elevation.

In patients without ACLF, hyperdynamic circulation and humoral abnormalities (activation of vasoconstrictor systems) reverse within 2-4 weeks after LT, although vasopressors can be rapidly stopped after surgery [105]. Time to hemodynamic normalization in ACLF is probably longer, feature that could explain the longer times of vasopressor support that these patients may require [6].

1. Weaning from mechanical ventilation

While rapid post-operative liberation from MV is the aim in the post-LT setting, this can be challenging in ACLF patients. Risk factors for failed extubation/prolonged MV include high MELD score (> 25), high transfusion requirements (> 1600 ml of packed red blood cells) and vasopressor use [106]. Spontaneous breathing modes can be implemented with recovery from anesthesia and patients should be extubated when protecting their airway, hemodynamically stable and return to operating room is not imminent. Prolonged times of MV are expected in these sick patients. The higher the severity of ACLF at LT, the longer the time of respiratory support. Strategies to avoid reintubation include the use of non-invasive positive pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC) [107, 108]. Factors that limit the use of NIPPV include altered mental status, shock, multi-organ failure, and extreme frailty where HFNC is preferable[108]. Acute respiratory failure following LT may be due causes associated with cirrhosis (i.e. hepatopulmonary syndrome, capillary leak/non-cardiogenic pulmonary edema, portopulmonary hypertension) along with those that are unrelated (pneumonia, atelectasis, pulmonary embolism). Risk factors for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) post-LT patients include massive transfusion, fluid overload, sepsis, and aspiration which

have a high prevalence in ACLF patients [109, 110]. ALI/ARDS post-LT is associated with up to a 2-fold increase in 1-year mortality [110]. The treatment of ALI/ARDS in post-LT is similar to treatment for general critical care patients with a lung protective strategy [45, 111, 112]. In the ACLF patient, post-LT high PEEP strategy (> 10 cm H_2O) is not recommended as it can impede venous return and cardiac preload [113, 114]. Different PEEP levels (0, 5, and 10 cm H_2O), did not impact flow velocities in the hepatic artery, portal vein, or hepatic veins and hence hepatic perfusion was not impaired by PEEP < 10 cmH2O [115]. In patients who require protracted ventilator support, consider early percutaneous tracheostomy [116].

2. Immunosuppression in ACLF

Improved graft and patient survival in LT recipients have been attributed to decreased rates of acute cellular rejection with improved immunosuppression regimens. The use of these agents can be associated with potential increasing toxicities in LT recipients with ACLF. AKI is the most frequent organ failure in ACLF. Calcineurin inhibitor (CNI) -based regimens are associated with a decrease of renal function ranging from 13% to 33% according to whether the CNI is administered alone or in combination with antimetabolite or induction therapy [117]. Lower target tacrolimus trough concentrations should therefore be considered in patients with ACLF to prevent AKI [118]. Furthermore, according to two large RCT, induction therapy with an anti-interleukine-2 receptor in combination to mycophenolate mofetil (MMF) and corticosteroids, and reduced/delayed initiation of CNI is associated with superior renal function and decreased need for RRT than early initiation of standard dosing of CNI [119, 120].

ACLF patients undergoing LT are immunocompromised and potentially more susceptible to infections/sepsis due to numerous immune alterations. There is no consensus on the management of immunosuppressive regimen in ACLF patients' post-LT at-risk of sepsis or with sepsis. It has been proposed to hold immunosuppression temporarily to improve sepsis recovery [121]. However, this strategy may increase the risk of allograft rejection. Maintenance of CNI in association with MMF with a rapid withdrawal of steroids may be proposed.

3. Perioperative antimicrobial prophylaxis

Patients with ACLF are at increased risk of post-LT infection, especially MDR pathogens [122]. Extended spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-PE) are become more prevalent with an incidence that has increased almost tenfold from 2001 to 2010 [123]. Patients with ACLF often have several risk factors for ESBL-E infections including high severity of illness, recent hospitalization and recent antimicrobial therapy [124]. A rectal swab is a screening tool to evaluate the risk of ESBL-PE or other MDRO infection after LT. In a recent study, 45% of patients with a preoperative rectal ESBL-E rectal carriage developed an ESBL-E infection within the first 90 days whereas post-LT ESBL-E infection occurred in only 3.5% of the non-carriers. In the same study, the authors evaluated the efficacy of a directed prophylaxis regimen against ESBL-PE in LT recipients. Incidence of ESBL-PE related infections following LT was lower in patients that received a perioperative antimicrobial prophylaxis targeting the colonizing ESBL-PE [124]. No studies have addressed the best surgical prophylaxis regimen among patient colonized with *carbapenem resistant Enterobacteriaceae*. Nevertheless, specific prophylactic regimens should be considered in these patients. Nasopharyngeal swab for *Staphylococcus aureus* testing is also

recommended in patients with ACLF at the time of transplantation. Colonized patients, mainly those carrying the methicillin-resistant strain, should be decolonized [125].

Patients transplanted for ACLF are prone to IFI after LT and frequently have risk factors (ie. MELD>30, AKI, RRT, previous broad-spectrum antimicrobial therapy) [126]. Some studies have shown that antifungal prophylaxis may reduce the incidence of IFI and its associated mortality [127]. The risk of IFI should be carefully evaluated in every ACLF patient at the time of LT. In high risk patients, prophylaxis using echinocandins as first-line therapy should be considered until risk factor disappearance.

4. Nutritional support

Malnutrition in ACLF may complicate recovery after LT. A multi-disciplinary approach including nutritionists/dietitians is associated with improved outcomes and reduced readmissions [66, 128-131]. An objective assessment of the patient's nutrition status should be performed on all patients prior to and post-LT. The Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition guidelines recommend the use of the Nutrition Risk in the Critically Ill (NUTRIC) score to identify patients that benefit most from nutrition support [132, 133]. Energy and protein requirements for nutrition support are calculated by predictive equation initially, using ideal body weight [66]. There is considerable inter-individual variability in patients with ACLF, and indirect calorimetry to measure resting energy expenditure should be used if available for more accurate assessment. Based on recent guidelines from the European Society for Clinical Nutrition and Metabolism [134], the European Association for the Study of Liver [135] and a recent position paper by the Enhanced Recovery after Liver Transplantation

(ERAS4OLT.org) Working Group [136], there is global agreement to screen for malnutrition and sarcopenia in all cirrhosis/ACLF patients listed for LT. While treating sarcopenia prior to LT is associated with improvement in body protein status and clinical outcomes, this is often not feasible in ACLF. Preoperatively, a total energy intake of 20-35 kcal/kg/d and a protein intake of 1.2-2 g/kg/d should be aimed for. Enhanced recovery after surgery (ERAS) protocols are the illustration of multipronged approaches and have been associated with improved short-term complications after LT and should be considered particularly in those patients with standard reconstructions (end to end, duct to duct) [137] . These protocols especially include preoperative carbohydrate loading and post-transplant enteral nutrition. Administration of micronutrients and vitamins are recommended to treat confirmed or clinically suspected deficiency. Enteral nutrition is preferred over parenteral nutrition [138, 139]. This should be started as soon as possible after transplantation is complete and the patient is not requiring high-dose vasopressors, though the exact vasopressor level is not known. Standard enteral formulas are indicated [133].

5. Physiotherapy

Severe deconditioning with muscle wasting in ACLF patients complicates recovery from LT. While prehabilitation in patients awaiting LT appears to improve aerobic capacity, and seems feasible and safe, it is often not feasible in ACLF [140]. Patients should be mobilized early in the postoperative period even if mechanical ventilation, continuous RRT, or low to moderate-dose vasopressor support is on-going [141].

6. Outcomes after LT

While several studies have demonstrated comparable post-LT survival outcomes in cirrhosis patients with and without ACLF [142], most investigations have demonstrated that ACLF patients have higher rates of post-LT complications and are more likely to be readmitted to hospital/ICU post-LT [143]. A recent meta-analysis comparing 22,238 patients with vs. 30,791 without ACLF, post LT survival in those with ACLF was lower as compared to other indications (e.g. 1 and 5 year 86.0% vs 91.9%, 66.9% vs 80.7, $p<0.01$) and associated with increased resource utilization (ICU and hospital stay) and higher post-transplant complications (including infectious complications) (74.4% vs 55.5%) [144]. In ACLF patients with AKI pre or post-LT, calcineurin inhibitors (i.e. tacrolimus) often may need to be avoided in the early post-transplant period (in favor of sirolumus based therapies) but may be re-evaluated when renal function has recovered. In summary, transplant in ACLF is resource intensive and requires multidisciplinary transplant and critical care teams that can provide significant physiological levels of care after LT. Careful consideration of post-operative protocols need to be individualized for the ACLF patient given their unique risk profile (i.e. infectious risk, AKI risk etc.) as recovery for ACLF patients post-LT can be protracted.

CURRENT GAPS AND FUTURE DIRECTIONS

Multiorgan failure was considered for many years a contraindication for LT in patients with advanced cirrhosis. Recent retrospective data suggest, on the contrary, that LT is feasible in this context and associated with improvement in short and long-term survival even in the most severe patients, those with 3 to 6 organ failures. Two main reasons could explain these positive results: 1) Accurate selection of patients to be transplanted; 2) Early transplantation: short window for

LT. Prospective studies should confirm these results and clarify an extremely important point: which are the independent predictive factors of death within 1 year after LT in ACLF 3 to design futility criteria for LT. Rate, time and determinants of extrahepatic organ recovery (organ support requirements), resources utilization and post-LT quality of life should also be investigated. Finally, type of grafts to be transplanted (i.e. donor type, use of preservation systems in suboptimal organs) and organ allocation policy should be redefined. An ongoing prospective investigation, the Chance study (https://www.clifresearch.com/chance/Home.aspx), will hopefully clarify some of these questions.

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Table 1. ICU management of ACLF

Management of septic shock

- Early antibiotic therapy (within the first hour) adjusted to local epidemiology.
- Continuous IV infusion of ß-lactams in the first 48-72 h.
- Early de-escalation based on fast microbiological tests and colonization data.
- Balanced crystalloids as first line fluids.
- Human albumin if substantial amounts of fluids are required.
- Administration of fluids guided by dynamic parameters (mainly bedside echocardiography)
- Goals of resuscitation: MAP>65 mm Hg and normalization of arterial lactates
- Norepinephrine as vasopressor of choice
- Continuous infusion of terlipressin/vasopressin when moderate/high doses of norepinephrine are required.
- Empirical antifungal therapy in patients with nosocomial septic shock and additional risk factors for fungal infection.[a]

Fluid therapy for other conditions

- Transfusion of blood products guided by VTE in bleeding patients.
- 20% albumin in patients with spontaneous bacterial peritonitis, HRS-AKI and in those requiring large volume paracentesis.

Respiratory support

- Non-invasive ventilation: high flow nasal cannula in moderate hypoxemic respiratory failure and non-invasive mechanical ventilation in patients with hypercapnia
- Invasive mechanical ventilation: apply protective strategies with low tidal volumes (6 ml/kg) and low plateau (<30 cm H_2O) and driving pressures (<15 cm H_2O).
- Early prone position in highly selected ACLF patients with refractory hypoxemia ($PaO2/FiO_2$ <150).
- Slight sedation using short half-life drugs (propofol/dexmedetomidine and fentanyl or remifentanil)

Management of kidney failure

- Fluid challenge in patients with infection induced AKI, no clear cause of AKI or signs of low preload (pre-renal AKI). Albumin as fluid of choice (1g/kg/day for 2 days)
- Terlipressin or norepinephrine plus albumin in patients with HRS-AKI
- Continuous RRT at standard doses (25-30 ml/kg/h) in patients with AKI and persistent hyperkalemia ($\geq$6-6.5 mmol/l), persistent metabolic acidosis (pH $\leq$7.2) or therapy-resistant fluid overload

Prevention of second infections

- Apply measures to prevent catheter-related infections[b] and ventilator-associated pneumonia[c]
- Patients at high risk for invasive aspergillosis[d] can benefit from the periodic determination of galactomannan antigen and from antifungal prophylaxis (nebulized amphotericin or echinocandins).

Nutritional support and physiotherapy

- Early enteral nutrition: 20-35 Kcal/Kg/day with 1.2-2 g of proteins ideal body weight/day
- Daily passive mobilization. Avoid active physiotherapy until clinical stabilization

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MAP: mean arterial pressure; Hb hemoglobin, VET: viscoelastic tests; HRS-AKI hepatorenal syndrome-acute kidney injury, RRT renal replacement therapy,

[a] Multiple colonization, parenteral nutrition, renal replacement therapy, steroids, long ICU stay
[b] Hand hygiene, use of alcohol/chlorhexidine-containing skin antiseptics with sterile dressing, sterile barrier precautions, catheter insertion site selection (subclavian > jugular > femoral), timely central line removal
[c] Elevation of the head of bed (>30º), chlorhexidine mouthwash, subglottic suctioning;
[d] Severe alcoholic hepatitis, poor liver function and prolonged steroid therapy

Table 2. Criteria for activation in the waiting list for LT of patients with ACLF and common bacterial or fungal infections

	LLAA consensus[15]	ILTS consensus[16]	AASLD guidelines[17]
Bacterial infections			
UTI without bacteremia	Not a contraindication	Not a contraindication	Not a contraindication
SBP	Clinical improvement and control tap showing a decrease in ascitic fluid PMN count (>25%) ≥ 48h after initiation of antibiotics	Appropriate antibiotic treatment for >72h.	Decrease in ascitic fluid PMN count >25% ≥ 48h after initiation of antibiotics
Pneumonia	Seven days of antibiotic therapy with clinical improvement achieving oxygen levels above "local standards."	Appropriate antibiotic treatment for >72h.	Seven days of appropriate antibiotic therapy with clinical improvement
Bacteremia	Documented clinical improvement with negative control cultures for ≥ 48h (activation on day 4-5)	-	Reactivation at ≥ 5 days of antibiotics with clinical improvement and negative repeat blood cultures for at least 48h
CDI	Therapy for at least 7 days with clinical improvement and normalization of WBC.	-	Therapy for at least 7 days with clinical improvement and normalization of WBC. Earlier if sigmoidoscopy shows mucosal healing. Consider prophylactic treatment peri-transplant
Skin and soft tissue infections			Reactivation at resolution or after 5 days of antibiotics with clinical improvement
Fungal infections			
Candidemia	Complete course of adequate antifungal therapy (2 weeks after obtaining negative blood cultures)	-	Negative blood cultures off therapy

Table 3. Suggested contraindications to proceed with LT in patients with ACLF-3

Definitive contraindications

- Elderly patients
- Severe frailty: clinical frailty scale ≥7
- Portal vein thrombosis
- Significant comorbidities
- Infection by pan-drug resistant bacteria

Temporal contraindications

- Ongoing sepsis with worsening clinical course
- Respiratory failure with PaO_2/FiO_2 ratio ≤200-150
- Circulatory failure requiring a dose of norepinephrine >0.5-1µg/kg/min
- Arterial lactate >4-9 mmol/L
- Transplantation for ACLF-3 Model, TAM score >2*

* [TAM]: age ≥53 years, pre-transplant arterial lactate ≥4 mmol/L, mechanical ventilation with PaO_2/FiO_2 ratio ≤200 and pre-transplant leucocyte ≤10 G/L

Table 4. Tests included in the fast-track evaluation for LT in patients with ACLF-3

Evaluation of relevant comorbidities
Echocardiography
CT scan of thorax, including coronary arteries, and abdomen
Direct coronarography in high-risk patients (i.e., MAFLD)*
Psychological and psychiatric history
Alcohol/other drugs dependency history
Social environment evaluation
Nutritional status
Frailty (before ICU)

*Significant lesions requiring stenting and double antiplatelet therapy temporarily contraindicate LT

Figure legend. Management of ACLF-3 patients in the ICU. From stabilization to liver transplantation. Patients are first stabilized. Clinical response is evaluated some days later. Patients still with ACLF-3 are considered for potential salvage liver transplantation (LT) and rapidly evaluated. In the absence of general contraindications, the patient is listed. The liver recipient is re-evaluated when a graft is offered. In the presence of clinical stability, LT is performed.

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: