Grand Rounds

JOURNAL OF HEPATOLOGY

Acute-on-chronic liver failure *vs.* traditional acute decompensation of cirrhosis

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Keywords: Cirrhosis; Organ failure; Prognosis; Liver transplantation.

Received 10 January 2018; received in revised form 22 August 2018; accepted 30 August 2018

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Clinical vignette

A 34-year-old woman with a history of chronic HCV-related cirrhosis was admitted to the hospital emergency department for an acute decompensation characterised by jaundice and ascites. A diagnosis of community-acquired spontaneous bacterial peritonitis complicated by bacteraemia with *Escherichia coli* was made. Despite prompt, adequate antibiotic treatment (ceftriaxone for 7 days), albumin infusion and adequate response (decrease of at least 25% of ascitic neutrophils at 48 h after the start of antibiotic), physicians observed a severe clinical deterioration with the development of neurological and respiratory failure. The patient was referred to the intensive care unit of University Hospital. At admission, the patient was mechanically ventilated with severe respiratory parameters (low tidal volume, positive end expiratory pressure [PEEP] of 15 cm H_2O and fractional inspired oxygen [FiO_2] 50%, resulting in arterial oxygen partial pressure [PaO_2] of 61 mmHg, PaO_2/FiO_2 ratio of 122), stage IV hepatic encephalopathy, type I hepatorenal syndrome that responded to terlipressin 4 mg per day (creatinine 1.1 mg/dl), international normalized ratio (INR) 3.58, and total bilirubin 22 mg/dl. Thoracic computed tomography showed slight bilateral pleural effusion and left basal condensation. A systematic microbiological screening including bronchoalveolar lavage, blood, urinary and ascitic cultures did not demonstrate any overt infection. After three days of intensive management, the clinical situation did not improve significantly (mechanical ventilation with PEEP 12 cmH_2O, FiO_2 50%, PaO_2 65 mmHg and a PaO_2/FiO_2 ratio of 130, stage IV hepatic encephalopathy, serum ammonia level of 376 μg/dl, INR 2.98, total bilirubin 30 mg/dl, creatinine 0.9 mg/dl under terlipressin 4 mg per day). Thus, orthotopic liver transplantation was considered the only long-term life-saving option for this patient. However, this candidate seemed to be too sick to receive an organ. This case prompts many clinical questions, including:

I. Are there specificities in this acute decompensation of cirrhosis? Is the concept of ACLF relevant for this case?
II. Which precipitating events and pathogenic mechanisms are responsible for ACLF?
III. Do we have tools to predict outcomes and clinical courses for ACLF?
IV. What are the current management strategies, supported by evidence, for patients with ACLF?
V. Is salvage liver transplantation a reasonable therapeutic option for ACLF? What is the ideal timing for liver transplantation?
VI. Are there therapeutic (including experimental) strategies to improve survival or to bridge the patient to liver transplantation?

Are there specificities in this acute decompensation of cirrhosis? Is the concept of ACLF relevant for this case?

Patients with decompensated cirrhosis exhibit clinical heterogeneity, which is associated with different prognoses. These patients must be stratified to define appropriate management. Some authors have suggested stratifying decompensation into three stages based on increasing two-year risk of death: patients who experience variceal bleeding alone (without other decompensating events) (20%), those with any first non-bleeding decompensating event (24%), or any second decompensating event (50–78%).[1] Moreover, beyond these stages, a more advanced stage has been suggested for patients with very bad short-term outcomes, including those with bacterial infections.[2] The term "acute-on-chronic liver failure (ACLF)" was first introduced to characterise this poorly defined situation.[3] The first definition was established by a consensus of the Asian Pacific Association for the Study of the Liver (APASL) who defined ACLF as "an acute hepatic insult manifesting as jaundice (total bilirubin ≥5 mg/dl) and coagulopathy (INR ≥1.5), complicated within four weeks by ascites and/or encephalopathy in a patient with chronic liver disease".[4] Thirty-day

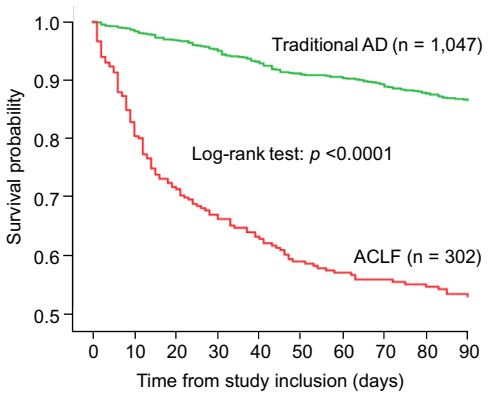

Fig. 1. Cumulative transplant-free survival curves of patients from the CANONIC study. Kaplan-Meier 90-day transplant-free cumulative survival curves of patients from the CANONIC study[7] with or without ACLF (traditional AD). Kaplan-Meier Curves were compared using the log-rank test. ACLF, acute-on-chronic liver failure; AD, acute decompensation.

mortality is estimated to be between 25% and 37% when APASL criteria are fulfilled, but the presence and severity of organ failures (OFs) defined by the sequential organ failure assessment (SOFA) score discriminates patients with different prognoses (58% with OF and 8% without).[5,6] A large, multicentre prospective, observational study (CANONIC study) in 1,343 patients with cirrhosis who were hospitalised for an acute decompensation (AD) of cirrhosis (large ascites, hepatic encephalopathy [HE], gastrointestinal haemorrhage and/or bacterial infection), provided the first evidence-based diagnostic criteria that permitted physicians to distinguish between ACLF and 'mere' AD (*i.e.*, traditional AD) (Table 1).[7] In this last study, 28-day and 90-day mortality rates were higher among patients who had ACLF at enrolment than among those who had traditional AD (34% and 51% *vs.* 5% and 14%, respectively). Large observational studies have been performed using prespecified ACLF criteria in patients with cirrhosis who were admitted to hospital, in the context of the North American Consortium for the Study of End-Stage Liver Disease (NACSELD).[8,9] Of note, NACSELD defined ACLF by the presence of at least two very severe extrahepatic OFs (shock, grade III/IV HE, renal replacement therapy, or mechanical ventilation), which are much more stringent criteria than those of the European Association for the Study of the Liver – Chronic Liver Failure (EASL-CLIF) consortium or the APASL. The NACSELD-defined ACLF is associated with a 30-day mortality rate of 41% compared to 7% for patients without ACLF. Accordingly, by definition, the main difference between traditional AD and ACLF is the short- and medium-term prognosis.

In the CANONIC study, Kaplan-Meier plots of the probability of survival revealed significantly poorer outcomes among patients with ACLF compared to those with traditional AD (Fig. 1).[7] Of note, the two curves separated very early, indicating that great effort should be made to improve patient care during the first days of the syndrome, or before it occurs. Moreover, responses to classical management of cirrhosis complications can be modulated by the presence and/or the grade of ACLF. One study observed that the response rate of hepatorenal syndrome to terlipressin plus albumin was 60% for patients with ACLF grade 1 (ACLF-1) compared to 29% for patients with ACLF-3.[10] Another showed that, in the case of severe alcoholic hepatitis (sAH), the response rate to corticosteroids was 77% in patients without ACLF compared to 38% in those with ACLF.[11] These data highlight the need to tailor therapeutic strategies and time frames to the presence of ACLF. They also suggest that emerging alternative therapies should be assessed in ACLF.

Key point

Patients with ACLF have significantly poorer outcomes than those with traditional decompensation.

Which precipitating events and pathogenic mechanisms are responsible for ACLF?

The nature of the precipitating events leading to ACLF differs according to country and can be categorised into hepatic or extrahepatic insults. One of the core differences in ACLF definitions is the origin of the precipitating event. Indeed, while EASL-CLIF and NACSELD-defined ACLF includes

Table 1. The EASL-CLIF definition of Acute-on-Chronic Liver Failure (ACLF).[7,23]

The CLIF Consortium-organ failure scoring system (CLIF-C OF score)			
Organ/system	Subscore = 1	Subscore = 2	Subscore = 3
Liver (total bilirubin, mg/dl)	<6	≥6–<12	≥12
Kidney (creatinine, mg/dl)	<2	≥2–<3.5	≥3.5 or RRT
Brain (West-Haven grade HE)	0	1–2	3–4
Coagulation (INR)	<2	≥2–<2.5	≥2.5
Circulation (MAP, mmHg)	≥70	<70	Vasopressors
Lung			
PaO_2/FiO_2 or	>300 or	≤300–>200 or	≤200 or
SpO_2/FiO_2	>357	≤357–>214	≤214

The shaded area describes criteria used to define organ failures. ACLF grade 1 (ACLF-1): patients with single kidney failure, patients with non-renal organ failure plus renal dysfunction (creatinine 1.5–1.9 mg/dl) and/or brain dysfunction (grade 1–2 HE). ACLF-2: patients with two organ failures. ACLF-3: patients with three or more organ failures. CLIF, chronic liver failure; RRT, renal replacement therapy; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.

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Table 2. Precipitating events in patients with traditional AD, ACLF, and in the whole cohort (CANONIC study).*

Event	Traditional AD (n = 1,040)	ACLF (n = 343)	All patients (N = 1,343)
Bacterial infection	226 (21.8)	98 (32.6)	324 (24.1)
Active alcoholism within the past 3 months	147 (14.9)	69 (24.5)	216 (16.1)
Gastrointestinal haemorrhage	180 (17.3)	40 (13.2)	220 (16.4)
Other event	34 (3.5)	25 (8.6)	59 (4.4)
More than 1 event	56 (5.7)	39(13.5)	95 (7.1)
No event	584 (58.9)	126 (43.6)	710 (52.9)

* Adapted from [7]. Values are n (%).

Key point

While the pathogenesis of ACLF remains unclear, a hallmark of the condition is excessive systemic inflammation, which could trigger organ failures.

both hepatic or extrahepatic insults (such as bacterial infection and variceal bleeding), APASL-defined ACLF only includes hepatic insults. In Western countries, the most commonly identified precipitating factors are bacterial infection, recent excessive alcohol use in the past three months (potentially sAH), and gastrointestinal haemorrhage (Table 2).[7] In Asia, classically, the most frequent precipitating hepatic insult is HBV reactivation and, less frequently, superimposed HEV and HAV.[12,13] Recently, a large multicentre study from the APASL ACLF research consortium (AARC) reported that alcohol consumption within the last four weeks represented nearly half of precipitating hepatic events, while HBV reactivation explained only 15% of cases.[14] Controversies remain regarding the maximum duration of alcohol abstinence (four weeks or three months) permitted for alcohol consumption to be considered a trigger of ACLF. Of note, the European experience has shown that 13.5% of patients with established ACLF had two precipitating factors or more (Table 2).[7] Interestingly, in ~44% of patients in the CANONIC study, the development of ACLF was not preceded by an identifiable precipitating factor.[7]

The pathophysiology of ACLF is still unclear. However, there is some information available on the landscape of systemic inflammation in AD. Compared to healthy individuals, patients with traditional AD exhibit features of systemic circulatory dysfunction (SCD) (*i.e.*, high plasma levels of renin and copeptin), and systemic inflammation (*i.e.*, high plasma levels of cytokines and chemokines).[15] Compared to patients with traditional AD, those with ACLF have much more marked SCD and systemic inflammation.[15] Of note, patients with AD have full-blown inflammation, involving pro- and anti-inflammatory cytokines. Since systemic inflammation can cause SCD, it has been suggested that inflammation-induced SCD, via tissue hypoperfusion, drives the development of end-organ failure in cirrhosis.[16] Experimental results suggest that inflammation could drive organ dysfunction/failure through induction of SCD and subsequent tissue hypoperfusion. For example, in arteriolar walls, cytokine-induced nitric oxide production can result in vasorelaxation, a major component of SCD. However, it has recently been shown that the strength of the association of ACLF with excessive systemic inflammation is significantly higher than with SCD.[15] These findings suggest that the amplification of systemic inflammation could trigger organ failures, at least in part, independently of SCD worsening, raising the question of whether immune cells modulated by cytokines and chemokines play a major role in the development of organ failures. Indeed, outside the context of cirrhosis, there is evidence that intense systemic inflammation may lead to organ dysfunction/failure through direct deleterious effects on microcirculatory homeostasis, mitochondrial function, and cell survival.[17] This hypothesis is reinforced by evidence in the kidney. Indeed, it has been shown in renal biopsies of patients with cirrhosis that cortical and medullary infiltration by mononuclear cells and polymorphonuclear leukocytes with tubular cell injury was independently associated with the presence of renal failure.[18]

Environmental (*e.g.*, bacterial infection, 'binge' alcohol drinking) and non-environmental (*e.g.*, gastrointestinal haemorrhage) precipitating factors are expected triggers of systemic inflammation in ACLF. It is important to note that similar precipitating factors have been found for traditional AD (Table 2). Thus, which mechanisms explain why, for a given precipitating factor, some patients will develop ACLF while others will develop traditional AD has become one of the major questions in the field. We should be aware that mechanistic differences could be dependent on the origin (intrahepatic *vs.* extrahepatic insults), the type (alcohol-induced liver injury, viral hepatitis, bacterial infection) of the trigger event, and the history of chronic liver disease (presence or absence of previous decompensation). For example, in the context of bacterial infection, differences in severity may be related to differences in environmental factors (characteristics of infecting bacteria), host non-genetic factors (age), and host genetic factors that increase predisposition to the development of severe sepsis.[19] Future research is needed to elucidate mechanisms of excessive inflammation in response to identified precipitating events.

Precipitating events are not detected in a substantial proportion of patients with traditional AD (with low grade inflammation) and ACLF (with high grade inflammation) (Table 2). One cannot

exclude the existence of a bacterial infection that routine diagnostic methods failed to detect. Alternatively, patients with cirrhosis but without overt infection may have increased intestinal permeability allowing bacterial by-products (*e.g.*, lipopolysaccharide) to translocate into the systemic circulation.[20] In this scenario, bacterial products would induce inflammation through their recognition by the innate immune system. If this hypothesis is true, it would raise important questions relating to how differences in the intensity of systemic inflammation between patients with traditional AD and those with ACLF can be explained.

Do we have tools to predict outcomes in patients with acute decompensation and a clinical course of ACLF?

The outcomes in cirrhotic patients with AD and ACLF and those with traditional AD differ dramatically in short- and intermediate-term analyses. In the CANONIC study, the 28-day and 3-month mortality rates were respectively, 33% and 51% in patients with ACLF, and 5% and 13% in patients with traditional AD (Fig. 1).[7] This last figure shows that some patients with traditional AD have a substantial risk of short-term mortality. A prognostic score (CLIF-Consortium AD [CLIF-C AD] score) was developed especially for this group of patients based on the variables associated with medium-term mortality (age, serum sodium, log-transformed white cell count, serum creatinine, and INR).[21] A CLIF-C AD score equal to or lower than 45 predicted a very low 90-day mortality rate (2%) and a score of 60 or higher was associated with 90-day mortality rate of 31%. This score was externally validated and seems to be useful for discriminating patients with AD who can be discharged early from those who require specific attention to prevent complications and development of ACLF.

When a patient fulfils ACLF diagnostic criteria, we have several potential tools for estimating outcomes. Based on the CANONIC study, the baseline grade of ACLF, the clinical course of the syndrome, and a specific score (CLIF-Consortium ACLF [CLIF-C ACLF] score) can accurately predict outcomes. The initial grade of ACLF is defined according to the number of OFs and the presence of kidney and/or neurological dysfunction (Table 1). The 28-day and 90-day mortality rates are 22% and 41% for ACLF-1, 32% and 52% for ACLF-2, and 77% and 79% for ACLF-3, respectively.[7] Moreover, in the CANONIC experience, ACLF was found to be a dynamic syndrome characterised by probabilities of resolution or improvement of 49%, stabilisation of 30%, and worsening of 20%.[22] The clinical course of ACLF is a more accurate predictor of short-term outcomes than its initial grade. In the CANONIC study, the majority of patients with ACLF (81%) reached their final ACLF grade between the 3rd and 7th day after diagnosis (day 3–7 ACLF) making this time point an ideal moment to assess prognosis.[22] Investigators also developed a prognostic score for patients with ACLF. A simplified form of the CLIF-SOFA score has been developed: the CLIF-C OF score, which is formulated by sub-scoring each organ system using a 3-point range (Table 1). Finally, a third score, called CLIF-C ACLF score, that incorporates the CLIF-C OF score, age and white blood cell count has been designed on the CANONIC data and validated in an independent cohort of critically ill cirrhotic patients.[23] This CLIF-C ACLF score consistently improved prediction error rates by ~20% for 28-day and 90-day mortality compared to classical scores (model for end stage liver disease [MELD], MELD-Na, and Child-Pugh). In a recent large study of cirrhotic patients admitted to the intensive care unit (ICU), the c-statistics of the CLIF-C ACLF score were 0.7 and 0.68 for 28-day and 90-day mortality and not better than those for the MELD score, questioning its accuracy and utility in decision-making for therapeutic management.[24] The AARC also developed a prognostic score (AARC score) which was externally validated and derived grades of ACLF in a large prospective cohort of patients with APASL-defined ACLF (n = 1,402).[14] This score includes total bilirubin, grade of HE, INR, lactate and serum creatinine and ranges from 5 to 15 (Table 3). In this cohort, AARC scores performed better than Child-Pugh, MELD, SOFA, and CLIF-SOFA scores in the prediction of 28-day mortality. Parallel to the CANONIC experience, the evolution of the score and the grade of ACLF during the first week predict the outcome of patients.

Because of the very bad outcomes associated with severe forms of ACLF and the need for expensive and limited resources, clinical teams frequently discuss the futility of intensive management. In the CANONIC study, only patients with initial ACLF-3 and ≥4 OFs or a CLIF-C ACLF score >64 at three to seven days after ACLF diagnosis reached the potential criterion of futility, with 90-day mortality of 100%.[22] A similar observation was made in another study. Indeed, a 28-day mortality of 100% was observed in a subgroup of patients with a bilirubin level >22 mg/dl, HE grade 3 or 4, INR >2.5 with either creatinine level >1 mg/dl, or lactate >1.5 mmol/L at baseline, and persistent derangement at day 4 or 7.[25] When these criteria are fulfilled and therapeutic options are contraindicated, *i.e.* for liver transplantation (LT), intensive organ support might be considered futile. These criteria must be validated in large independent cohorts, before implementation in clinical practice, and challenged by new therapeutic (including experimental) strategies.

Some of these scores can be calculated at the European Foundation for the study of Chronic Liver Failure (EF-CLIF) (http://www.efclif.com) and/or at the AARC websites (http://www.aclf.in/?page=doctor_aarc_grade_cal).

Table 3. AARC score and ACLF grading system.

AARC score					
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

AARC ACLF grade		
Grade	**Points**	**28-day mortality rates (%)**
I	5–7	12.7
II	8–10	44.5
III	11–15	85.9

AARC score (adapted from [14]). AARC, APASL ACLF Research Consortium; ACLF, acute-on-chronic liver failure; APASL, the Asian Pacific Association for the Study of the Liver; HE, hepatic encephalopathy; INR, international normalized ratio.

Key point

The current strategy for management of ACLF is to treat the precipitating factor, whilst providing intensive monitoring and support of failing organs.

What are the current management strategies, supported by evidence, for patients with ACLF?

Currently, the accepted strategy for management of ACLF is to treat its underlying precipitating factor: (antibiotics for bacterial infections, corticosteroids for sAH and nucleos(t)ide analogues for HBV flare). The management of ACLF *per se* is mainly supportive with intensive monitoring and support of failing organs. There is currently no evidence to justify alternative strategies for the management of organ failures in patients with cirrhosis compared to other critically ill patients (goals of resuscitation, fluid therapy, norepinephrine infusion, lung protective ventilation using low tidal volume).[26] When acute kidney injury related to hepatorenal syndrome is suspected, vasoconstrictors (terlipressin, octreotide/midodrine, if terlipressin is unavailable, or norepinephrine) associated with intravenous albumin are recommended.[27] Continuous renal replacement therapy (CRRT) is frequently preferred to intermittent haemodialysis in critically ill cirrhotic patients because it provides greater cardiovascular stability.[28] Relative adrenal insufficiency (RAI), demonstrated by short synacthen test, is frequent in decompensated cirrhosis (~30%) and in cirrhosis with septic shock (~70%).[29,30] In a non-randomised controlled trial (RCT) with cirrhotic patients in septic shock, intravenous infusion of hydrocortisone (50 mg every 6 h) in the case of RAI improved survival compared to historical data from the same unit.[30]

Is salvage liver transplantation a reasonable therapeutic option for ACLF? What is the ideal timing for liver transplantation?

Clinical deterioration despite maximal supportive management is associated with very poor outcomes and leads physicians to consider potential salvage LT.[22,31] This option remains highly controversial and should be addressed in the future through large studies. Indeed, transplantation in sicker recipients is unquestionably associated with an improved survival benefit but could result in less acceptable longer term survival rates after LT. Due to the scarcity of deceased liver donors, we need a strategy of rationing where the success of deceased-donor LT (DDLT) will be maximised.[32] Alternative strategies to increase the donor pool (living-donor liver transplantation [LDLT], marginal livers, ABO incompatible donation) should be explored for patients with ACLF. LDLT is now an option, with impressive results reported in expert Eastern centres, including centres in India. However, in Western countries, this option is used sparingly because of distressing experiences with severe and life-threatening complications. Moreover, the need to perform LDLT urgently in the case of ACLF reduces the time for clinical assessment of the donor and increases the pressure on the donor, resulting in a potential coercion.

Experiences with DDLT in patients with ACLF from European centres are increasingly being published. In CANONIC, DDLT of patients with ACLF (38% had ACLF-3) was associated with an acceptable one-year post-LT survival of 75%.[22] A recent retrospective study from three French liver centres reported that 73 patients with ACLF-3 received DDLT with an outstanding one-year post-LT survival of 84%, suggesting that ACLF-3 *per se* should not be viewed as a contraindication for LT.[33] Several reports from Eastern countries have shown similar outcomes for patients with ACLF receiving LDLT as for those receiving DDLT.[34,35]

Because a large proportion of patients with ACLF die on the waiting list, a better rule for organ allocation is probably needed for this group. The objective nature of the MELD score and the MELD-Na score has greatly improved the outcomes of patients on the waiting list.[36,37] The MELD score does not consider cerebral, circulatory, and pulmonary failures, giving low specific priority for patients with ACLF. The specific scores for ACLF (CLIF-C ACLF and AARC scores) are more accurate for prediction of short-term outcomes than the MELD score. The implementation of these scores could decrease the mortality on the waiting list, but they need further evaluation and validation.

Events that precipitate ACLF are challenging for LT. Firstly, active infections are recognised as contraindications for this procedure. Several studies have reported that patients who recovered fully from an episode of bacterial infection had similar post-LT survival rates despite longer post-LT hospital stays.[38,39] This observation was also made for controlled infections but a standardised definition of controlled infections is lacking.[33,40] Active alcoholism and sAH is a frequent precipitating event of ACLF in Western and Eastern countries. Classically, transplant teams ask for a period of six months of alcohol abstinence before acceptance for listing. Long-term abstinence after LT is also observed in patients who do not reach this period of six months and a wait-and-see strategy of six months is clearly unacceptable for some patients with ACLF. Several studies have shown that the alcohol relapse observed in highly selected candidates with active alcohol consumption and severe AH non-responsive to corticosteroids was 10%–11%, similar to patients with six months of abstinence pre-LT.[41,42]

The reversibility of extrahepatic organ failure after LT is essential to provide a satisfactory post-LT outcome. The most frequent extrahepatic failing organ in ACLF patients is the kidney. Several reports have shown that the presence of acute tubular necrosis and duration of pre-LT renal replacement therapy predicts the non-recovery of renal failure and mortality after LT.[43,44]

Another challenge for LT in the setting of ACLF is defining the ideal timing for this option. Indeed, optimising a patient's clinical condition by resolving or improving organ/system failures before LT is associated with a significantly better post-LT outcome. In the CANONIC experience, liver transplanted patients with resolution of ACLF had a one-year post-LT survival of 90% compared to 75% for those that still had ACLF at the time of LT.[22] Moreover, the impressive post-LT results for ACLF-3 patients in the French study could also be due to the clinical improvement observed between ICU admission and LT.[33] On the other hand, in the case of clinical deterioration, a prompt decision regarding LT must be made. However, the limits defining when a patient should be considered too sick for transplantation and LT should be considered futile are currently largely unknown. The concept of a timing window is suggested for LT in ACLF (Fig. 2).

Are there therapeutic (including experimental) strategies for improving survival or bridging the patient to liver transplantation?

Blood purification or detoxification systems

Liver failure is associated with a rise in various endogenous substances (such as bilirubin, ammonia, protein breakdown products, lactate, glutamine, free fatty acids, endogenous benzodiazepines, and pro-inflammatory cytokines) perpetuating the loss of liver function and extrahepatic organ dysfunction. This provides a rationale for the use of detoxification devices which attempt to remove these toxic substances. CRRT is capable of removing toxic substances from the circulation, but its efficacy is low because most toxic substances are protein bound or have high molecular weights. In some studies, patients with acute or chronic liver dysfunction on CRRT showed a significant reduction in serum ammonia levels.[45,46] Albumin dialysis (molecular adsorbent recirculating system, MARS®; fractionated plasma separation and adsorption system, Prometheus®) failed to demonstrate a clear survival benefit for patients with ACLF, but the efficacy of these devices was assessed in a group of patients with ACLF that was not precisely defined.[47,48] Eastern experiences of plasma exchange (PE) for HBV-related ACLF have been published. Indeed, some non-randomised trials show a survival benefit for PE compared to standard of care.[49,50] Only one RCT in acute liver failure showed that high-volume PE improved transplant-free survival compared to standard medical treatment, providing proof of concept.[51] Currently, we need high-quality trials evaluating PE as a treatment and/or a bridge to LT for patients with ACLF.

Immunomodulatory treatments

Subcutaneous administration of granulocyte colony-stimulating factor (G-CSF) (5 μg/kg) has shown promising results in terms of short-term survival benefits in two small RCTs.[52,53] G-CSF improved liver function and SOFA scores and prevented the occurrence of hepatorenal syndrome, HE, and sepsis. The suggested mechanisms of action of G-CSF in ACLF are mobilisation of bone marrow stem cells and/or proliferation of hepatic progenitor cells. The use of G-CSF remains experimental and these results must be confirmed.

Key point

The concept of a timing window is suggested for LT in ACLF, to optimise treatment outcomes.

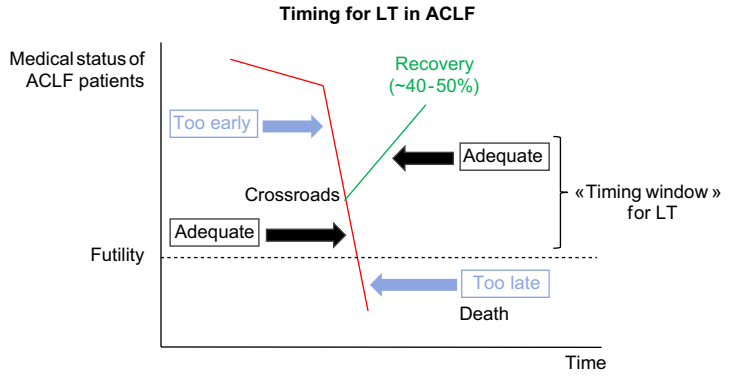

Fig. 2. The figure illustrates the concept of a timing window for liver transplantation in ACLF. The appropriate timing for LT corresponds either ideally to clinical improvement or deterioration that does not reach the futility limits in the pre-LT period. ACLF, acute-on-chronic liver failure; LT, liver transplantation.

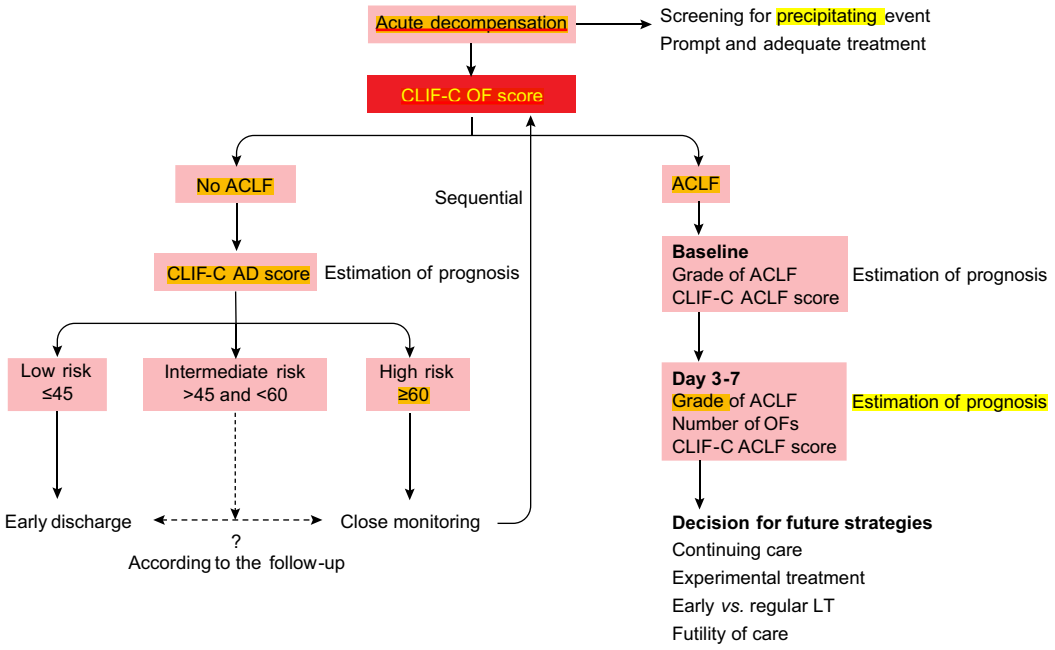

Fig. 3. Algorithm for management of patients with acute decompensation. Proposed algorithm to predict outcomes and to manage patients with AD of cirrhosis with a special interest in the detection and treatment of ACLF. ACLF, acute-on-chronic liver failure; AD, acute decompensation.

Cell therapy

Cell therapy is beginning to be assessed in ACLF in Asia but in small trials and with different diagnostic criteria. Cell therapy could repair damaged hepatocytes, promote liver regeneration, and regulate immune responses. One open-label controlled trial in HBV-related ACLF showed improved MELD scores and 90-day survival rates after umbilical cord-derived mesenchymal stem cell infusion.[54] An RCT showed that peripheral infusions of allogenic bone marrow-derived mesenchymal stromal cells significantly increased six-month survival rates in patients with HBV-related ACLF.[55] Moreover, in a small trial, the combination of umbilical cord-derived mesenchymal stem cell infusions and PE improved outcomes of HBV-related ACLF compared to PE alone.[56]

Faecal microbiota transplantation

Based on the hypothesis that bacterial intestinal dysbiosis/translocation is a contributing factor for ACLF, a small pilot study on healthy donor faecal microbiota transplantation in eight patients with sAH who were ineligible for corticosteroids showed an improvement in liver parameters and a better one-year survival rate compared to historical controls.[57]

Back to the clinical case

The patient was admitted to the hospital with AD without ACLF (according to EASL-CLIF criteria) triggered by spontaneous bacterial peritonitis. At admittance, her CLIF-C AD score was 55 with an estimated probability of dying of 5% at one month and 14% at three months, putting the patient in the grey zone of CLIF-C AD score (between 45 and 60) with an uncertain outcome. Unfortunately, she very quickly developed an ACLF-3 with four OFs (liver, coagulation, lung, and brain) requiring ICU admission and leading to a CLIF-C ACLF score of 55 with an estimated probability of dying at one month of 37%. After three days of critical management, she remained in poor clinical condition without improvement (ACLF-3 and four OFs). According to the CANONIC experience, this clinical course was associated with a mortality rate without LT of 90% at one month and 100% at three months.[22] The option of salvage LT was considered. Clearly, the patient was beyond the available recommendations to perform LT,[58] but the most valid data about LT in ACLF-3 with one-year post-LT survival of 84%, from three French centres, suggested some limit criteria for this option: active gastrointestinal bleeding, control of sepsis for less than 24 h, haemodynamic instability requiring >50 μg/min of norepinephrine, lung failure defined as a PaO_2/FiO_2 ratio <150.[33] Our patient was again beyond these criteria (*i.e.* for the lung). To try to bridge the patient to LT, CRRT was started and three plasma exchange sessions were performed in parallel on six days. Neurological improvement (stage II HE and reduction of 69% for serum ammonia levels), in parallel with resolution of respiratory failure (PaO_2/FiO_2 ratio of 304) resulting in extubation, was observed. The patient was transferred to the ward and placed on the waiting list for LT with an MELD score of 27 and was transplanted two weeks later. Currently, she is still alive six months after LT.

Areas of uncertainty

Distinguishing between ACLF and traditional AD should not only require prognostic criteria but also diagnostic criteria in the form of biomarkers and/or tests. We currently lack these tools, which make the definition of ACLF and the distinction with traditional AD controversial. The inflammatory process is quantitatively enhanced in ACLF compared with traditional AD but significant overlap in inflammatory mediators is observed between conditions. The goal of future investigations should be to identify tools able to distinguish ACLF from traditional AD, to suggest differential pathophysiology and potential therapeutic targets for ACLF. Currently, the management strategy is not clearly different for patients with ACLF compared to those with traditional AD. The development of specific diagnostic tests for ACLF would warrant management changes and potentially improve prognosis.

Conclusions

There are challenges in the management of AD of cirrhosis, particularly in the distinction between those with and those without ACLF (ACLF *vs.* traditional AD). At this time, the presence of ACLF diagnostic criteria and its clinical course help physicians to stratify patients with AD according to outcomes. The management of acute failing organs in cirrhosis is mainly supportive. Liver supports, immune treatment and cell therapies are clearly experimental, while the objective place of salvage LT is unspecified. In summary, based on published prospective data, we have proposed an algorithm for the assessment and management of patients with AD (Fig. 3).

Financial support

The authors received no financial support in relation to the production of the manuscript.

Conflicts of interest

TG and RM have nothing to disclose.

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

Authors' contributions

TG designed the manuscript. TG and RM wrote the manuscript. TG prepared the final version. RM approved the final version of the manuscript to be published.

Acknowledgements

We would like to acknowledge the contribution of a medical writer, Sandy Field, PhD, for editing this manuscript and Marco Pavesi for providing us the Kaplan-Meier curves from the CANONIC study (Fig. 1).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.08.024.

References

Author names in bold designate shared co-first authorship

[1] D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. New concepts on the clinical course and stratification of compensated and decompensated cirrhosis. Hepatol Int 2017. https://doi.org/10.1007/s12072-017-9808-z.

[2] Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010;139:1246–1256. https://doi.org/10.1053/j.gastro.2010.06.019, 1256.e1–e5.

[3] Jalan R, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif 2002;20:252–261. https://doi.org/10.1159/000047017.

[4] 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. https://doi.org/10.1007/s12072-008-9106-x.

[5] **Jalan R**, **Stadlbauer V**, Sen S, Cheshire L, Chang Y-M, Mookerjee RP. Role of predisposition, injury, response and organ failure in the prognosis of patients with acute-on-chronic liver failure: a prospective cohort study. Crit Care Lond Engl 2012;16:R227. https://doi.org/10.1186/cc11882.

[6] Dhiman RK, Agrawal S, Gupta T, Duseja A, Chawla Y. Chronic Liver Failure-Sequential Organ Failure Assessment is better than the Asia-Pacific Association for the Study of Liver criteria for defining acute-on-chronic liver failure and predicting outcome. World J Gastroenterol 2014;20:14934–14941. https://doi.org/10.3748/wjg.v20.i40.14934.

[7] Moreau R, Jalan R, Gines 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. https://doi.org/10.1053/j.gastro.2013.02.042, 1437.e1–e9.

[8] 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. Hepatol Baltim Md 2014;60:250–256. https://doi.org/10.1002/hep.27077.

[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. Hepatol Baltim Md 2018. https://doi.org/10.1002/hep.29773.

[10] Piano S, Schmidt HH, Ariza X, Amoros A, Romano A, Hüsing-Kabar A, et al. Association Between Grade of Acute on Chronic Liver Failure and Response to Terlipressin and Albumin in Patients With Hepatorenal Syndrome. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc 2018. https://doi.org/10.1016/j.cgh.2018.01.035.

[11] 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. https://doi.org/10.1016/j.jhep.2018.02.022.

[12] 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. Hepatol Baltim Md 2015;62:232–242. https://doi.org/10.1002/hep.27795.

[13] Garg H, Kumar A, Garg V, Sharma P, Sharma BC, Sarin SK. Clinical profile and predictors of mortality in patients of acute-on-chronic liver failure. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver 2012;44:166–171. https://doi.org/10.1016/j.dld.2011.08.029.

[14] Choudhury A, Jindal A, Maiwall R, Sharma MK, Sharma BC, Pamecha V, et al. Liver failure determines the outcome in patients of acute-on-chronic liver failure (ACLF): comparison of APASL ACLF research consortium (AARC) and CLIF-SOFA models. Hepatol Int 2017;11:461–471. https://doi.org/10.1007/s12072-017-9816-z.

[15] **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. https://doi.org/10.1002/hep.28740.
[16] 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. https://doi.org/10.1016/j.jhep.2015.07.004.
[17] Gomez H, Ince C, De Backer D, Pickkers P, Payen D, Hotchkiss J, et al. A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. Shock Augusta Ga 2014;41:3–11. https://doi.org/10.1097/SHK.0000000000000052.
[18] Trawalé J-M, Paradis V, Rautou P-E, Francoz C, Escolano S, Sallée M, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. Liver Int Off J Int Assoc Study Liver 2010;30:725–732. https://doi.org/10.1111/j.1478-3231.2009.02182.x.
[19] Moreau R. The pathogenesis of ACLF: the inflammatory response and immune function. Semin Liver Dis 2016;36:133–140. https://doi.org/10.1055/s-0036-1583199.
[20] Arroyo V, Moreau R, Kamath PS, Jalan R, Ginès P, Nevens F, et al. Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primer 2016;2:16041. https://doi.org/10.1038/nrdp.2016.41.
[21] Jalan R, Pavesi M, Saliba F, Amorós A, Fernandez J, Holland-Fischer P, et al. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. J Hepatol 2015;62:831–840. https://doi.org/10.1016/j.jhep.2014.11.012.
[22] **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. https://doi.org/10.1002/hep.27849.
[23] **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. https://doi.org/10.1016/j.jhep.2014.06.012.
[24] Karvellas CJ, Garcia-Lopez E, Fernandez J, Saliba F, Sy E, Jalan R, et al. Dynamic prognostication in critically ill cirrhotic patients with multiorgan failure in ICUs in Europe and North America: a multicenter analysis. Crit Care Med 2018. https://doi.org/10.1097/CCM.0000000000003369.
[25] Choudhury AK, Sharma MK, Maiwall R, Jain P, Mahtab MA, Chawla YK, et al. The decision for liver transplant in acute on chronic liver failure (ACLF) – first week is the crucial period – analysis of the APASL ACLF Research Consortium (AARC) prospective data of 1021 patients. J Hepatol 2016;64:S151, Barcelona, Spain: Elsevier.
[26] Nadim MK, Durand F, Kellum JA, Levitsky J, O'Leary JG, Karvellas CJ, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. J Hepatol 2016;64:717–735. https://doi.org/10.1016/j.jhep.2015.10.019.
[27] Gluud LL, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. Hepatol Baltim Md 2010;51:576–584. https://doi.org/10.1002/hep.23286.
[28] RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361:1627–1638. https://doi.org/10.1056/NEJMoa0902413.
[29] Acevedo J, Fernández J, Prado V, Silva A, Castro M, Pavesi M, et al. Relative adrenal insufficiency in decompensated cirrhosis: relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. Hepatol Baltim Md 2013;58:1757–1765. https://doi.org/10.1002/hep.26535.
[30] Fernández J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. Hepatology 2006;44:1288–1295. https://doi.org/10.1002/hep.21352.
[31] Putignano A, Gustot T. New concepts in acute-on-chronic liver failure: implications for liver transplantation. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 2017;23:234–243. https://doi.org/10.1002/lt.24654.
[32] Biggins SW. Futility and rationing in liver retransplantation: when and how can we say no? J Hepatol 2012;56:1404–1411. https://doi.org/10.1016/j.jhep.2011.11.027.
[33] 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. https://doi.org/10.1016/j.jhep.2017.06.009.
[34] Duan B-W, Lu S-C, Wang M-L, Liu J-N, Chi P, Lai W, et al. Liver transplantation in acute-on-chronic liver failure patients with high model for end-stage liver disease (MELD) scores: a single center experience of 100 consecutive cases. J Surg Res 2013;183:936–943. https://doi.org/10.1016/j.jss.2013.03.008.
[35] Bahirwani R, Shaked O, Bewtra M, Forde K, Reddy KR. Acute-on-chronic liver failure before liver transplantation: impact on posttransplant outcomes. Transplantation 2011;92:952–957. https://doi.org/10.1097/TP.0b013e31822e6eda.
[36] Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–96. https://doi.org/10.1053/gast.2003.50016.
[37] Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018–1026. https://doi.org/10.1056/NEJMoa0801209.
[38] Sun H-Y, Cacciarelli TV, Singh N. Impact of pretransplant infections on clinical outcomes of liver transplant recipients. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 2010;16:222–228. https://doi.org/10.1002/lt.21982.
[39] **Lin K-H**, **Liu J-W**, Chen C-L, Wang S-H, Lin C-C, Liu Y-W, et al. Impacts of pretransplant infections on clinical outcomes of patients with acute-on-chronic liver failure who received living-donor liver transplantation. PLoS ONE 2013;8:e72893. https://doi.org/10.1371/journal.pone.0072893.
[40] Bertuzzo VR, Giannella M, Cucchetti A, Pinna AD, Grossi A, Ravaioli M, et al. Impact of preoperative infection on outcome after liver transplantation. Br J Surg 2017;104:e172–e181. https://doi.org/10.1002/bjs.10449.
[41] Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790–1800. https://doi.org/10.1056/NEJMoa1105703.
[42] Im GY, Kim-Schluger L, Shenoy A, Schubert E, Goel A, Friedman SL, et al. Early liver transplantation for severe alcoholic hepatitis in the United States–a single-center experience. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 2016;16:841–849. https://doi.org/10.1111/ajt.13586.
[43] Nadim MK, Genyk YS, Tokin C, Fieber J, Ananthapanyasut W, Ye W, et al. Impact of the etiology of acute kidney injury on outcomes following liver transplantation: acute tubular necrosis versus hepatorenal syndrome. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 2012;18:539–548. https://doi.org/10.1002/lt.23384.
[44] Wong F, Leung W, Al Beshir M, Marquez M, Renner EL. Outcomes of patients with cirrhosis and hepatorenal syndrome type 1 treated with liver transplantation. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 2015;21:300–307. https://doi.org/10.1002/lt.24049.
[45] Slack AJ, Auzinger G, Willars C, Dew T, Musto R, Corsilli D, et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int Off J Int Assoc Study Liver 2014;34:42–48. https://doi.org/10.1111/liv.12221.
[46] Cardoso FS, Gottfried M, Tujios S, Olson JC, Karvellas CJUS Acute Liver Failure Study Group. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. Hepatol Baltim Md 2017. https://doi.org/10.1002/hep.29488.
[47] 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. Hepatol Baltim Md 2013;57:1153–1162. https://doi.org/10.1002/hep.26185.
[48] 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. https://doi.org/10.1053/j.gastro.2011.12.056, 782e.3–789.e3.
[49] Yue-Meng W, Yang L-H, Yang J-H, Xu Y, Yang J, Song G-B. The effect of plasma exchange on entecavir-treated chronic hepatitis B patients with hepatic decompensation and acute-on-chronic liver failure. Hepatol Int 2016;10:462–469. https://doi.org/10.1007/s12072-015-9667-4.
[50] Mao W, Ye B, Lin S, Fu Y, Chen Y, Chen Y. Prediction value of model for end-stage liver disease scoring system on prognosis in the acute on chronic liver failure patients with plasma exchange treatment. ASAIO J Am Soc Artif Intern Organs 1992;2010:475–478. https://doi.org/10.1097/MAT.0b013e3181e6bf13.
[51] Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol 2016;64:69–78. https://doi.org/10.1016/j.jhep.2015.08.018.
[52] Garg V, Garg H, Khan A, Trehanpati N, Kumar A, Sharma BC, et al. Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure. Gastroenterology 2012;142. https://doi.org/10.1053/j.gastro.2011.11.027, 505.e1–512.e1.
[53] Duan X-Z, Liu F-F, Tong J-J, Yang H-Z, Chen J, Liu X-Y, et al. Granulocyte-colony stimulating factor therapy improves survival in patients with hepatitis B virus-associated acute-on-chronic liver failure. World J Gastroenterol 2013;19:1104–1110. https://doi.org/10.3748/wjg.v19.i7.1104.
[54] Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, et al. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. Stem Cells Transl Med 2012;1:725–731. https://doi.org/10.5966/sctm.2012-0034.
[55] **Lin B-L**, **Chen J-F**, Qiu W-H, Wang K-W, Xie D-Y, Chen X-Y, et al. Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: a randomized controlled trial. Hepatol Baltim Md 2017;66:209–219. https://doi.org/10.1002/hep.29189.

[56] Li Y-H, Xu Y, Wu H-M, Yang J, Yang L-H, Yue-Meng W. Umbilical Cord-Derived Mesenchymal Stem Cell Transplantation in Hepatitis B Virus Related Acute-on-Chronic Liver Failure Treated with Plasma Exchange and Entecavir: a 24-Month Prospective Study. Stem Cell Rev 2016;12:645–653. https://doi.org/10.1007/s12015-016-9683-3.

[57] Philips CA, Pande A, Shasthry SM, Jamwal KD, Khillan V, Chandel SS, et al. Healthy donor fecal microbiota transplantation in steroid-ineligible severe alcoholic hepatitis: a pilot study. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc 2017;15:600–602. https://doi.org/10.1016/j.cgh.2016.10.029.

[58] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: liver transplantation. J Hepatol 2016;64:433–485. https://doi.org/10.1016/j.jhep.2015.10.006.