

## **Supplementary Appendix\_R2 version**

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: European Association for the Study of the Liver: **EASL Clinical Practice Guidelines on acute-on-chronic liver failure**

## Table of Content

Document	Pages
<b>Supplemental questions, recommendations, statements and companion texts</b>	<b>3</b>
Table S1. The Chronic Liver Failure-Consortium Organ Failure scoring system	<b>14</b>
Table S2. Stratification of patients with acutely decompensated cirrhosis according to EASL-CLIF criteria	<b>15</b>
Table S3. Stratification of patients with acutely decompensated HBV-related chronic liver disease according to the Chinese Group on the Study of Severe Hepatitis B (COSSH)	<b>16</b>
Table S4. Definition of organ system failures by the NACSELD (North American Consortium for the Study of End-stage Liver Disease)	<b>17</b>
Table S5. Asian Pacific Association for the Study of the Liver ACLF Research Consortium (AARC) scoring system	<b>18</b>
Table S6. List of drugs that may cause acute kidney injury (separate document)	Separate document
Table S7. Organ system assessment with the HBV-SOFA scoring system developed by the Chinese Group on the Study of Severe Hepatitis B (COSSH)	<b>19</b>
<b>Table S8. General ICU management of ACLF</b>	<b>20</b>
References	<b>25</b>

## Supplemental questions, recommendations, statements and companion texts

**Related to the section entitled: Resuscitation for hypotension requiring vasopressor therapy**

**Does the use of albumin during the resuscitation process improve outcomes in patients with ACLF who require vasopressors for hypotension?**

**Patient and population:** Patients with ACLF who require vasopressors for hypotension

**Intervention:** Resuscitation using concentrated human albumin (4-5-20%)

**Comparison:** Crystalloid solutions (balanced and unbalanced fluids)

**Outcome:** Resolution of shock, AKI, renal-replacement therapy, dynamics of ACLF course (either increases, no change or decreases in ACLF grade) during the first week after admission, 28 and 90-day transplantation-free mortality

### Recommendations

- In patients with ACLF and hypotension, human albumin or crystalloids should be used for initial fluid therapy (**LoE 4, strong recommendation, consensus**).
- Human albumin is recommended for the treatment of ACLF patients requiring substantial amounts of fluids and vasopressors (**LoE 5, weak recommendation, consensus**).

Timely restoration of plasma volume is the first therapeutic goal in patients with septic shock. It prevents tissue hypoxia and mitochondrial dysfunction and preserves organ function.<sup>1</sup> Both crystalloids and colloids are used as intravenous fluid therapy in this

setting. Data derived from studies performed in the general population suggest crystalloids as first-line therapy in patients with hypotension and signs of hypoperfusion.<sup>2</sup> Among crystalloids, balanced solutions are preferred to 0.9% saline given the risk of hyperchloremic acidosis and renal failure.<sup>3</sup> However, balanced crystalloids should be avoided in patients with hyperkalemia or severe renal failure due to their high concentration in potassium.<sup>4</sup>

Albumin (4-5%-20%) is the only colloid solution currently recommended in patients with septic shock. Gelatins, starches and dextrans are contraindicated in this setting given the risk of AKI.<sup>5</sup> Despite not being superior to crystalloids in studies performed in the general population, current Surviving Sepsis Campaign guidelines recommend the use of albumin solutions after initial resuscitation with crystalloids, especially in patients requiring substantial amounts of fluids.<sup>2</sup> Albumin has oncotic effects and non-oncotic functions including antioxidant, immunomodulatory, scavenging and endothelium protective properties that could be beneficial in patients with sepsis and septic shock.<sup>6</sup>

The rationale for albumin administration in patients with ACLF and hypotension requiring vasopressors is probably stronger than in other populations. These patients present a marked proinflammatory and pro-oxidant state that contribute to organ failure. Both alterations could be attenuated by albumin therapy. Hypoalbuminemia and albumin dysfunction, almost universal in patients with ACLF, can also be partially reverted by albumin infusion.<sup>7</sup>

Only two studies have evaluated the efficacy and clinical impact of different intravenous solutions in patients with ACLF and septic shock. Both investigations reported contradictory data on albumin safety and impact on survival. In an open-label single center RCT, 308 patients with cirrhosis and sepsis-induced hypotension were

randomized to receive 5% albumin or saline serum. Albumin was more effective than crystalloids in the early resuscitation of these patients, was well-tolerated and improved 1-week survival (43.5% vs. 38.3%,  $p=0.03$ ).<sup>8</sup> Another investigation published recently compared the efficacy and safety of 20% albumin (0.5-1 g/kg over 3 h) to balanced crystalloid (plasmalyte: 30 ml/kg over 3 h) in 100 cirrhotic patients with sepsis-induced hypotension.<sup>9</sup> Again, albumin was more effective than crystalloids in the early resuscitation of these patients (mean arterial pressure [MAP] >65 mm Hg at 3 h: 62% vs. 22%, respectively;  $p<0.001$ ). However, its administration was associated with a higher rate of pulmonary complications. Treatment was interrupted in 22% of patients in the albumin group compared to no discontinuation in the plasmalyte group. Short-term survival was similar between groups (58% vs. 62%, respectively). The authors concluded that plasmalyte is safer and better tolerated than 20% albumin in patients with cirrhosis and sepsis induced hypotension. Further larger RCT are specifically needed to address this controversial area.

Considering the data currently available we recommend the use of human albumin (4%, 5%, 20%) or crystalloids (mainly balanced solutions) in the early resuscitation of hypotensive patients with ACLF. Patients requiring substantial amounts of fluids and vasopressors should be treated with albumin solutions. Fluid administration should always be guided by dynamic parameters to avoid fluid overload (Table 6). In any case, further larger trials are specifically needed in the ACLF population to address this controversial area.

**Is norepinephrine more effective and safer than vasopressin or its analogue terlipressin (continuous infusion) as the first vasopressor in patients with ACLF who require vasopressors for hypotension?**

**Patient and population:** Patients with ACLF who require vasopressors for hypotension

**Intervention:** Norepinephrine

**Comparison:** Vasopressin or terlipressin in continuous infusion

**Outcome:** Resolution of shock, side-effects (including ischemic events and respiratory failure/pulmonary edema), AKI, renal-replacement therapy, dynamics of ACLF course (either increases, no change or decreases in ACLF grade) during the first week after admission, 28-day and 90-day transplantation-free transplantation mortality

### **Recommendation**

- Based on data coming from the ICU general population, norepinephrine is the first-line vasopressor for patients with ACLF and hypotension unresponsive to fluid therapy (**LoE 4, strong recommendation, strong consensus**).
- Dopamine is not recommended in patients with ACLF (**LoE 4, strong recommendation, strong consensus**).

### **Statements**

- Continuous infusion of terlipressin or vasopressin are potential second-line agents in patients with poor response to norepinephrine (**LoE 4, consensus**).

Patients not responding to fluid therapy require the rapid initiation of vasopressors to preserve organ perfusion and prevent organ damage. Current Surviving Sepsis Campaign guidelines recommend the use of norepinephrine, a potent  $\alpha$ -1 and  $\beta$ -1 adrenergic receptor agonist, as first-line vasopressor in patients with septic shock from

the general population.<sup>2</sup> Patients with inadequate response to norepinephrine (low MAP despite moderate-to-high doses of norepinephrine: 0.25–0.5 µg/kg/min) should receive vasopressin, a V<sub>1</sub>-receptor agonist. Resistance to norepinephrine is frequently caused by the internalization of its receptors due to tissue hypoxia. The combination of both drugs reduces the catecholamine burden, and the risk of arrhythmias and could improve survival, especially in patients with less severe forms of septic shock.<sup>10</sup> Epinephrine is only recommended in patients who do not respond to the combination of norepinephrine and vasopressin due to the high risk of ischemic events. Dopamine, an α-1, β-1 adrenergic and dopaminergic receptor agonist, is no longer recommended in the management of septic shock. It increases the risk of major adverse events, mainly cardiac arrhythmias (24.1% vs. 12.4%, p<0.001) and short-term mortality in comparison with norepinephrine.<sup>11,12</sup>

Following the recommendations established in the general ICU population, norepinephrine is considered the first-line vasopressor to be initiated in ACLF patients due to its safe profile. Continuous infusion of terlipressin or vasopressin are potential second-line agents in patients with refractory septic shock.<sup>7</sup> An open label investigation including 82 patients with septic shock compared the efficacy and safety of norepinephrine (7.5-60 µ/min) and terlipressin (2-8 mg over 24 h) as first line therapy in cirrhotic patients with septic shock. Terlipressin was associated with a more rapid hemodynamic stabilization, lower risk of variceal bleeding (0% vs. 9.5%, p=0.01) and improved survival at 48h (95.2% vs. 71.4%, p=0.003). Hospital survival was markedly low and similar between groups. A higher rate of adverse effect (40% vs. 21%, p=0.06), mainly peripheral ischemia and lactic acidosis, was observed in patients on terlipressin therapy.<sup>7,13</sup> New RCT are needed before considering terlipressin a safe alternative to norepinephrine in patients with ACLF and septic shock. On the contrary, continuous

infusion of terlipressin is considered the first-line option in patients with hepatorenal syndrome (HRS, now known as HRS-AKI).<sup>14</sup>

**Does a MAP target of 65 to 70 mm Hg improve prognosis in patients with ACLF who require vasopressors for hypotension?**

**Patient and population:** Patients with ACLF who require vasopressors for hypotension

**Intervention:** MAP target of 65-70 mm Hg

**Comparison:** MAP target of 60 mm Hg

**Outcome:** Resolution of shock, AKI, renal-replacement therapy, dynamics of ACLF course (either increases, no change or decreases in ACLF grade) during the first week after admission, 28- and 90-day transplantation-free mortality

**Recommendation**

- In patients with ACLF who require vasopressors for hypotension, we recommend a strategy to achieve a MAP equal or more than 65 mm Hg (**LoE 5, strong recommendation, consensus**).

MAP determines systemic filling pressure and tissue blood flow. Organ perfusion decreases when it falls below 60 mm Hg. Consequently, the standard target for resuscitation recommended in the general ICU patients with shock is a MAP  $\geq$ 65 mm Hg. Higher arterial pressures (75-85 mm Hg) are recommended in patients with systemic hypertension since they are associated with lower requirements of dialysis.<sup>15</sup>



Since patients with ACLF show lower arterial pressure than general ICU patients, some experts suggest reach a lower MAP target (60 mm Hg) in patients with hypotension requiring vasopressors. However, this threshold could compromise organ hypoperfusion and induce organ failure(s).<sup>7</sup> Permissive hypotension strategies have never been compared to “usual care” (MAP  $\geq$ 65 mm Hg) in patients with ACLF who require vasopressors. Until this point is clarified, we recommend a target of a MAP  $\geq$ 65 mm Hg in patients with ACLF and shock, as suggested in the general population (Surviving Sepsis Campaign guidelines).<sup>2</sup> Normalization of arterial lactate levels and of peripheral perfusion (capillary refill time) are also part of the resuscitation strategy. Repeated monitoring of fluid responsiveness and cardiac function through non-invasive (echocardiography) or invasive methods are also highly recommended in all patients with septic shock, especially if signs of hypoperfusion persists in order to individualize the therapeutic strategy.<sup>7,16</sup>

### **Refractory septic shock**

**Do steroids (hydrocortisone 200 mg/d) improve outcome in patients with ACLF and refractory septic shock?**

**Patient and population:** Patients with ACLF and septic shock and increasing doses of norepinephrine ( $>0.25$   $\mu$ g/kg/min)

**Intervention:** Hydrocortisone 200 mg/d

**Comparison:** No steroids

**Outcome:** Resolution of shock and 28-day and 90-day transplantation-free mortality

### **Recommendation**

- Stress dose steroids might be used in patients with ACLF who require moderate or high doses of norepinephrine ( $>0.25 \mu\text{g}/\text{kg}/\text{min}$ ) for hypotension (**LoE 3/4, weak recommendation, consensus**).

### Statement

- Relative adrenal insufficiency is highly prevalent in patients with ACLF and refractory septic shock and is associated with poor outcome (**LoE 4, consensus**)

An inadequate production of cortisol by the hypothalamic-pituitary adrenal axis is frequently observed in critically ill patients with cirrhosis and sepsis or shock in response to stress (51-75%).<sup>17</sup> This condition known as relative adrenal insufficiency (also known as critical illness-related corticosteroid insufficiency) is characterized by low total serum cortisol levels with respect to peripheral demands. This hormone is essential to modulate systemic inflammation, maintain vascular tone and permeability and adapt the metabolism to stress. Its deficiency is associated with a higher risk of refractory shock, multiple organ failure and death.<sup>18</sup> Adrenal insufficiency also occurs in patients with advanced cirrhosis (26%) and in ACLF (48% in ACLF 1 and 70% in ACLF-2/3) and is also associated with poor prognosis.<sup>19,20</sup> Although there is no consensus on the test that should be used to diagnose relative adrenal insufficiency, a delta total serum cortisol value  $<9 \mu\text{g}/\text{dl}$  one hour after cosyntropin administration (250  $\mu\text{g}$ ) or a random total serum cortisol of  $<10 \mu\text{g}/\text{dl}$  are the most accepted and reliable diagnostic criteria of this entity.<sup>21</sup>

The administration of stress dose steroids (hydrocortisone 200 mg/day) in patients with septic shock from the general population is associated with favorable hemodynamic effects (decrease in vasopressor requirements and faster reversal of

shock), with unclear effects on survival.<sup>22</sup> These positive hemodynamic effects, consistently reported in patients without cirrhosis, have also been observed in the cirrhotic population. In a double-blind placebo-controlled trial, hydrocortisone therapy was associated with higher rates of shock reversal (62% vs. 39%,  $p=0.05$ ). However, steroid supplementation was associated with a higher rate of shock relapse (34% vs. 14%,  $p=0.03$ ), more adverse events, mainly gastrointestinal bleeding, and did not impact 28-day case-fatality rate (85% vs. 72%).<sup>23</sup> Due to concerns about survival benefits, current guidelines in the general ICU population (Surviving Sepsis Campaign guidelines),<sup>2</sup> and in patients with cirrhosis as well,<sup>7</sup> only recommend the administration of stress dose steroids in patients with vasopressor-resistant shock (norepinephrine  $\geq 0.25 \mu\text{g}/\text{kg}/\text{min}$ ). Once started, steroids should be tapered down as soon as shock is solved with the aim to prevent adverse events related to prolonged therapy (myopathy, secondary infections, and gastrointestinal bleeding). Steroids should not be administered for more than 10 days.<sup>7</sup>

**Related to the section entitled: “Secondary infections”**

**Do bundles to prevent catheter-related infections and ventilator-associated pneumonia, that are currently used in general ICUs, improve prognosis in ACLF patients admitted to the ICU?**

**Patient and population:** Patients with ACLF in the ICU

**Intervention:** Bundles to prevent catheter-related infections and ventilator-associated pneumonia

**Comparison:** No bundles

**Outcome:** Rate of device-related infections, dynamics of ACLF course (either increases, no change or decreases in ACLF grade) during the first week after admission, 28 and 90-day transplantation-free mortality

### **Recommendation**

- Bundles of measures aimed to prevent the development of catheter-related bacteremia and ventilator-associated pneumonia should be used in patients with ACLF admitted to the ICU (**LoE 3, strong recommendation, strong consensus**).

### **Statement**

- Patients with ACLF admitted to the ICU are at high risk of nosocomial infections (**LoE 3, strong consensus**)

Patients with ACLF are at very high risk for bacterial infections at short-term. Cumulative incidence exceeds 60% at 28 days compared to less than 20% in patients with acute decompensation. The higher the severity of ACLF, the higher the risk of infection, reaching >80% in ACLF-3. Pneumonia, bacteremia and spontaneous bacterial peritonitis are the most frequent infections complicating the course of the syndrome. These infections are mainly nosocomial, many of them are related to instrumentation or organ support (invasive mechanical ventilation, central lines, and urinary catheters) and are frequently caused by MDROs. They negatively impact the clinical evolution of ACLF and survival.<sup>24</sup> Therefore, their prevention is of paramount clinical relevance.

Several bundles of measures are applied in the prevention of the two main infections associated with healthcare invasive devices in the general ICU population, catheter-related bacteremia, and ventilator-associated pneumonia.<sup>22,25-26</sup> Adequate hand hygiene, use of alcohol/chlorhexidine-containing skin antiseptics with sterile dressing, maximal sterile barrier precautions, catheter insertion site selection (subclavian >jugular >femoral) and timely central line removal are measures that effectively and sustainedly decrease the incidence of bacteremia related to catheter infection in the general ICU population.<sup>22</sup> Measures to prevent micro-aspiration of bacteria that accumulate in the upper airway (elevation of the head of the bed >30°, oral washing with chlorhexidine, subglottic suctioning, maintaining endotracheal cuff pressure at 25 cm H<sub>2</sub>O) and actions aimed at preventing the introduction of bacteria from environment (hand hygiene, bacterial filters, and minimal manipulation of the endotracheal tube) are able to decrease the incidence of ventilator-associated pneumonia in the general ICU population.<sup>25,26</sup> Minimization of sedation and shorter mechanical ventilation time are also key in the prevention of ventilator-associated pneumonia.

Given the high risk of nosocomial infections observed in patients with ACLF, bundles of measures aimed to prevent the development of catheter-related bacteremia and ventilator-associated pneumonia should be applied in patients with ACLF admitted to the ICU. The impact of the application of these bundles on prognosis should be evaluated in appropriate RCT.

Table S1. The Chronic Liver Failure-Consortium Organ Failure scoring system <sup>a</sup>				
Organ system	Variable	Scale <sup>b</sup>		
		1 point <sup>c</sup>	2 points <sup>c</sup>	3 points <sup>c</sup>
Liver	Bilirubin (mg/dl)	<6.0	≥6.0 to <12.0	≥12
Kidney	Creatinine (mg/dl)	<1.5	≥2.0 to <3.5	≥3.5
		>1.5 to <2.0		or use of RRT
Cerebral	HE grade (West Haven criteria)	0	I - II	III – IV or endotracheal intubation for HE
Coagulation	INR	<2.0	≥2.0 to <2.5	≥2.5
Circulation	MAP (mm Hg)	≥70	<70	Use of vasopressors
Respiration <sup>d</sup>	PaO <sub>2</sub> /FiO <sub>2</sub>	>300	>200 to ≤300	≤200
	SpO <sub>2</sub> /FiO <sub>2</sub>	>357	>214 to ≤357	≤214 Or use of mechanical ventilation

<sup>a</sup> Adapted from Jalan et al.<sup>27</sup> HE denotes hepatic encephalopathy, MAP mean arterial pressure, PaO<sub>2</sub> partial pressure of arterial oxygen, FiO<sub>2</sub> fraction of inspired oxygen, and SpO<sub>2</sub> pulse oximetry saturation.

<sup>b</sup> The Chronic Liver Failure Consortium (CLIF-C) Organ Failure (OF) scoring system assigns a score on a scale of 1 (close to normal) to 3 (most abnormal) to each of the six major organ systems (kidneys, lungs, liver, coagulation, brain, circulation). Aggregated scores range from 6 to 18, with higher scores indicating more marked severity and determine the CLIF-C OF score which is used to calculate the CLIF-C ACLF score (which is equal to  $10 \times [0.33 \times \text{CLIF-C OF score} + 0.04 \times \text{Age} + 0.63 \times \text{Ln}(\text{white-cell count}) - 2]$ ). A calculator is available at [www.efclif.com](http://www.efclif.com).

<sup>c</sup> The red and orange colors indicate the values that are used to define organ system failure and organ dysfunction, respectively. Organ system failures and dysfunction are used to define ACLF (see Table S2).

<sup>d</sup> SpO<sub>2</sub> is used when PaO<sub>2</sub> is not available.

**Table S2. Stratification of patients with acutely decompensated cirrhosis according to EASL-CLIF criteria<sup>a</sup>**

**Acutely decompensated cirrhosis without acute-on-chronic liver failure (ACLF)<sup>28</sup>**

Refers to:

Patients with no organ failure

Patients with single failure (affecting any of the following: liver, coagulation, circulation, respiration) and serum creatinine levels <1.5 mg/dL without hepatic encephalopathy

Patients with single cerebral failure and creatinine levels <1.5 mg/dL

**Acutely decompensated cirrhosis with ACLF<sup>28</sup>**

Refers to patients assigned to one of the three following grades: ACLF-1, ACLF-2, and ACLF-3.

ACLF-1 includes:

- Patients with single kidney failure
- Patients with single liver, coagulation, circulatory or lung failure associated with creatinine levels ranging from 1.5 mg/dL to 1.9 mg/dL or hepatic encephalopathy grade 1 or 2, or both
- Patients with single brain failure with creatinine levels ranging from 1.5 to 1.9 mg/dL

ACLF-2 includes patients with 2 organ failures

ACLF-3 includes patients with 3 organ failures or more (maximum of 6).

<sup>a</sup> Adapted from Moreau et al.<sup>28</sup>

**Table S3. Stratification of patients with HBV-related ACLF according to the Chinese Group on the Study of Severe Hepatitis B (COSSH)<sup>a</sup>**

**Acutely decompensated cirrhosis with ACLF<sup>28</sup>**

Refers to patients assigned to one of the three following grades: ACLF-1, ACLF-2, and ACLF-3.

ACLF-1 includes:

- Patients with single kidney failure
- Patients with single liver failure with an INR  $\geq 1.5$  and/or kidney dysfunction and/or HE grade I or II
- Patients with single type of organ failure of the coagulation, circulatory or respiratory systems and/or kidney dysfunction and/or HE grade I or II and
- Patients with single brain failure with creatinine levels ranging from 1.5 to 1.9 mg/dL

ACLF-2 includes patients with 2 organ failures

ACLF-3 includes patients with 3 organ failures or more (maximum of 6).

<sup>a</sup> Adapted from Wu et al.<sup>29</sup> The investigators from COSSH use the CLIF-C OF score to diagnose organ system failures (see Table S1).



**Table S4. Definition of organ system failures by the NACSELD (North American Consortium for the Study of End-stage Liver Disease)<sup>a</sup>.**

Organ system	Definition of organ system failure <sup>b</sup>
Kidney	Need for dialysis or other forms of renal-replacement therapy
Brain	HE grade III or IV (West Haven Criteria)
Circulation	Shock: MAP <60 mm Hg or a reduction of 40 mm Hg in systolic blood pressure from baseline, despite adequate fluid resuscitation and cardiac output
Respiration	Need for mechanical ventilation
<p><sup>a</sup> From Bajaj et al.<sup>30</sup> HE denotes hepatic encephalopathy, and MAP mean arterial pressure.</p> <p><sup>b</sup> The number of organ system failures determines the NACSELD score, which therefore ranges from 1 to 4.<sup>31</sup></p>	

**Table S5. Asian Pacific Association for the Study of the Liver ACLF Research Consortium (AARC) scoring system<sup>a</sup>**

Points <sup>b</sup>	Total bilirubin (mg/dl)	HE Grade	INR	Lactate (mmol/l)	Creatinine (mg/dl)
1	<15	0	<1.8	<1.5	<0.7
2	15 - 25	I - II	1.8 – 2.5	1.5 – 2.5	0.7 – 1.5
3	>25	III - IV	>2.5	>2.5	>1.5

<sup>a</sup> Adapted from Sarin et al.<sup>32</sup> HE denotes hepatic encephalopathy, and INR international normalized ratio.

<sup>b</sup> The AARC scoring system assigns a score on a scale of 1 (close to normal) to 3 (most abnormal) to each of the 5 variables shown here. Aggregated scores define the AARC score which ranges from 5 to 15, with higher scores indicating more marked severity. As per Asia Pacific investigators the AARC score is not used to define acute-on-chronic liver failure (ACLF) but to assess ACLF severity; ACLF being defined as per criteria of the Asian Pacific Association for the Study of the Liver.<sup>32</sup> AARC scores ranging from 5 to 7 define ACLF-1, those ranging from 8 to 10 define ACLF-2, and those ranging from 11 to 15 define ACLF-3.

**Table S7. Organ system assessment with the HBV-SOFA scoring system developed by the Chinese Group on the Study of Severe Hepatitis B (COSSH)<sup>a</sup>**

Organ system	Variable	Scale <sup>b</sup>		
		1 point	2 points	3 points
Kidney	Creatinine (mg/dl)	<1.1	1.2 – 2.3	>2.3
Brain	HE grade (West Haven criteria)	0	I - II	III - IV
Circulation	MAP (mm Hg)	≥70	<70	Vasopressors
Respiration	PaO <sub>2</sub> /FiO <sub>2</sub>	>300	201 - 300	≤200
	SpO <sub>2</sub> /FiO <sub>2</sub>	>357	215 - 357	≤214

<sup>a</sup> Adapted from Wu et al.<sup>29</sup> HE denotes hepatic encephalopathy, MAP mean arterial pressure, PaO<sub>2</sub> partial pressure of arterial oxygen, FiO<sub>2</sub> fraction of inspired oxygen, and SpO<sub>2</sub> pulse oximetry saturation.

<sup>b</sup> The HBV-SOFA scoring system assigns a score on a scale of 1 (close to normal) to 3 (most abnormal) to each of following four major organ systems: kidneys, brain, respiration, circulation. Aggregated scores range from 4 to 12, with higher scores indicating more marked severity, and determine the HBV-SOFA score which is used to calculate the COSSH-ACLF score (equal to  $0.741 \times \text{INR} + 0.523 \times \text{HBV-SOFA score} + 0.026 \times \text{age} + 0.003 \times \text{total bilirubin}$ ).

**Table S8. General ICU management of ACLF**

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**Management of infections****Diagnosis**

A systematic workup for the detection of infection (chest X-ray and analysis/cultures of blood, urine, ascites fluid and respiratory samples, rectal and nasal swabs) should be done at diagnosis of ACLF and whenever the patient clinically deteriorates.

**Treatment**

Empiric antibiotic strategies should be tailored according to the severity of the infection and the local epidemiological pattern of antibiotic resistance covering all potential pathogens.

Antibiotics should be started as soon as possible, ideally immediately after obtaining blood cultures (within the first 1h-3h after diagnosis of infection).

Strategies aimed at optimizing the pharmacokinetic/pharmacodynamic profile of antibiotics should be applied in patients with severe infections: i.e., continuous IV infusion of  $\beta$ -lactams in the first 48h-72 h.

Empirical antimicrobial therapies should be rapidly de-escalated based on fast microbiological tests (MALDI-TOF-MS, PCR), conventional microbiology and epidemiological surveillance data (colonization).

Short-term treatments are recommended in the majority of patients (5-7 days).<sup>a</sup>

Empirical antifungal therapy should be initiated in patients with nosocomial infection, septic shock and additional risk factors for fungal infection.<sup>b</sup>

**Management of septic shock**

Crystalloids (balanced solutions are preferred over saline) and human albumin can be used as first-line fluids in the resuscitation of hypotensive patients. Human albumin may be used for the treatment of ACLF patients requiring substantial amounts of fluids and vasopressors.

Administration of fluids should be guided by dynamic parameters including response to passive leg raising, stroke volume or pulse pressure variation and echocardiography.

Static parameters (central venous pressure) are of less value.

Goals of resuscitation: 1. Maintain a mean arterial pressure (MAP) equal or more than 65 mm Hg (macrocirculation). 2. Normalize serum lactate levels (microcirculation). 3. Normalize peripheral perfusion (capillary refill time and mottling score).

Norepinephrine is the vasopressor of choice in patients with septic shock (first-line vasopressor).

Continuous infusion of terlipressin or vasopressin should be started when MAP is inadequate despite moderate doses of norepinephrine.

Steroids (hydrocortisone 200 mg/d) might be administered in patients with ongoing requirement of vasopressor therapy (norepinephrine  $>0.25$   $\mu\text{g}/\text{kg}/\text{min}$ ).

Transfusion policy: threshold for red blood cell transfusion is Hb  $<70$  g/l. Less restrictive approaches could be need (Hb  $<80$  g/l) if microcirculation is altered.

Deep vein thrombosis prophylaxis is recommended in this setting. The selection between LMWH or intermittent pneumatic compression devices will depend on the grade of coagulopathy.

Stress ulcer prophylaxis with the use of PPIs is recommended meanwhile organ support is needed. Thereafter a step by step approach is suggested.

### **Fluid therapy for conditions other than septic shock**

Crystalloids, preferably balanced solutions, should be used as first-line therapy in the resuscitation of hypotensive patients.

Threshold for red blood cell transfusion is Hb <70 g/l.

Transfusion of fresh frozen plasma, platelets or fibrinogen will be guided by viscoelastic tests in bleeding patients.

20% albumin is the fluid of choice in patients with ACLF and spontaneous bacterial peritonitis, HRS-AKI and in those requiring large volume paracentesis.

### **Respiratory support**

High flow nasal cannula is preferred over non-invasive mechanical ventilation in patients with sepsis-induced hypoxemic respiratory failure.

Non-invasive mechanical ventilation is indicated in patients with hypercapnic respiratory failure.

Protective ventilation with low tidal volumes (6 ml/kg) and low plateau (<30 cm H<sub>2</sub>O) and driving pressures (plateau pressure-PEEP <15 cm H<sub>2</sub>O). should be used in patients with acute respiratory distress syndrome (ARDS) requiring invasive mechanical ventilation.

Oxygen saturation should range between 92% and 100%.

Highly selected ACLF patients with refractory hypoxemia (PaFiO<sub>2</sub> <150) could benefit from prone position. It should be indicated early and maintained for at least 16h-24 h.

Early extracorporeal membrane oxygenation (ECMO) is contraindicated (futile intervention) in the majority of ACLF patients with ARDS and refractory hypoxemia or hypercapnia due to the high mortality of these patients.

Tracheostomy should only be performed in highly selected patients on prolonged invasive mechanical ventilation (10-14 days).

Slight sedation using short half-life drugs (propofol and fentanyl or remifentanyl) is recommended in patients requiring invasive mechanical ventilation.

Daily passive mobilization is recommended. Active physiotherapy should be avoided until clinical stabilization.

### **Management of kidney failure**

Patients with HRS-AKI should be treated with vasopressors (mainly terlipressin in continuous infusion) plus albumin.

Continuous RRT should be started at standard doses (25-30 ml/kg/h) in patients with acute tubular necrosis and one of the following criteria: persistent hyperkalemia (>6.5 mmol/l), persistent metabolic acidosis (pH <7.2), therapy-resistant fluid overload, anuria (<50 ml/12 h).

### **Prevention of second infections**

Bundles aimed to prevent catheter-related infections<sup>c</sup> and ventilator-associated pneumonia<sup>d</sup> are highly recommended in the management of ACLF patients while in the ICU.

The impact of decolonization strategies (oral non-absorbable antibiotics) in patients colonized by resistant strains is unknown.

Patients with ACLF and additional risk factors for invasive aspergillosis (severe alcoholic hepatitis, poor liver function and prolonged steroid therapy). can benefit from the periodic determination of galactomannan antigen and from antifungal prophylaxis (i.e., nebulized amphotericin or echinocandins).

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MALDI-TOF MS denotes matrix-assisted laser desorption ionization-time of flight mass spectrometry, Hb hemoglobin, LMWH low molecular weight heparin, HRS-AKI hepatorenal syndrome-acute kidney injury, PPIs proton-pump inhibitors, RRT renal replacement therapy, and ICU intensive care unit.

- <sup>a</sup> Except for infections caused by *S. aureus*, intracellular strains, fungal infection, abscesses, parapneumonic empyema, biofilm formation or infections with predefined duration of treatment.
- <sup>b</sup> Multiple colonization, parenteral nutrition, renal replacement therapy, steroids, long ICU stay.
- <sup>c</sup> Adequate hand hygiene, use of alcohol/chlorhexidine-containing skin antiseptics with sterile dressing, maximal sterile barrier precautions, catheter insertion site selection (subclavian > jugular > femoral), timely central line removal.
- <sup>d</sup> Elevation of the head of de bed (>30°), oral washing with chlorhexidine, subglottic suctioning, maintaining endotracheal cuff pressure at 25 cm H<sub>2</sub>O.



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