Review

JHEP|Reports

# Acute-on-chronic liver failure: Definitions, pathophysiology and principles of treatment

Giacomo Zaccherini,[1,2,†] Emmanuel Weiss,[2,3,4,†] Richard Moreau[2,4,5,*]

## Summary

**The term acute-on-chronic liver failure (ACLF) defines an abrupt and life-threatening worsening of clinical conditions in patients with cirrhosis or chronic liver disease. In recent years, different definitions and diagnostic criteria for the syndrome have been proposed by the major international scientific societies. The main controversies relate to the type of acute insult (specifically hepatic or also extrahepatic), the stage of underlying liver disease (cirrhosis or chronic hepatitis) and the concomitant extrahepatic organ failure(s) that should be considered in the definition of ACLF. Therefore, different severity criteria and prognostic scores have been proposed and validated. Current evidence shows that the pathophysiology of ACLF is closely associated with an intense systemic inflammation sustained by circulating pathogen-associated molecular patterns and damage-associated molecular patterns. The development of organ failures may be a result of a combination of tissue hypoperfusion, direct immune-mediated damage and mitochondrial dysfunction. Management of ACLF is currently based on the supportive treatment of organ failures, mainly in an intensive care setting. For selected patients, liver transplantation is an effective treatment that offers a good long-term prognosis. Future studies on potential mechanistic treatments that improve patient survival are eagerly awaited.**



Keywords: Acute decompensation; Multiorgan failure; Inflammatory response; Bacterial infections; Bacterial translocation; Sterile inflammation; Immunopathology; Metabolism

*Received 7 June 2020; received in revised form 29 July 2020; accepted 18 August 2020; available online 2 September 2020*

## Background

It is universally accepted that the term "acutely decompensated cirrhosis" defines patients with cirrhosis who are non-electively admitted to the hospital for recent onset ascites, gastrointestinal haemorrhage, newly developed hepatic encephalopathy, bacterial infections, or any combination of these disorders.[1–5] Recently, the term acute-on-chronic liver failure (ACLF) has been used to define a syndrome which was observed among patients with acutely decompensated cirrhosis and characterised by high 28-day mortality.[2] The other characteristics of ACLF included its association with an intense systemic inflammatory response, its frequent and close association with a precipitating condition (infections, alcoholic hepatitis), and its association with single- or multiple organ failures (OFs). However, there is not yet a universally recognised definition of ACLF. Herein, we summarise the current knowledge and controversies in ACLF.

## Definitions of ACLF

In the last decade, different definitions of ACLF have been developed by international consortia.[2–7] These definitions are summarised in Table 1.

### Definitions according to the European, North American and Chinese consortia

All these definitions account for intra- and extrahepatic precipitants of ACLF and consider both liver and extrahepatic OFs. Moreover, patients who have had prior episode(s) of liver disease decompensation are not excluded by these definitions.

In 2013, the European Association for the Study of the Liver – Chronic Liver Failure (EASL-CLIF) Consortium proposed a definition based on the results of the large (1,343 patients), prospective, observational CANONIC study.[2] This definition applies to patients non-electively hospitalised for acutely decompensated cirrhosis. The diagnosis of organ failures is based on the Chronic Liver Failure-Consortium (CLIF-C) OF (CLIF-C OF) scoring system which assesses 6 organ systems (liver, kidney, brain, coagulation, circulation, and respiration) (Fig. 1A).[8] The European definition of ACLF includes patients with a high risk of short-term death (including patients with single kidney failure; those with single "non-kidney" organ failure if it is associated with kidney of brain dysfunction; and those with ≥2 OFs) (Table 1). Accordingly, 4 groups of patients with acutely decompensated cirrhosis are defined: 1 group of patients without ACLF and 3 groups of patients with increasing severity of ACLF (grade 1, grade 2 and grade 3) on the basis of the type and number of OF(s).[2]

The definition by the North American Consortium for the Study of End-stage Liver Disease (NACSELD) is based on observational data from 507 patients with acutely decompensated cirrhosis non-electively hospitalised for infection (Table 1).[3]

[1]*Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy;* [2]*European Foundation for the Study of Chronic Liver Failure (EF-CLIF), Barcelona, Spain;* [3]*Department of Anesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Paris, France;* [4]*Inserm et Université de Paris, Centre de Recherche sur l'Inflammation (CRI), Paris, France;* [5]*Service d'Hépatologie, Hôpital Beaujon, AP-HP, Clichy, France*

† *Co-first authors.*

* Corresponding author. Address: INSERM U1149, Centre de Recherche sur l'Inflammation (CRI), 16 rue Henri Huchard, 75890 PARIS cedex 18, France.
*E-mail address:* richard.moreau@inserm.fr (R. Moreau).

ELSEVIER

EASL The Home of Hepatology

The North American definition uses standard definitions of shock, the need for mechanical ventilation, the need for renal replacement therapy and West Haven grade III or IV hepatic encephalopathy for the diagnosis of extrahepatic OFs (Fig. 1B). This definition does not include changes in liver function and coagulation. ACLF is defined by the presence of ≥2 extrahepatic OFs.[3] A second study by the NACSELD has validated the definition of ACLF in a large cohort of patients with acutely decompensated cirrhosis, precipitated or not by infection.[9]

The Chinese Group on the Study of Severe Hepatitis B (COSSH) developed a definition for HBV-related ACLF.[4] This definition applies to patients with acutely decompensated HBV-related chronic liver disease (with or without cirrhosis). The Chinese investigators use the CLIF-C OF scoring system for the diagnosis of OFs and distinguish 3 grades of ACLF which are very similar to those defined by the European investigators. However, ACLF grade 1 in the Chinese classification includes an additional subgroup comprising patients with single liver failure who have an international normalised ratio (INR) of ≥1.5 (Table 1).[4]

### Definition according to the Asian Pacific Association for the Study of the Liver ACLF Research Consortium

Based on expert opinion, the Asian Pacific Association for the Study of the Liver (APASL) published a definition in 2009,[6] which was subsequently updated by the APASL ACLF Research Consortium (AARC) in 2014[7] and 2019.[5] This definition considers patients with compensated cirrhosis (diagnosed or undiagnosed) and those with non-cirrhotic chronic liver disease, who have a first episode of acute liver deterioration due to an acute insult directed to the liver. The acute hepatic insult is defined by jaundice (total bilirubin levels of ≥5 mg/dl) and coagulopathy (INR of ≥1.5, or prothrombin activity of <40%) complicated within 4 weeks by clinical ascites, hepatic encephalopathy, or both.[5] Patients who have extrahepatic precipitants and those with kidney, circulatory, or respiratory failures are excluded from this definition (Table 1).

## Clinical phenotypes

The clinical phenotypes of patients with ACLF differ according to the definition used.

### ACLF phenotype according to the EASL-CLIF definition

In the CANONIC study, the primary causes of cirrhosis were alcohol-related liver disease, followed by chronic hepatitis C and a combination of both.[2] The most frequent precipitating disorders for acutely decompensated cirrhosis, with or without ACLF, were both hepatic (alcohol-induced liver injury) and extrahepatic (bacterial infections or gastrointestinal haemorrhage). However, in a significant proportion of cases (up to 30-40%), no apparent precipitating event was found.[2] The most prevalent OFs were kidney failure (55.8% of patients with ACLF) and liver failure (43.6%), followed by coagulation (27.7%) and cerebral (24.1%) failures. Cardiovascular and respiratory failures were less frequent (16.8 and 9.2% respectively).[2] At presentation, the prevalence of ACLF grade 1, 2, and 3 was 49%, 35%, and 16%, respectively. The 28-day transplant-free mortality was 32.8% in patients with ACLF compared to 1.9% in patients without ACLF.[2] Among patients with ACLF, the observed 28-day transplant-free mortality was 23%, 31% and 74% for grade 1, grade 2 and grade 3 ACLF, respectively.[2]

**Key points**

- Different definitions of ACLF have been proposed by the major international scientific societies, depending on the types of precipitants and organ failures included.
- According to the definition used, the clinical phenotypes of patients with ACLF vary in terms of aetiology of underlying liver diseases, nature of precipitating event and patient prognosis.
- In ACLF, pathogen-associated molecular patterns and damage-associated molecular patterns are the drivers of an intense systemic inflammation which is also associated with features of immunosuppression.
- Systemic inflammation is involved in the development of organ failures through tissue hypoperfusion, immune-mediated tissue damage and mitochondrial dysfunction.
- Current management of ACLF relies on supportive therapy for organ failures.
- Given the high rate of sepsis-related ACLF, an empirical antibiotic therapy tailored to the suspected site of the infection and the local ecology should be rapidly initiated.
- Albumin treatment may have beneficial effects on systemic inflammation and infusion is recommended after high volume paracentesis, in case of spontaneous bacterial peritonitis, and in patients with AKI KDIGO stage 2-3.
- Patients with ACLF should be promptly assessed for liver transplantation.

Among patients with ACLF, the phenotype differed according to the precipitating disorder. Compared to patients with ACLF unrelated to infection, those with infection-related ACLF more often had cerebral failure (31% *vs.* 17% in non-infected patients), circulatory failure (34% *vs.* 18%), and respiratory failure (20% *vs.* 10%). More importantly, patients with infection-related ACLF had more intense systemic inflammation and a higher 90-day mortality rate (51% *vs.* 38%).[10]

Several studies have investigated risk factors and predictors of ACLF development.[11–13] Data from a large retrospective cohort from the U.S. Veterans Health Administration reported the lowest incidence of ACLF among patients with underlying chronic HCV infection or non-alcoholic fatty liver disease. Conversely, patients with alcoholic cirrhosis or concomitant alcohol and HCV infection had the highest incidence rates.[11] In a large single-centre Italian prospective cohort of outpatients with cirrhosis, ascites, higher model for end-stage liver disease (MELD) score, lower mean arterial pressure and lower haemoglobin levels were identified as independent predictors for ACLF development.[12] Interestingly, grade III obesity (BMI >40 kg/m$^2$) was identified as a risk factor for ACLF in a large retrospective population of patients with cirrhosis waitlisted for liver transplantation.[13]

Data obtained from the CANONIC cohort showed that ACLF is a very dynamic syndrome that may evolve to resolution, improvement or worsening in a short period of time.[2,14] Its clinical course after 3-7 days from diagnosis is a better predictor of outcome than its initial severity. A reassessment of ACLF grade and CLIF-C OF score within this timeframe reliably predicted patient prognosis, enabling the authors to stratify patients by severity and to monitor their response to treatment.[14] Patients with grade 3 ACLF 3-7 days after diagnosis showed the worst prognosis. However, among these severely ill patients, the prognosis differed according to the number of OFs. Indeed, those with 3 OFs had lower 28-day transplant-free mortality than those with ≥4 OFs (53% *vs.* >90%, respectively). For patients with

**Table 1. Characteristics of definitions of ACLF developed by 4 different consortia.**

| Characteristics | European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium* | North American Consortium for the Study of End-stage Liver Disease (NACSELD) | Chinese Group on the Study of Severe Hepatitis B (COSSH) | Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC)** |
|---|---|---|---|---|
| Category of article(s) defining ACLF | Original article reporting the results of the CANONIC study, which is a prospective, observational study performed in 1,343 patients with cirrhosis non-electively admitted to 29 liver units in 12 European countries[2] | Original article reporting results of an analysis of 507 patients with cirrhosis whose data were prospectively collected in the NACSELD database, which includes non-electively hospitalised patients in 18 liver units across the USA and Canada[3] | Original article reporting the results of the COSSH study, which is a prospective, observational study performed in 1,322 patients with cirrhosis or severe liver injury due to chronic hepatitis B, non-electively hospitalised in 13 liver centres in China[4] | Consensus document involving international experts from the APASL, published in 2009[6] and updated in 2014[7] and 2019,[5] in the context of AARC; the last 2 updates used internally reviewed data from 1,402 patients, and 3,300 patients, respectively |
| Patients considered in the definition | Patients with acutely decompensated cirrhosis, with or without prior episode(s) of decompensation | Patients with acutely decompensated cirrhosis, with or without prior episode(s) of decompensation | Patients with acute decompensation of HBV-related chronic liver disease, with or without cirrhosis | Patients with compensated cirrhosis (diagnosed or undiagnosed) or non-cirrhotic chronic liver disease, who had a first episode of acute liver deterioration due to an acute insult directed to the liver |
| Precipitating disorders | Intrahepatic (alcoholic hepatitis), extrahepatic (infection, gastrointestinal haemorrhage), or both | Extrahepatic (infection) | Intrahepatic (HBV reactivation), extrahepatic (bacterial infection) or both | Intrahepatic |
| Major organ systems considered for the definition | There are 6: liver, kidney, brain, coagulation, circulation and respiration (see Fig. 1A) | There are 4: kidney, brain, circulation and respiration (see Fig. 1B). Liver and coagulation are not considered | There are 6: Liver, kidney, brain, coagulation, circulation and respiration (see Fig. 2B) | Liver dysfunction is central to the definition; hepatic encephalopathy may be present, as a consequence |
| Basis of the definition | The definition of ACLF is based on the existence of the failure of 1 of the 6 major organ systems. The failure of each organ system is assessed using the CLIF-C Organ Failure scale* | The definition of ACLF is based on the existence of 2 organ system failures or more (maximum 4) (see Fig. 1B) | The definition of ACLF is based on the failure of 1 of the 6 major organ systems. The failure of each organ system is assessed using the CLIF-C Organ Failure scale* | The definition of ACLF is based on the presence of liver dysfunction.<br>Extrahepatic organ failures may subsequently develop but are not included in the definition |
| Definition and stratification of ACLF | ACLF is divided into 3 grades of increasing severity.<br>• ACLF grade 1 includes 3 subgroups:<br>– patients with single kidney failure<br>– patients with single liver, coagulation, circulatory or lung failure that is associated with creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl or hepatic encephalopathy grade 1 or grade 2, or both<br>– patients with single brain failure with creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl<br>• ACLF grade 2 includes patients with 2 organ failures<br>• ACLF grade 3 includes patients with 3 organ failures or more had ACLF grade 3 | Patients are stratified according to the number of organ failures 2, 3, or all 4 organ failures, respectively | ACLF is divided into 3 grades of increasing severity.<br>• ACLF grade 1 includes 4 subgroups:<br>– patients with single kidney failure<br>– patients with single liver failure and either an INR of 1.5 or more, creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl, hepatic encephalopathy grade I or II, or any combination of these alterations<br>– patients with single type of organ failure of the coagulation, circulatory or respiratory systems and either creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl, hepatic encephalopathy grade I or II, or both<br>– patients with cerebral failure alone plus creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl<br>• ACLF grade 2 includes patients with 2 organ failures<br>• ACLF grade 3 includes patients with 3 organ failures or more | Acute hepatic insult manifesting as jaundice (total bilirubin levels of 5 mg/dl or more) and coagulopathy (INR of 1.5 or more, or prothrombin activity of less than 40%) complicated within 4 weeks by clinical ascites, encephalopathy, or both.<br>The severity of ACLF is assessed using the AARC score** (see Fig. 2C). The grading system, defines Grade 1 by scores of 5–7, Grade 2 by scores 8–10 and Grade 3 for 11–15 (see Fig. 2D) |

(*continued on next page*)

**Table 1** (*continued*)

| Characteristics | European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium* | North American Consortium for the Study of End-stage Liver Disease (NACSELD) | Chinese Group on the Study of Severe Hepatitis B (COSSH) | Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC)** |
|---|---|---|---|---|
| Short-term mortality rate of ACLF according to stratification | By 28 days:<br>Grade 1: 20%<br>Grade 2: 30%<br>Grade 3: 80% | By 30 days:<br>2 organ failures: 49%<br>3 organ failures: 64%<br>4 organ failures: 77% | By 28 days:<br>Grade 1: 23%<br>Grade 2: 61%<br>Grade 3: 93% | By 28 days:<br>Grade 1: 13%<br>Grade 2: 45%<br>Grade 3: 86% |

* The CLIF-C OF score includes sub-scores ranging from 1 to 3 for each of 6 components (liver, kidneys, brain, coagulation, circulation, and lungs), with higher scores indicating more severe organ system impairment. Aggregated scores range from 6 to 18 and provide information on overall severity. See also Fig. 1A and ref.8.
** The AARC score includes sub-scores ranging from 1 to 3 for each of 5 components (total bilirubin, hepatic encephalopathy grade, INR, creatinine levels, blood lactate levels). Aggregated scores range from 5 to 15, with higher scores indicating more severe ACLF. See also Fig. 2C, 2D and ref.5. ACLF, acute-on-chronic liver failure; INR, international normalised ratio.

≥4 OFs, discontinuation of intensive support should be considered when liver transplantation is contraindicated or not available.[14] These findings may have implications for clinical decision making in patients with ACLF.

Of note, the EASL-CLIF definition of ACLF has been applied in different cohorts worldwide.[4,15–18] In a Chinese population of patients with cirrhosis associated with hepatitis B, patients with and without ACLF showed an average 28-day mortality rate of 44% and 2.6%, respectively. Moreover, the observed 28-day mortality for patients with grade 1, grade 2 and grade 3 ACLF was 23.6%, 40.8%, 60.2%, respectively.[15] In a large retrospective U.S. cohort derived from 127 Veteran Affairs hospitals, patients without ACLF had a 28-day mortality rate of 10.4% compared to 25.5% in patients with ACLF (16.9%, 26.8% and 53.3% for grade 1, grade 2 and grade 3 ACLF, respectively).[17] Similar results were also obtained when applying EASL-CLIF criteria to a prospective cohort in India.[18]

Another Chinese study retrospectively applied the EASL-CLIF criteria to a prospective cohort of patients with acutely decompensated cirrhosis, in whom 2 forms of ACLF were identified: one precipitated by hepatic insults (characterised by liver and coagulation failures) and the other by extrahepatic insults (characterised by extrahepatic OFs).[19]

### ACLF phenotype according to the NACSELD definition

The epidemiology of liver diseases, the main causes of cirrhosis and potential precipitating events for acutely decompensated cirrhosis are similar between Europe and North America.[2,3,20] In the first study conducted in the context of NACSELD, the most prevalent organ system failures were brain (36%), followed by circulatory (16%), kidney (13%), and respiratory (9%).[3] The observed 30-day mortality rate progressively increased from 4% in patients without any OF, to 27%, 49%, 64% and 77% in patients with 1, 2, 3, or 4 OFs, respectively.[3] In a large series of infected and non-infected patients with acutely decompensated cirrhosis, the 30-day mortality rate was 41% among patients with NACSELD-ACLF compared to 7% among patients without NACSELD-ACLF.[9]

Of note, when compared with the EASL-CLIF definition of ACLF, the NACSELD definition considered only very severe and high-risk patients. The comparison of the 2 definitions in a large North American population showed that less than 40% of patients with EASL-CLIF ACLF were captured by NACSELD criteria.[17] However, the 28- and 90-day mortality rates were still substantial among North American patients who did not fulfil the NACSELD criteria of ACLF.[17]

### ACLF phenotype according to the COSSH definition

Seventy percent of patients with HBV-related ACLF, as defined by COSSH criteria, had cirrhosis. The most common precipitating disorder was, as expected in China, hepatic insult due to HBV reactivation alone (59% of cases), followed by a combination of a hepatic insult (most often HBV reactivation) and extrahepatic insult (bacterial infection) in 14% of cases. Of note, bacterial infection alone was a precipitating disorder in 9% of cases.[4] Among patients with HBV-related ACLF, the most common failing organ systems were the liver (95%), coagulation (70%), kidney (13%), and brain (7%). There were very few cases of circulatory and respiratory failures. At presentation, the prevalence of ACLF grade 1, 2, and 3 was 60.6%, 33%, and 6.4%, respectively. The 28-day mortality rate for ACLF grade 1, grade 2, and 3 was 23%, 61%, and 93%, respectively.[4] Together these findings indicate

**A**

| The Chronic Liver Failure-Consortium Organ Failure scale | | | | |
|---|---|---|---|---|
| **Organ system** | **Variable** | **Scale** | | |
| | | 1 point | 2 points | 3 points |
| **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 or use of RRT |
| | | >1.5 to <2.0 | | |
| **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** | $PaO_2/FiO_2$<br>$SpO_2/FiO_2$ | >300<br>>357 | >200 to ≤300<br>>214 to ≤357 | ≤200<br>≤214<br>Or use of mechanical ventilation |

**B**

| The definition of organ system failures by the NACSELD (North American Consortium for the Study of End-stage Liver Disease) | |
|---|---|
| **Organ system** | **Definition of organ system failure** |
| **Kidney** | Need for dialysis or other forms of renal-replacement therapy |
| **Brain** | HE grade III or IV (West Haven Criteria) |
| **Circulation** | Shock: MAP <60 mmHg or a reduction of 40 mmHg in systolic blood pressure from baseline, despite adequate fluid resuscitation and cardiac output |
| **Respiration** | Need for mechanical ventilation |

**Fig. 1. Definitions of organ system failures used by European and Chinese investigators and North American investigators for defining ACLF.** (A) Chronic Liver Failure-Consortium Organ Failure (known as CLIF-C OF) scale used by investigators from Europe (European Association for the Study of the Liver – Chronic Liver Failure Consortium)) and China (Chinese Group on the Study of Severe Hepatitis B).[4,6] The red and yellow boxes indicate the thresholds for organ system failure and organ dysfunction, respectively. (B) Definitions of organ system failures used by the investigators of the North American Consortium for the Study of End-stage Liver Disease (known as NACSELD).[3] E, epinephrine; $FiO_2$, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalised ratio; MAP, mean arterial pressure; NE, norepinephrine; $PaO_2$, partial pressure of arterial oxygen; RRT, renal replacement therapy; $SpO_2$, oxygen saturation as measured by pulse oximetry.

that although the European and Chinese definitions of ACLF were very similar, the clinical phenotypes of the syndrome differed between the 2 continents. For example, compared to European patients, Chinese patients more frequently had liver and coagulation failures and less frequently kidney and brain failures. Moreover, the mortality associated with ACLF, particularly the mortality associated with grade 2 ACLF, was greater in the Chinese cohort (Table 1).

### ACLF phenotype according to the AARC definition

Studies using AARC criteria have shown that, as expected, HBV reactivation was the most frequent trigger of ACLF.[5,20] Other potential precipitating disorders were HEV infection and drug-induced liver injury.[5,20] Various bacterial, parasitic and fungal infections (directly and primarily affecting the liver) are also listed among triggers of ACLF in Asia.[5] Using the AARC criteria, up to 95% of cases of ACLF present with an identifiable precipitating event,[5] in contrast to only 60% of cases in Western countries. A study has investigated the course of patients with ACLF defined by AARC criteria.[21] Almost 80% of patients had complications, including bacterial or fungal infection in 32% of patients, hepatorenal syndrome in 15%, and gastrointestinal haemorrhage in 9%. The 28-day transplantation-free mortality rate was 28%.

## Prognostic scoring systems

Prognostic score systems are shown in Box 1 and Fig. 2A-D.[4,5,8,21,22]

## Pathophysiology of ACLF

### Inducers of systemic inflammation

Systemic inflammation can be induced by the presence in body fluids of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (Table 2; Fig. 3).[23–26] PAMPs – expressed by microbes – are unique molecular structures that are recognised by dedicated receptors called pattern-recognition receptors (PRRs), an example being Toll-like receptors (TLRs), which are expressed in innate myeloid

**Box 1. Prognostic scoring systems used in patients with ACLF.**

Several scores have been developed and proposed to assess patient prognosis and help clinician decision-making. European investigators have developed a score named CLIF-C ACLF score that predicts mortality in patients with ACLF. This score was based on the CLIF-C OF score and enriched with the 2 best independent predictors of death in the CANONIC cohort: age and white blood cell-count, a marker of systemic inflammation (Fig. 2A).[8] Both scores can be found and calculated on the EF-CLIF website (http://www.efclif.com). The accuracy for predicting death was better with the CLIF-C ACLF score than with other scores, including the MELD, MELD-Na, Child-Pugh and CLIF-C OF scores, all measured in the CANONIC population and in an external validation cohort.[8] The CLIF-C ACLF score has also been shown to be a better predictor of mortality than the usual ICU prognostic scores (including the SOFA and APACHE II scores). Moreover, the kinetics of the CLIF-C ACLF score during ICU stay reliably predicted patient outcome.[22]

Investigators of the COSSH have developed the COSSH-ACLF score (Fig. 2A) based on a modified CLIF-C OF score (named HBV-SOFA scale; Fig. 2B), including specific risk factors for mortality observed in patients with HBV-ACLF. The new score evaluated in patients with HBV-related liver disease, showed a higher predictive value for 28-day and 90-day mortality compared to other scores, including CLIF-C ACLF, CLIF-C OF, MELD, MELD-Na and Child-Pugh scores.[4]

Investigators of the AARC developed and validated an AARC ACLF score.[5,21] Baseline total bilirubin, HE West-Haven grade, INR, serum lactate and creatinine were found to be independent predictors of 28-day mortality in patients with ACLF according to AARC criteria. The individual parameters were then scored from 1 to 3 considering their predictive accuracy for a low (<15%), medium (around 50%) and high (>80%) 28-day mortality rate (Fig. 2C). Therefore, the AARC ACLF score ranges from 5 to 15. Patients with ACLF were then categorised as grade 1 (5-7 points), grade 2 (8-10 points) or grade 3 (11-15 points) (Fig. 2D), with a 28-day mortality rate of 13%, 45% and 86%, respectively (Table 1). In patients with ACLF according to AARC criteria, the score was found to be superior to MELD and CLIF-SOFA score in predicting short-term mortality.[5] The score can be found and calculated on the APASL-AARC website (http://www.aclf.in).

AARC, Asian Pacific Association for the Study of the Liver ACLF Research Consortium; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure-Consortium; COSSH, Chinese Group on the Study of Severe Hepatitis B; HE, hepatic encephalopathy; ICU, intensive care unit; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; OF, organ failure; SOFA, sequential organ failure assessment.

cells (*i.e.*, monocytes and neutrophils) and other cells of the innate immune system.[23–26] PRR engagement drives intracellular signalling cascades, ultimately leading to the transcription and synthesis of inflammatory mediators. A classical paradigm of these mechanisms is the engagement of TLR4 by lipopolysaccharide, a PAMP derived from the cell wall of gram-negative bacteria, resulting in the downstream transcription and activation of multiple inflammatory mediators and cytokines.[24,26] High levels of circulating PAMPs, which are unrelated to ongoing bacterial infections but mostly related to translocation of bacterial products from the intestinal lumen may contribute to cases of ACLF without any identified precipitating disorder.[1,27] These translocated PAMPs are the final result of intestinal bacterial overgrowth, increased permeability of the intestinal mucosa, and impaired function of the intestinal innate immune system.[28] Of note, bacterial virulence factors can induce inflammation, not through their direct recognition by PRRs but through functional effects they induce in cells; for example, pore-forming toxins induce a $K^+$ efflux through the cell membrane that contributes to the activation of the NLRP3 (NLR family pyrin domain containing 3) inflammasome.[24]

Systemic inflammation can also occur in the absence of infection.[25] This sterile inflammation is due to the release of circulating DAMPs by dying or damaged host cells that bind to and activate specific PRRs (Table 2).[25] DAMPs consist of intracellular components from various compartments.[29] Several forms of liver injury are well-known causes of DAMP release. In alcoholic hepatitis, alcohol-induced hepatocyte apoptosis has been shown to be triggered by endoplasmic reticulum (ER) stress involving the ER-resident adaptor STING, a cytosolic PRR for cytosolic DNA.[30] Ischemia-reperfusion liver injury is characterised by the release of high mobility group box 1 (HMGB1) from hepatocytes exposed to hypoxia and oxidative stress.[31] Moreover, HMGB1 can induce cytokine production and promote chemotaxis by binding to several receptors (Table 2). Also, the submassive hepatic necrosis that characterises patients with HBV-associated ACLF may give rise to the release of DAMPs and high levels of inflammatory cytokines.[32]

## Outcomes of systemic inflammation

### *Tissue hypoperfusion*

PAMPs and inflammatory mediators can induce inducible nitric oxide (NO) synthase in splanchnic arteriolar walls. The resulting NO overproduction causes splanchnic vasodilation which decreases effective arterial blood volume, triggering homeostatic overactivation of the endogenous neurohumoral vasoconstrictor system (Fig. 3). Neurohumoral mediators then cause intense vasoconstriction, particularly in the renal circulation, resulting in kidney hypoperfusion, decreased glomerular filtration rate and acute kidney injury (AKI).[1]

### *Immune-mediated tissue damage*

Like sepsis in the general population, ACLF is commonly associated with blood leukocytosis, comprising activated immune cells that may migrate into tissues and cause immunopathology[1] (Fig. 3). There is some evidence for this hypothesis in the context of cirrhosis. For example, tumour necrosis factor-α and NF-κB-dependent signalling pathways may play a role in impaired left ventricular contractility,[33] in NO-mediated pulmonary dysfunction and macrophage accumulation in lung microvasculature,[34] and in hepatocyte apoptosis.[35] Like sepsis-induced AKI, ACLF-associated AKI may not only involve tissue hypoperfusion (see above) but also capillary leukocyte infiltration, vascular microthrombosis, and cell apoptosis.[36] Moreover, the direct inflammatory damage to tissues and cells leads to the release of a huge amount of circulating cellular products, which act as DAMPs on immune cell receptors. Therefore, a vicious cycle sustains and exacerbates inflammatory responses, providing the mechanistic link between systemic inflammation, cell injury and organ failure (Fig. 3).[23]

### *Mitochondrial dysfunction*

High-throughput blood metabolomics performed in a large cohort of patients with acutely decompensated cirrhosis (CANONIC cohort), revealed that, in ACLF, peripheral organs may have a marked decrease in mitochondrial fatty acid β-oxidation in peripheral organs, resulting in decreased oxidative

A

| Scores assessing the risk of death in patients with ACLF | |
|---|---|
| **Score name** | **Formula** |
| **CLIF-C ACLF score** | 10 x [0.33 x CLIF-C OF score + 0.04 x Age + 0.63 x Ln(white-cell count)-2] |
| **COSSH-ACLF score** | 0.741 × INR + 0.523 × HBV-SOFA score + 0.026 × age + 0.003 x total bilirubin |

B

| Organ system assessment with the HBV-SOFA scale developed by the COSSH | | | | |
|---|---|---|---|---|
| **Organ system** | **Variable** | **Scale** | | |
| **Kidney** | Creatinine (mg/dl) | <2 | 2-3.4 | ≥3.5 |
| **Brain** | HE grade (West Haven criteria) | 0 | I-II | III-IV |
| **Circulation** | MAP (mmHg) | ≥70 | <70 | Vasopressors |
| **Respiration** | $PaO_2/FiO_2$ | >300 | 201-300 | ≤200 |
| | $SpO_2/FiO_2$ | >357 | 215-357 | ≤214 |

C

| AARC scoring system | | | | | |
|---|---|---|---|---|---|
| **Points** | **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 |

D

| AARC-ACLF grade according to AARC scores | |
|---|---|
| **ACLF grade** | **AARC scores** |
| **1** | **5-7** |
| **2** | **8-10** |
| **3** | **11-15** |

**Fig. 2. Scores developed by different consortia to assess the prognosis of ACLF.** (A) Scores developed by European (CLIF-C ACLF score) and Chinese (COSSH-ACLF score) groups.[4,6] (B) The organ system assessment with the HBV-SOFA scale enables calculation of the HBV-SOFA score.[6] (C) Components of the AARC scoring system.[5] (D) Grading of ACLF according to AARC scores.[5] AARC, Asian Pacific Association for the Study of the Liver ACLF Research Consortium; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure-Consortium; COSSH, Chinese Group on the Study of Severe Hepatitis B; $FiO_2$, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalised ratio; MAP, mean arterial pressure; $PaO_2$, partial pressure of arterial oxygen; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; $SpO_2$, oxygen saturation as measured by pulse oximetry.

phosphorylation and ATP production.[37] These findings suggest that defective energy production may play a role in the development of OFs in ACLF (Fig. 3).

### Immunosuppression in ACLF

Investigators in Europe,[10] North America[3,38] and Asia[21,39,40] all agree that secondary infections are common complications of ACLF. Moreover, among patients with ACLF, 90-day mortality was higher in those who develop secondary infection than in those who remain free of this complication during the entire period of follow-up,[10,41] indicating the extreme severity of secondary infection in this context. More importantly, the high risk of secondary infections indicates that patients with ACLF are immunosuppressed. Among patients with ACLF who are free of infections at presentation, higher blood levels of immunosuppressive molecules, including interleukin-10 and the tryptophan metabolite quinolinate are predictors of secondary infections.[42]

There are findings suggesting that, in ACLF, some subsets of immune cells have defective antimicrobial functions that contribute to the high risk of secondary infection. Defective

**Table 2. Exogenous and endogenous inducers of inflammation and their receptors.**

| Inducers of inflammation | Receptor(s) |
|---|---|
| **Exogenous: pathogen-associated molecular patterns** | |
| Triacyl lipoprotein | Toll-like receptor (TLR)1 |
| Lipoprotein | TLR2 |
| Double-stranded RNA | TLR3 |
| Lipopolysaccharide | TLR4, caspases 4/5 |
| Flagellin | TLR5, NLRC4 (IPAF), NAIP5 and NAIP6 |
| Diacyl lipoprotein | TLR6 |
| Single-stranded RNA | TLR7, TLR8 |
| Unmethylated DNA with CpG motifs | TLR9 |
| Unknown | TLR10 |
| Profilin-like molecule | TLR11* |
| Profilin | TLR12* |
| 23S ribosomal RNA | TLR13* |
| γ-D-glutamyl-mesodiaminopimelic acid (iE-DAP) | Nucleotide-binding oligomerisation domain (NOD) 1 |
| Muramyl dipeptide (MDP) | NOD2, hexokinase |
| RNA (vita-PAMP) | NLRP3 |
| Short double-stranded RNA, 5'triphosphate double-stranded RNA | Retinoic acid-inducible gene (RIG)-I |
| Long double-stranded RNA | Melanoma differentiation-associated protein 5 (MDA5) |
| β-Glucan | Dectin-1, dectin-2 (also known as C-type lectin domain containing 6A, CLEC6A) |
| Double-stranded DNA | Absent in melanoma (AIM)-2, interferon gamma-inducible protein 16 (IFI16), Z-DNA binding protein 1 (ZBP1), cyclic GMP-AMP synthase (cGAS) |
| Double-stranded DNA, single-stranded DNA | High mobility group box (HMGB) proteins, LRRFIP1, Leucine rich repeat (in FLII) interacting protein 1 (LRRFIP1) |
| Cyclic diadenosine monophosphate (c-diAMP; vita-PAMP**) | Stimulator of interferon genes protein (STING) |
| Endogenous inducers: damage-associated molecular patterns (DAMPs) | |
| Released by dying cells | |
| Double-stranded DNA | TLR9, AIM2 |
| High mobility group box 1 (HMBG1) | TLR2, TLR4, TLR9, advanced glycation end products receptor (AGER; alias, RAGE), CD24 |
| Histones | TLR2, TLR4 |
| Sin3A-associated protein (SAP) 130 | C-type lectin domain family 4 member E (CLEC4E; alias MINCLE) |
| Mitochondrial DNA | TLR9, NLRP3 |
| Mitochondrial N-formyl peptides | Formyl peptide receptor (FRP)-1 |
| Cytochrome c | Unknown |
| ATP | Purinoceptors |
| N-myc and STAT interactor (NMI) | TLR4 |
| Interferon-induced protein 35 (IFP35) | TLR4 |
| S100 calcium-binding proteins | |
| S100A8, S100A9 | TLR4 |
| S100A12 | AGER |
| $K^+$ ions | $K^+$ channels |
| Cold-inducible RNA binding protein (CIRBP) | TLR4-MD2 complex |
| Peroxiredoxins | TLR2, TLR4 |
| Heat shock proteins (HSP60, HSP70, HSP90, GP96) | TLR2, TLR4, CD14, CD40, CD24 |
| Calreticulin | LDL Receptor Related Protein 1 (LRP1, alias CD91), C1Q |
| Defensins | CCR6, TLR4 |
| Galectins | CD2 |
| Interleukin (IL)-1α | IL-1R1 (specific receptor), IL-1R3 (co-receptor) |
| IL-33 | IL-1R4 (specific receptor), IL-1R3 (co-receptor) |
| Extracellular DAMPs | |
| Short-fragment hyaluronan | CD44-TLR4-Lymphocyte antigen 96 (MD2) complex, TLR2 |
| Biglycan | TLR2, TLR4 |
| Versican | TLR4 |
| Heparan sulfate | TLR4 |
| Extracellular matrix fragments from collagen, elastin, laminin | CD14, TLR4, Serum hyaluronan-associated protein (SHAP) |

NOTE: TLRs form homodimers except TLR2 that heterodimerises with TLR1 or TLR6. NLRC4, NLR family, CARD domain containing 4; IPAF, ice protease-activating factor; NAIP, nucleotide-binding oligomerisation domain (NOD)-like receptor (NLR) family, apoptosis inhibitory protein; NLRP3, NLR family, pyrin domain containing 3.

* Expressed in mice but not humans.

** A vita-PAMP is a PAMP which indicates the presence of a living microbe.

responses to PAMPs have been shown in macrophages derived from circulating monocytes obtained from patients with ACLF. Moreover, patients with ACLF have a higher frequency of $CD14^+$ monocytes expressing the receptor tyrosine kinase MerTK and $CD14^+CD15^-HLA\text{-}DR^-$myeloid-derived suppressor cells,[43,44] with both monocyte subsets suppressing innate responses to bacterial PAMPs. Another study found decreased frequencies of other myeloid mononuclear cells (conventional and plasmacytoid dendritic cells) in patients with severe alcoholic hepatitis, including patients who had ACLF.[45] Finally, studies have shown that neutrophils in patients with decompensated cirrhosis have a marked defect in both the production of antimicrobial superoxide anion and bactericidal activity.[46]

Collectively, these "humoral" and immune-cell alterations may favour the development of serious infections that are frequent complications of ACLF. Of note, although the lymphoid

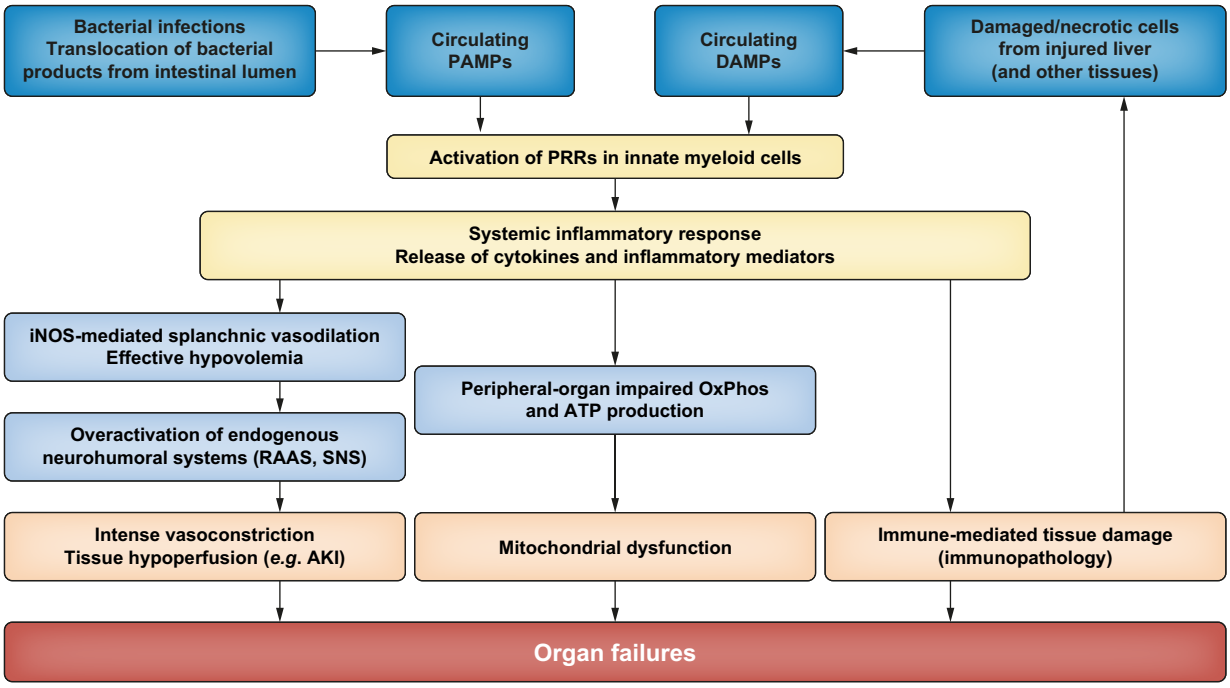


**Fig. 3. Pathophysiology of ACLF.** Schematic of induction of systemic inflammation and its role in the development of organ failures. ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; PRRs, pattern-recognition receptors; iNOS, inducible nitric oxide synthase; OxPhos, oxidative phosphorylation; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

lineage plays a major role in host resistance to infection, little is known about lymphocyte frequency and function in acutely decompensated cirrhosis. Future studies should investigate lymphocytes in patients with acutely decompensated cirrhosis with and without ACLF.

## Management of ACLF

Principles of treatment of ACLF are provided in Fig. 4. Several recommendations are based on results of studies conducted in critically ill patients without cirrhosis.[1]

### Admission of patients with ACLF to the intensive care unit

The admission of patients with cirrhosis to the intensive care unit (ICU) should no longer be denied solely because of the existence of the underlying chronic liver disease. The proportion of patients with ACLF admitted to the ICU is therefore increasing and several studies have shown that the ICU prognosis of cirrhotic patients has improved in recent years (period effect independently associated with mortality).[47,48] Nevertheless, ICU mortality rates remain high in some patient groups and some factors can be used to guide the admission of these patients to ICUs. As for patients without cirrhosis, the prognosis of critically ill patients with cirrhosis admitted to the ICU largely relies on the presence of OF(s), graded using different scores.[22,49] CLIF-sequential organ failure assessment and CLIF-C ACLF scores perform better than general ICU scores, such as Acute Physiology And Chronic Health Evaluation (APACHE) II or Simplified Acute Physiology Score (SAPS) II scores, and liver-specific scores, such as MELD or Child-Pugh.[22,50] In addition, the reason for ICU admission should be considered; the prognosis of gastrointestinal haemorrhage being better than the prognosis of septic shock. Finally, some evidence suggests a better prognosis in case of early admission to the ICU.

### Treating acute precipitants

*Antimicrobial therapy*

In a recent study, about 37% of patients with ACLF presented with a bacterial infection at diagnosis. Furthermore, 46% of the remaining patients with ACLF developed bacterial infections within the next 4 weeks.[10] Multidrug-resistant (MDR) pathogens are involved in one-third of cases with differences in prevalence according to region.[10,51] A systematic search for infection, including microbiological and cytological examination of ascitic fluid, should therefore be systematically performed at admission. An empirical antibiotic therapy tailored to the suspected site of infection and the local ecology should be rapidly initiated.[1] Broad-spectrum molecules should be preferred in case of severe infection or in the presence of risk factors for MDR pathogens.

*Corticosteroids for alcoholic hepatitis*

Corticosteroids remain the first-line treatment for severe alcoholic hepatitis. The response to corticosteroids can be assessed by calculating the Lille score after 7 days of treatment.[1,52,53] The prognosis of patients who do not respond is poor. The probability of response to corticosteroids depends on the presence or absence of ACLF at presentation. Indeed, the probability of response is lower in patients with ACLF compared to those without ACLF (38% and 77%, respectively).[54] Moreover, the probability of response to corticosteroids decreases with ACLF

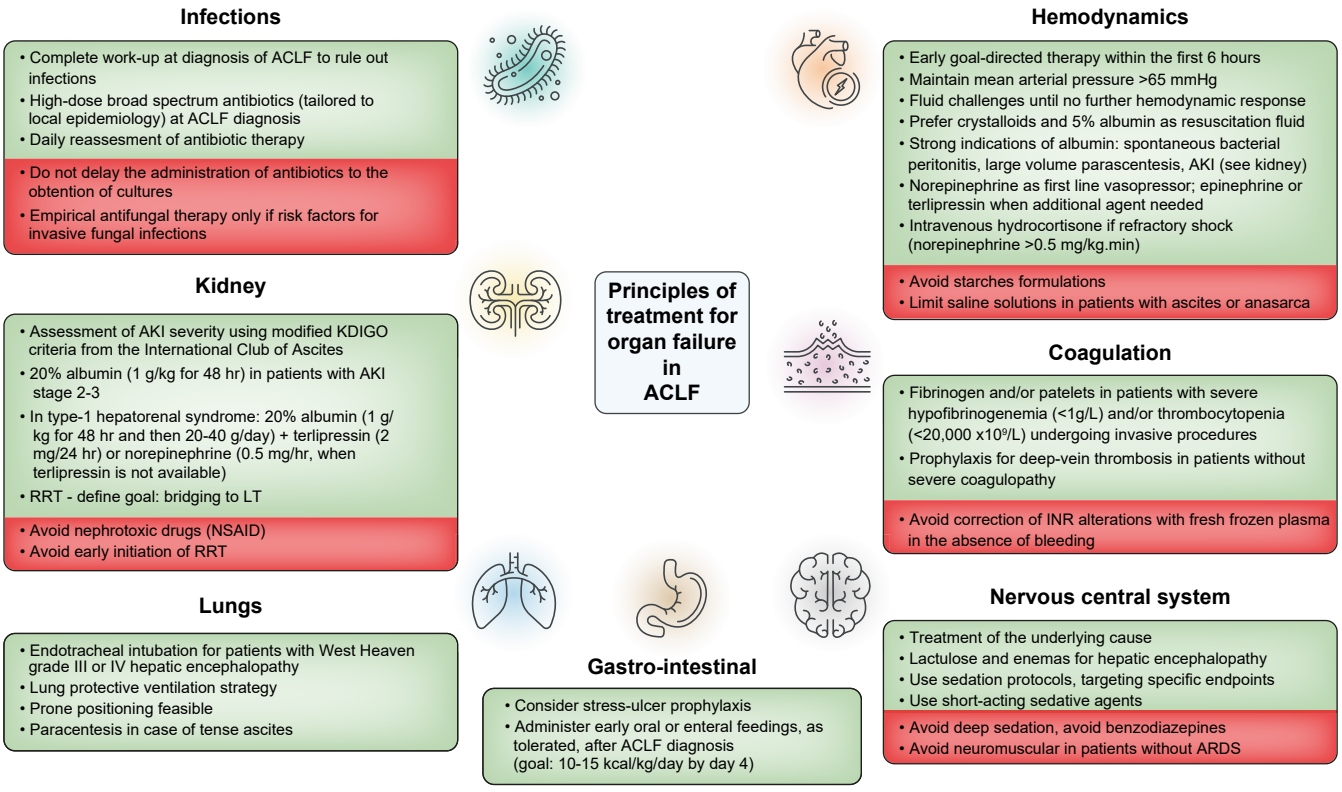


**Fig. 4. Principles of treatment of organ failure in ACLF.** What should be done is shown in green boxes. What should be avoided is shown in red boxes. ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes; LT, liver transplantation; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; RRT, renal replacement therapy.

grade, being 52%, 42% and 8% for grade 1, grade 2 and grade 3, respectively.[54] Nevertheless, among responders, a beneficial effect of corticosteroids on patient survival has been shown.[54,55] Given the risk of bacterial infection, the risk to benefit ratio should be carefully evaluated before initiating corticosteroids in patients with ACLF and severe alcoholic hepatitis.

*Acute variceal haemorrhage*

The use of transjugular intrahepatic portosystemic shunting is summarised in Box 2.[56]

## Organ support

*Intravenous fluids*

Fluid therapy should use crystalloids, while balanced salt solutions may limit the risk of hyperchloremic acidosis and subsequent adverse kidney events. Nevertheless, beneficial effects of albumin resuscitation have been demonstrated in patients with cirrhosis and may be related to more than mere volume expansion. Indeed, besides the overall decrease of albumin, the function of albumin is also impaired with alterations in its chemical structure, resulting in reduced binding capacity to bacterial products, reactive oxygen species, and other mediators involved in ACLF.[57] Some studies suggested that albumin may modulate systemic oxidative stress and inflammation[58,59] or restore immune defense.[60]

The intravenous use of human albumin is discussed in Box 2.[52,61,62]

*Renal replacement therapy*

The use of renal replacement therapy is discussed in Box 2.[63–65]

*Extracorporeal liver support*

To date, the best-known devices are based on the principle of albumin dialysis. Two multicentre randomised European trials in patients with acutely decompensated cirrhosis compared these systems with standard medical treatment. These studies showed an improvement of biological cholestasis and hepatic encephalopathy in patients treated with albumin dialysis but did not demonstrate any benefit on 28- and 90-day survival.[66,67] More recently, the use of an artificial liver support system was associated with improved short-term survival (14- and 28-day) in patients with ACLF and multiple OFs in a retrospective study[68] and a meta-analysis.[69] Therefore, these devices may be interesting as a bridge to liver transplantation or recovery. Finally, evidence points to the possible use of plasma exchange to remove endotoxins and inflammatory mediators and replace albumin. A randomised clinical trial (APACHE-trial, NCT03702920) is currently ongoing. Regenerative medicine using stem cell technology such as heterologous human adult liver-derived progenitor cells (HepaStem) is another strategy currently being developed, although safety issues remain to be solved.[70]

*Liver transplantation*

Liver transplantation for critically ill patients with cirrhosis and extrahepatic OFs is becoming more and more

**Box 2. Use of albumin, use of TIPS for acute variceal haemorrhage, use of RRT, and prioritisation for LT.**

**Albumin**

Current guidelines recommend the infusion of human albumin in 3 clinical situations:[52,61]

- After high-volume paracentesis (more than 4-5 litres, 8 g of albumin per litre of ascites removed);
- In patients with AKI stage 2-3 of the modified KDIGO classification specifically redefined by the International Club of Ascites (1 g/kg/day for 2 days), and in patients with hepatorenal syndrome (1 g/kg on day 1 and then 20-40 g/day), associated with vasoconstrictors (terlipressin 2 mg/24 h as first choice);
- In patients with SBP (at a dose of 1.5 g/kg at diagnosis and 1 g/kg on day 3), but not in those with other infections.

In patients with cirrhosis and infections unrelated to SBP, albumin treatment does not improve survival but is associated with lower systemic inflammation, a higher rate of ACLF resolution and a lower rate of nosocomial infections.[62]

**TIPS for acute variceal haemorrhage**

In a large multicentre international study in patients with acute variceal haemorrhage, Trebicka *et al*. recently identified ACLF as an independent risk factor for rebleeding and mortality at 42 days.[56] This study also suggested that pre-emptive TIPS may improve the survival of patients with acute variceal haemorrhage and ACLF. Nevertheless, further studies are needed to validate the role of pre-emptive TIPS on outcomes in patients with ACLF before encouraging their transfer to hospitals with access to TIPS.

**RRT**

In the general population, the timing of initiation of RRT is controversial and delaying RRT initiation, with close patient monitoring might lead to a reduced use of RRT, thereby saving healthcare resources.[63] These questions have not been specifically addressed in patients with cirrhosis. However, among patients with type 1 HRS who did not respond to vasoconstrictor therapy, no difference in 30- and 180-day survival was found between those who received RRT and those who did not receive RRT.[64] Therefore, RRT could reasonably be seen as a bridge to LT.

In a recent pilot randomised-controlled trial, continuous RRT during LT was feasible and safe with no difference in complications.[65] Continuous RRT may therefore be considered for intraoperative management of patients with ACLF because of the high risk of metabolic disorders.

**Prioritisation of patients with ACLF for LT**

It remains problematic. Studies have shown that the MELD score was not accurate enough to predict survival in patients with multiorgan failure. Sundaram *et al*. analysed the waitlist outcomes of 100,594 patients from the United Network for Organ Sharing database and showed that ACLF classification may help in identifying patients at high risk of short-term death.[71] In their analysis of waitlist outcome, mortality of patients with ACLF grade 3 approached 44% even at an MELD score <25 and was significantly greater than that seen among patients with an MELD score >35 but without ACLF.[71] Those data were confirmed by Hernaez *et al*. who showed, in another US cohort of 71,894 patients with decompensated cirrhosis, that patients with ACLF grade 1, 2 and 3 were respectively 1.52, 1.46 and 1.50 more likely to die within the next 90 days than would be expected based on MELD-Na alone.[75] The importance of early LT and consideration of transplant priority was recently underlined for patients with ACLF grade 3 that had a greater risk of 14-day mortality than those listed as status 1a (highest priority on the waiting list), independently of MELD-Na score.[76]

On the other hand, an appropriate assessment of a patient's global condition should be performed in order to avoid futile LT in too-sick-to-transplant patients with grade 3 ACLF.[77] Some studies identified prognostic markers predicting post-LT survival in patients transplanted with concomitant grade 3 ACLF that may help clinical decision-making.[71,78] Factors associated with poor survival after LT included mechanical ventilation at the time of transplantation, pre-LT lactate level >4 mmol/L, normal pre-LT leukocyte count, older age of recipient, use of marginal-organs.[71,78]

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; CLIF-C, Chronic Liver Failure-Consortium; HRS, hepatorenal syndrome; KDIGO, Kidney Disease Improving Global Outcomes; LT, liver transplantation; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

frequent.[1,71] While post-transplant survival rates of patients with grade 1 and 2 ACLF seem similar to those of patients without ACLF, 1-year survival of patients with grade 3 ACLF greatly differs between studies and ranges from 44 to 83%.[72,73] Given the poor short-term prognosis of patients with ACLF without liver transplantation, these data strongly support the use of liver transplantation as a therapeutic strategy for patients with ACLF.[74] However, as discussed in Box 2, prioritisation of these patients for liver transplantation remains problematic.[71,75–78]

## Conclusions

ACLF is a major medical problem worldwide and its occurrence is a challenging clinical event for hepatologists and intensivists, due to its acute presentation, rapid clinical course and associated high short-term mortality. Geographical differences exist regarding the definition of ACLF and its diagnostic criteria, resulting in varying clinical phenotypes. The therapeutic management of patients with ACLF is currently based on the treatment and support of different OFs. A better understanding of ACLF pathophysiology may help in the development of mechanistic treatments, either curative or preventive.

## Abbreviations

AARC, APASL ACLF Research Consortium; ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; APASL, Asian Pacific Association for the Study of the Liver; CLIF, Chronic Liver Failure-Consortium; COSSH, Chinese Group on the Study of Severe Hepatitis; DAMPs, damage-associated molecular patterns; EASL, European Association for the Study of the Liver - Chronic Liver; ER, endoplasmic reticulum; HMGB1, high mobility group box 1; ICU, intensive care unit; INR, international normalised ratio; MELD, model for end-stage liver disease; NACSELD, North American Consortium for the Study of End-stage Liver Disease; NO, nitric oxide; OF, organ failure; PAMPs, pathogen-associated molecular patterns; PRR, pattern-recognition receptors; TLR, Toll-like receptor; UNOS, United Network for Organ Sharing.

## Financial support
The authors report no specific grants for this research.

## Conflicts of interest
E. Weiss reports personal fees form Baxter, MSD France, Biomerieux and Akcea therapeutics, and travel reimbursements from MSD France, outside the present work. The other authors report no conflict of interest related to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions
Drafting of the manuscript (GZ, EW); critical revision of the manuscript for important intellectual content (RM).

## Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2020.100176.

## References
*Author names in bold designate shared co-first authorship.*

[1] Arroyo V, Moreau R, Jalan R. Acute-on-chronic liver failure. N Engl J Med 2020;382:2137–2145.
[2] Moreau R, Jalan R, Ginès P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–1437.
[3] Bajaj JS, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014;60:250–256.
[4] **Wu T**, **Li J**, **Shao L**, Xin J, Jiang L, Zhou Q, et al., on behalf of the Chinese Group on the Study of Severe Hepatitis B (COSSH). Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut 2018;67:2181–2191.
[5] Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL): an update. Hepatol Int 2019;13:353–390.
[6] Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL). Hepatol Int 2009;3:269–282.
[7] Sarin SK, Kedarisetty CK, Abbas Z, Amarapurkar D, Bihari C, Chan AC, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. Hepatol Int 2014;8:453–471.
[8] **Jalan R**, **Saliba F**, **Pavesi M**, Amoros A, Moreau R, Ginès P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol 2014;61:1038–1047.
[9] O'Leary JG, Reddy KR, Garcia-Tsao G, Biggins SW, Wong F, Fallon MB, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology 2018;67:2367–2374.
[10] Fernández J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018;67:1870–1880.
[11] Mahmud N, Kaplan DE, Taddei TH, Goldberg DS. Incidence and mortality of acute-on-chronic liver failure using two definitions in patients with compensated cirrhosis. Hepatology 2019;69:2150–2163.
[12] Piano S, Tonon M, Vettore E, Stanco M, Pilutti C, Romano A, et al. Incidence, predictors and outcomes of acute-on-chronic liver failure in outpatients with cirrhosis. J Hepatol 2017;67:1177–1184.
[13] Sundaram V, Jalan R, Ahn JC, Charlton MR, Goldberg DS, Karvellas CJ, et al. Class III obesity is a risk factor for the development of acute-on-chronic liver failure in patients with decompensated cirrhosis. J Hepatol 2018;69:617–625.
[14] **Gustot T**, **Fernandez J**, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243–252.
[15] **Li H**, **Chen LY**, **Zhang NN**, Li ST, Zeng B, Pavesi M, et al. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. Sci Rep 2016;6:25487.
[16] **Kim TY**, **Song DS**, Kim HY, Sinn DH, Yoon EL, Kim CW, et al. Characteristics and discrepancies in acute-on-chronic liver failure: need for a unified definition. PLoS One 2016;11:e0146745.
[17] **Hernaez R**, **Kramer JR**, Liu Y, Tansel A, Natarajan Y, Hussain KB, et al. Prevalence and short-term mortality of acute-on-chronic liver failure: a national cohort study from the USA. J Hepatol 2019;70:639–647.
[18] Amarapurkar D, Dharod MV, Chandnani M, Baijal R, Kumar P, Jain M, et al. Acute-on-chronic liver failure: a prospective study to determine the clinical profile, outcome, and factors predicting mortality. Indian J Gastroenterol 2015;34:216–224.
[19] Shi Y, Yang Y, Hu Y, Wu W, Yang Q, Zheng M, et al. Acute-on-chronic liver failure precipitated by hepatic injury is distinct from that precipitated by extrahepatic insults. Hepatology 2015;62:232–242.
[20] Abbas Z, Shazi L. Pattern and profile of chronic liver disease in acute on chronic liver failure. Hepatol Int 2015;9:366–372.
[21] Chen T, Yang Z, Choudhury AK, Al Mahtab M, Li J, Chen Y, et al. Complications constitute a major risk factor for mortality in hepatitis B virus-related acute-on-chronic liver failure patients: a multi-national study from the Asia-Pacific region. Hepatol Int 2019;13:695–705.
[22] Karvellas CJ, Garcia-Lopez E, Fernandez J, Saliba F, Sy E, Jalan R, et al. Dynamic prognostication in critically ill cirrhotic patients with multi-organ failure in ICUs in Europe and North America: a multicenter analysis. Crit Care Med 2018;46:1783–1791.
[23] **Clària J**, **Stauber RE**, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis. Characterization and role in acute-on-chronic liver failure. Hepatology 2016;64:1249–1264.
[24] Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nat Immunol 2015;16:343–353.
[25] Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol 2007;81:1–5.
[26] Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015;63:1272–1284.
[27] Moreau R, Elkrief L, Bureau C, Perarnau JM, Thevenot T, Saliba F, et al. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. Gastroenterology 2018;155:1816–1827.e9.
[28] Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol 2014;60:197–209.
[29] Medzhitov R. Origin and physiological roles of inflammation. Nature 2008;454:428–435.
[30] Petrasek J, Iracheta-Vellve A, Csak T, Satishchandran A, Kodys K, Kurt-Jones EA, et al. STING-IRF3 pathway links endoplasmic reticulum stress with hepatocyte apoptosis in early alcoholic liver disease. Proc Natl Acad Sci USA 2013;110:16544–16549.
[31] **Evankovich J**, **Cho SW**, Zhang R, Cardinal J, Dhupar R, Zhang L, et al. High mobility group box 1 release from hepatocytes during ischemia and reperfusion injury is mediated by decreased histone deacetylase activity. J Biol Chem 2010;285:39888–39897.
[32] **Li H**, **Xia Q**, **Zeng B**, Li ST, Liu H, Li Q, et al. Submassive hepatic necrosis distinguishes HBV-associated acute on chronic liver failure from cirrhotic patients with acute decompensation. J Hepatol 2015;63:50–59.
[33] Bortoluzzi A, Ceolotto G, Gola E, Sticca A, Bova S, Morando F, et al. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. Hepatology 2013;57:266–276.
[34] Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome - a liver-induced lung vascular disorder. N Engl J Med 2008;358:2378–2387.
[35] Gustot T, Durand F, Lebrec D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. Hepatology 2009;50:2022–2033.
[36] Alobaidi R, Basu RK, Goldstein SL, Bagshaw SM. Sepsis-associated acute kidney injury. Semin Nephrol 2015;35:2–11.
[37] **Moreau R**, **Clària J**, **Aguilar F**, **Fenaille F**, Lozano JJ, Junot C, et al. Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF. J Hepatol 2020;72:688–701.
[38] Bajaj JS, Reddy RK, Tandon P, Wong F, Kamath PS, Biggins SW, et al. Prediction of fungal infection development and their impact on survival using the NACSELD cohort. Am J Gastroenterol 2018;113:556–563.
[39] Li C, Su HB, Liu XY, Hu JH. Clinical characteristics and 28-d outcomes of bacterial infections in patients with hepatitis B virus-related acute-on-chronic liver failure. World J Clin Cases 2020;8:1042–1055.
[40] Su H, Tong J, Liu X, Li C, Chen J, Xu X, et al. Characteristics and outcome of nosocomial bloodstream infection in patients with acute-on-chronic liver failure. Eur J Gastroenterol Hepatol 2020. In press.
[41] Cai J, Zhang M, Han T, Jiang HQ. Characteristics of infection and its impact on short-term outcome in patients with acute-on-chronic liver failure. Medicine (Baltimore) 2017;96:e8057.

[42] **Clària J**, **Moreau R**, Fenaille F, Amoros A, Junot C, Gronbaek H, et al. Orchestration of tryptophan-kynurenine pathway, acute decompensation, and acute-on-chronic liver failure in cirrhosis. Hepatology 2019;69:1686–1701.

[43] Bernsmeier C, Pop OT, Singanayagam A, Triantafyllou E, Patel VC, Weston CJ, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. Gastroenterology 2015;148:603–615.e14.

[44] Bernsmeier C, Triantafyllou E, Brenig R, Lebosse FJ, Singanayagam A, Patel VC, et al. $CD14^+$ $CD15^-$ $HLA\text{-}DR^-$ myeloid-derived suppressor cells impair antimicrobial responses in patients with acute-on-chronic liver failure. Gut 2018;67:1155–1167.

[45] **Weichselbaum L**, **Azouz A**, **Smolen KK**, Das J, Splittgerber M, Lepida A, et al. Epigenetic basis for monocyte dysfunction in patients with severe alcoholic hepatitis. J Hepatol 2020;73:303–314.

[46] Rolas L, Boussif A, Weiss E, Lettéron P, Haddad O, El-Benna J, et al. NADPH oxidase depletion in neutrophils from patients with cirrhosis and restoration via toll-like receptor 7/8 activation. Gut 2018;67:1505–1516.

[47] McPhail MJW, Parrott F, Wendon JA, Harrison DA, Rowan KA, Bernal W. Incidence and outcomes for patients with cirrhosis admitted to the United Kingdom critical care units. Crit Care Med 2018;46:705–712.

[48] Galbois A, Aegerter P, Martel-Samb P, Housset C, Thabut D, Offenstadt G, et al. Improved prognosis of septic shock in patients with cirrhosis: a multicenter study. Crit Care Med 2014;42:1666–1675.

[49] Karvellas CJ, Bagshaw SM. Advances in management and prognostication in critically ill cirrhotic patients. Curr Opin Crit Care 2014;20:210–217.

[50] Weil D, Levesque E, McPhail M, Cavallazzi R, Theocharidou E, Cholongitas E, et al. Prognosis of cirrhotic patients admitted to intensive care unit: a meta-analysis. Ann Intensive Care 2017;7:33.

[51] Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology 2019;156:1368–1380.e10.

[52] European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–460.

[53] Gustot T, Jalan R. Acute-on-chronic liver failure in patients with alcohol-related liver disease. J Hepatol 2019;70:319–327.

[54] Sersté T, Cornillie A, Njimi H, Pavesi M, Arroyo V, Putignano A, et al. The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis. J Hepatol 2018;69:318–324.

[55] Forrest EH, Atkinson SR, Richardson P, Masson S, Ryder S, Thursz MR, et al. Prevalent acute-on-chronic liver failure and response to corticosteroids in alcoholic hepatitis. J Hepatol 2018;69:1200–1201.

[56] **Trebicka J**, **Gu W**, Ibáñez-Samaniego L, Hernandez-Gea V, Pitarch C, Garcia E, et al. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. J Hepatol 2020;73:1082–1091.

[57] Bernardi M, Angeli P, Claria J, Moreau R, Gines P, Jalan R, et al. Albumin in decompensated cirrhosis: new concepts and perspectives. Gut 2020;69:1127–1138.

[58] **Fernández J**, **Clària J**, Amorós A, Aguilar F, Castro M, Casulleras M, et al. Effects of albumin treatment on systemic and portal hemodynamics and systemic inflammation in patients with decompensated cirrhosis. Gastroenterology 2019;157:149–162.

[59] Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014;61:396–407.

[60] O'Brien AJ, Fullerton JN, Massey KA, Auld G, Sewell G, James A, et al. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. Nat Med 2014;20:518–523.

[61] Paugam-Burtz C, Levesque E, Louvet A, Thabut D, Amathieu R, Bureau C, et al. Management of liver failure in general intensive care unit. Anaesth Crit Care Pain Med 2020;39:143–161.

[62] Fernández J, Angeli P, Trebicka J, Merli M, Gustot T, Alessandria C, et al. Efficacy of albumin treatment for patients with cirrhosis and infections unrelated to spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol 2020;18:963–973.e14.

[63] **Gaudry S**, **Hajage D**, Benichou N, Chaibi K, Barbar S, Zarbok A, et al. Delayed *vs.* early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet 2020;395:1506–1515.

[64] Zhang Z, Maddukuri G, Jaipaul N, Cai CX. Role of renal replacement therapy in patients with type 1 hepatorenal syndrome receiving combination treatment of vasoconstrictor plus albumin. J Crit Care 2015;30:969–974.

[65] Karvellas CJ, Taylor S, Bigam D, Kneteman NM, Shapiro AMJ, Romanovsky A, et al. Intraoperative continuous renal replacement therapy during liver transplantation: a pilot randomized-controlled trial (INCEPTION). Can J Anaesth 2019;66:1151–1161.

[66] Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology 2013;57:1153–1162.

[67] Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz C, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology 2012;142:782–789.e3.

[68] **Gerth HU**, **Pohlen M**, Thölking G, Pavenstadt H, Brand M, Husing-Kabar A, et al. Molecular adsorbent recirculating system can reduce short-term mortality among patients with acute-on-chronic liver failure - a retrospective analysis. Crit Care Med 2017;45:1616–1624.

[69] **Shen Y**, **Wang XL**, Wang B, Shao JG, Liu YM, Qin Y, et al. Survival benefits with artificial liver support system for acute-on-chronic liver failure: a time series-based meta-analysis. Medicine (Baltimore) 2016;95:e2506.

[70] **Smets F**, **Dobbelaere D**, McKiernan P, Dionisi-Vici C, Broué P, Jacquemin E, et al. Phase I/II trial of liver-derived mesenchymal stem cells in pediatric liver-based metabolic disorders: a prospective, open label, multicenter, partially randomized, safety study of one cycle of heterologous human adult liver-derived progenitor cells (HepaStem) in urea cycle disorders and Crigler-Najjar syndrome patients. Transplantation 2019;103:1903–1915.

[71] Sundaram V, Jalan R, Wu T, Volk ML, Asrani SK, Klein AS, et al. Factors associated with survival of patients with severe acute-on-chronic liver failure before and after liver transplantation. Gastroenterology 2019;156:1381–1391.e3.

[72] **Levesque E**, **Winter A**, Noorah Z, Daurès JP, Landais P, Feray C, et al. Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation. Liver Int 2017;37:684–693.

[73] Artru F, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. J Hepatol 2017;67:708–715.

[74] Arroyo V. Acute-on-chronic liver failure in cirrhosis requires expedited decisions for liver transplantation. Gastroenterology 2019;156:1248–1249.

[75] Hernaez R, Liu Y, Kramer JR, Rana A, El-Serag HB, Kanwal F. Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure. J Hepatol 2020. In press.

[76] Sundaram V, Shah P, Wong RJ, Karvellas CJ, Fortune BE, Mahmud N, et al. Patients with acute on chronic liver failure grade 3 have greater 14-day waitlist mortality than status-1a patients. Hepatology 2019;70:334–345.

[77] Weiss E, Saner F, Asrani SK, Biancofiore G, Blasi A, Lerut J, et al. When is a critically ill cirrhotic patient too sick to transplant? Development of consensus criteria by a multidisciplinary panel of 35 international experts. Transplantation 2020. In press.

[78] **Artzner T**, **Michard B**, Weiss E, Barbier L, Noorah Z, Merle JC, et al. Liver transplantation for critically ill cirrhotic patients: stratifying utility based on pretransplant factors. Am J Transplant 2020;20:2437–2448.