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Acute-on-Chronic Liver Failure: Getting ready for prime-time

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Abbreviations: AD: acute decompensation, HE: hepatic encephalopathy, MELD: model for end-stage liver disease, ACLF: acute on chronic liver failure, LT: liver transplantation, ICU: intensive care unit, WGO: World Gastroenterology Organization, NACSELD: North American Consortium for the Study of End-Stage Liver Disease, EASL-CLIF: European Association for the Study of the Liver-Chronic Liver Failure, APASL: Asia Pacific Association for the Study of Liver, PGE2: Prostaglandin E2, SCD: systemic circulatory dysfunction, DAMP: damage-associated molecular patterns, PAMP: pathogen-associated molecular patterns, PRR: pattern recognition receptors, ARDS: acute respiratory distress syndrome, AKI: acute kidney injury, HRS1: Hepatorenal syndrome type 1

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Abstract:

Acute on chronic liver failure (ACLF) is a culmination of chronic liver disease and extra-hepatic organ failures, which is associated with a high short-term mortality and immense healthcare expenditure. There are varying definitions for organ failures and ACLF in Europe, North America and Asia. These differing definitions need to be reconciled to enhance progress in the field. The pathogenesis of ACLF is multi-factorial and related to interactions between the immunoinflammatory system, microbiota and the precipitating factors. Individual organ failures related to the kidney, brain, lungs and circulation have cumulative adverse effects on mortality and are often complicated or precipitated by infections. Strategies to prevent and rapidly treat these organ failures are paramount in improving survival. With the aging population and paucity of organs for liver transplant, the prognosis of ACLF patients is poor, highlighting the need for novel therapeutic strategies. The role of liver transplant in ACLF is evolving and needs further investigation across large consortia. A role for early palliative care and management of frailty as approaches to alleviate disease burden and improve patient-reported outcomes is being increasingly recognized. Conclusion: ACLF is a clinically relevant syndrome that is epidemic worldwide and which requires a dedicated multi-national approach focused on prognostication and management. Investigations are underway worldwide to get ACLF ready for prime time.

Compensated cirrhosis with >90% 1-year survival can transition into the decompensated stage with the onset of jaundice, ascites, variceal bleeding and hepatic encephalopathy (HE) (1) Acute on chronic liver failure (ACLF) is associated with rapid deterioration of liver function leading to liver failure, multiple extra-hepatic organ failures and high short-term mortality (2). Even if patients survive the acute insult, they may never return to their pre-episode functional state (3). The term "acute decompensation" has been used to characterize ascites, gastrointestinal bleeding, hepatic encephalopathy or infections without organ failure (4). There are several gaps in knowledge surrounding ACLF, which will be highlighted in this review.

The prevalence of ACLF is difficult to assess due to varying regional definitions (5). ACLF, once thought to occur only in decompensated cirrhosis, has been recognized even in chronic liver disease without cirrhosis (5). ACLF occurs in approximately 10-30% of hospitalized cirrhotic patients (6-8). Because of its acuity, patients are frequently admitted into the intensive care unit (ICU), and every effort is made to stabilize these patients for liver transplantation (LT). This drives healthcare costs (9). Despite this intensive management, ACLF is associated with substantial morbidity and mortality. Because curative LT is only available to <10% of cirrhotic patients each year and ACLF patients are often delisted, the morbidity and mortality rates remain high, especially with an increasing number of organ failures (10).

Gap:

- *True cost and burden of ACLF worldwide*

Definition of ACLF

ACLF is characterized by rapid progression in liver injury culminating in multiple organ failures and possible mortality (5). Distinction should be made between definition, diagnosis, and prognostic criteria for ACLF. Defining a disease requires demonstration of a distinct pathophysiology, and a confirmatory diagnostic sign, symptom, or test. The current disagreements between the various definitions are largely because criteria used (ascites and

jaundice in the Asian-Pacific “definition”; organ failure in European and North American “definitions”) are diagnostic or prognostic criteria and not defining criteria (6, 8, 11, 12). There are currently three widely used definitions of ACLF. Among these definitions, there are commonalities, such as high mortality, but also significant differences that give the impression that ACLF is not the same disease worldwide (tables 1 and 2). Lack of standardization in definitions is probably related to variability in precipitating events and underlying liver disease. For example, in the West, bacterial infection is a common precipitating event whereas in the East, both hepatitis B and alcoholic hepatitis are considered precipitating events. The definition of organ failures is also variable (table 3). To arrive at a universally acceptable definition, the World Gastroenterology Organization (WGO) proposed a working definition. ACLF was defined as *“a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis, characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the international normalized ratio or INR) and one or more extrahepatic organ failures, associated with increased mortality up to three months”* (5). The WGO definition was proposed to narrow down the group of patients in whom data were to be collected, so that ultimately the syndrome could be better defined. Accordingly, when sufficient data are collected, ACLF should be defined with the following qualifications:

1. Distinguishable from chronic liver disease, compensated cirrhosis and traditional decompensated cirrhosis.
2. A distinct pathophysiology.
3. Identification of a diagnostic sign, symptom, or confirmatory test.
4. The diagnosis of ACLF will warrant management change.

The duration of “acute” is also important. Data on ACLF in patients with cirrhosis who have undergone surgery where the timing of the precipitating event is certain and the course postoperatively closely monitored, the increased risk of mortality is for a period of 12 weeks. Therefore, the duration of the ACLF “event” should be 12 weeks. Until such time that a

validated definition is available, we propose a generic definition of ACLF, namely that *“ACLF is a condition in patients with underlying chronic liver disease with or without cirrhosis that is associated with mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation”*. Examples of ACLF in patients with underlying cirrhosis include Wilson disease and alcoholic hepatitis. Examples of ACLF in chronic liver disease without cirrhosis include reactivation of chronic hepatitis B, alcoholic hepatitis, and either acute viral hepatitis or drug-induced liver injury in the background of NAFLD.

It is also important to distinguish diagnostic criteria from prognostic criteria. Diagnostic criteria should be such that ACLF is recognized early enough that it can be reversed by appropriate management. The Asian-Pacific “definition” of ACLF is associated with a high 28-day mortality has merit in terms of diagnostic criteria(12). The criteria are sensitive but not specific for diagnosis of ACLF. Current European and North American “definitions” include scores of multiple organ failure; such scores reflect or describe the dying process (8, 11). These scores are more specific for mortality within 14 days but are not sensitive beyond that period.

Therefore, using multiple organ failures as diagnostic criteria may not allow early intervention. Organ failure scores should preferably be used to exclude patients from studies or to define futility in treatment. The term "acute decompensation" has been used to characterize ascites, gastrointestinal bleeding, hepatic encephalopathy or infections without organ failure(4)

Prognosis is the art for telling disease course and such scores should help select specific therapies: when is ICU care sufficient; which patient benefits from regenerative therapy or liver support devices; who requires early LT; and when treatment is futile. Multiple prognostic scores have been used including the Model for end-stage liver disease (MELD) score, chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score, acute physiology and chronic health evaluation (APACHE) score and the North American Consortium for the study of end-stage liver disease (NACSELD) score. None of these scores have consistently demonstrated a

'c' statistic greater than 0.8, which is the accepted threshold for an excellent model. ACLF-specific prognostic scores need to be developed.

Gaps:

- *Uniform definition worldwide for natural history studies and treatment trials*
- *Homogenizing and distinguishing definition, diagnostic criteria and prognostic criteria for ACLF.*
- *Infections as a consequence or precipitant of ACLF?*
- *Contrasting ACLF associated with compensated vs. decompensated cirrhosis vs chronic liver disease without cirrhosis*
- *Diagnosing ACLF early enough to allow interventions that can reverse disease course*

Pathogenesis of ACLF

Mechanistic features that differentiate ACLF from traditional acute decompensation (AD)

Compared to healthy subjects, patients with traditional AD (previously called 'mere' AD) exhibit features of systemic circulatory dysfunction (SCD), and systemic inflammation, and these become much more pronounced in patients with ACLF(13). Excessive systemic inflammation can cause 'intense' SCD and subsequent low tissue perfusion pressure resulting in organ failure. (14). However, the strength of association of ACLF with excessive systemic inflammation is significantly higher than with 'intense' SCD(13). These findings suggest that systemic inflammation can drive ACLF, at least in part, independently of SCD (and tissue perfusion). Future research measuring systemic inflammatory markers could help define signatures to improve our understanding of inflammation in ACLF (primary prophylaxis).and inform preventative strategies.

Mechanisms of Inflammation: Environmental factors (bacterial infection, excessive alcohol use) are the most common identified triggers for inflammation in ACLF(8). Infection by viable bacteria (Figure 1) can induce inflammation via two classes of molecules: pathogen-associated

molecular patterns (PAMPs) and virulence factors (Figure S1) (15). PAMPs are recognized by innate pattern recognition receptors (PRRs), a process called structural feature recognition (15). Virulence factors are indirectly recognized by PRRs via a process called functional feature recognition (Figure S1) (15). Both processes result in the production of inflammatory molecules (Figure S2A and S2B). The inflammatory response to bacteria can be excessive and cause tissue damage, which causes the release of damage-associated molecular patterns (DAMPs). DAMP recognition by specific receptors perpetuates or accentuates inflammation triggered by bacterial inducers (Figure S1, S2A-B) (15). Patients with infection-related ACLF exhibit a 'storm' of inflammatory cytokines (13).

Both chronic alcohol use and binge have substantial immunosuppressive effects that weaken the already impaired host immune responses in cirrhosis, and increase the risk of infection (16).

Excessive alcohol use has at least two other major effects; first, alcohol binge results in a multifactorial "leaky gut", resulting in translocation of bacterial PAMPs (such as lipopolysaccharide (endotoxin), CpG DNA), but not viable bacteria (17), which stimulate liver inflammation (Figure 1). Second, alcohol results in release of hepatic DAMPs such as uric acid and ATP that elicit NLRP3 inflammasome formation (18) to produce mature interleukin (IL)-1 β (Figure S2B). This cytokine up-regulates other pro-inflammatory cytokines, sensitizes hepatocytes to other insults, promotes liver fibrosis and inhibits liver regeneration (19, 20). NLRP3 formation can cause pyroptosis, a form of programmed cell death (Figure S2B). The diseased liver can contribute to systemic inflammation by two mechanisms: dying hepatic cells release pro-inflammatory DAMPs (Figure S2) and liver inflammation can result in cytokine/chemokine spillover to the blood (Figure 2). In other words, in the context of severe alcoholic hepatitis, liver inflammation may contribute to systemic inflammation and subsequent multi-organ failure.

Precipitating factors: Bacterial infection is the most common precipitating factor of AD. However, for a given infection, the reasons why some patients develop infection-related ACLF but not others are poorly understood. Differences in severity may be related to differences in

environmental factors (characteristics of infecting bacteria, alcoholic binge), host non-genetic factors (age), and genetic factors, increasing predisposition to develop infection (21-23). Similarly, in alcohol misuse, the reasons why some develop ACLF but not others are unclear (18, 24). Moreover, a substantial proportion of ACLF patients do not have any identifiable precipitating event (8). In these cases, ACLF might result from bacterial or fungal infections that have gone undetected, unrecognized drug-induced liver injury, or subclinical intestinal translocation of bacterial PAMPs and increased DAMP release.

Immunodeficiency: It has been hypothesized as a contributor to development of nosocomial infections and ACLF(21, 25, 26). However, the blood immune cell subset frequencies, immune cell-surface protein expression and transcriptomic signatures have not yet been systematically investigated in ACLF. Studies have demonstrated changes in PGE₂ and higher subset of monocytes overexpressing surface tyrosine-protein kinase Mer (encoded by *MERTK*)(27, 28). Improving our knowledge of immune cell subsets exhibiting features of immune suppression should lead to identify targets for new therapies aiming to prevent nosocomial infections and subsequent patients' worsening (secondary prophylaxis).

Failed tolerance: Infection is associated with two injury mechanisms: first, the immune response to infection can be excessive and cause tissue damage; second, infective organisms can directly damage tissues(29). The host can reduce this through tissue-intrinsic mechanisms (i.e., tolerance or endurance mechanisms) and it is suggested that disease severity could be related to failed disease tolerance(30). Among patients with ACLF, for any given level of systemic inflammation, patients with prior episodes of decompensation of liver disease have a lower risk of death than those without prior episodes(8), suggesting that the former, but not the latter, have developed protective tolerance mechanisms.

Microbiome-host interactions: Cirrhotic patients with/without alcohol misuse have alterations in their gut microbiome and intestinal barrier, which correlates with disease severity (31). However,

the interactions between the alterations in the intestinal barrier and gut dysbiosis are poorly understood (2, 31, 32). Microbiota in sites other than the gut also needs to be explored.

Role of tissue-resident immune cells: In non-cirrhotic conditions, it has been shown that macrophages residing in an injured tissue secrete cytokines and chemokines that attract and activate leukocytes with the objective of restoring tissue homeostasis (33). Cytokine spillover from damaged tissues might contribute to high systemic cytokine and chemokine levels in ACLF, but this needs to be investigated systematically.

Gaps:

- *Unclear why some patients but not others develop ACLF*
- *Absence of precipitating factors in a major proportion of patients*
- *Role of microbiota and tissue-resident immune cells is unclear*

Individual organ failures and their management

ACLF is primarily characterized by extra-hepatic organ failures, the specific definitions of which vary between regions. However, most definitions of ACLF are associated with failures of the renal, brain, respiratory and circulatory systems (8, 11, 12). The only consistent definition is of brain failure defined as Grade 3-4 HE.

Respiratory complications are broadly categorized into acute complications (e.g. the acute respiratory distress syndrome, pneumonia, or pulmonary edema) and those which are directly associated with liver disease (e.g. hepatopulmonary syndrome and portopulmonary hypertension). Previous studies have demonstrated that patients who require mechanical ventilation have high rates of mortality (6, 8, 11). However, this is more related to the severity of underlying liver disease and not a requirement for mechanical ventilation (34). Currently, there is no evidence to support alternative strategies for management of respiratory failure in cirrhotic patients compared to other critically ill patients and typical recommendations are for lung protective ventilation strategies using low tidal volumes (35, 36).

Circulatory disorders are superimposed on the typical cirrhotic hemodynamic state of a hyperdynamic circulation with high cardiac output and low systemic vascular resistance (37). Additional structural and functional cardiac abnormalities (cirrhotic cardiomyopathy) occur in approximately 40-50% cirrhotic patients (38). Whereas this could support end-organ perfusion in compensated patients, tissue perfusion may become inadequate in patients with ACLF with their worsening systemic hypotension, thereby requiring hemodynamic support. Assessment of volume status and cardiovascular function can be particularly challenging in the cirrhotic patient due to significant volume overload. The optimal method for assessing both volume and hemodynamic status has yet to be determined. Dynamic measures of cardiovascular function such as bedside echocardiography, and in appropriate situations, use of pulmonary artery catheters may guide both fluid and pharmacologic resuscitation end-points (39).

Renal complications range from acute kidney injury (AKI) to acute-on-chronic kidney failure and finally the need for renal replacement therapy. AKI, defined as an increase in serum creatinine by ≥ 0.3 mg/dL in <48 hours, or a 50% increase from a stable baseline within the past 3 months (40), occurs in about 20% of all hospitalized cirrhotics (41). Therefore, renal failure, a severe expression of AKI, is also the most common organ failure in patients with ACLF, with type 1 hepatorenal syndrome (HRS1) as the more severe prototype. The precipitating event for the renal failure in ACLF may be related to infection, hypovolemia, or structural renal damage. The pathogenesis of renal failure in ACLF is due to a combination of severe inflammation and systemic hemodynamic instability. When compared to patients with AD, AKI events in patients with ACLF are more likely to be associated with structural renal damage, be prolonged and progress to a more severe stage of renal dysfunction (42). Therefore, patients who have AKI with ACLF are more likely to require renal replacement therapy, and have less AKI resolution, associated with higher mortality, even after recovery (43). Volume expansion, preferably using colloid solutions, is the first step in the management. Albumin is the most commonly used due to its oncotic and non-oncotic properties (44). Once structural disease has been excluded,

treatment should be started as soon as possible, as a lower pre-treatment serum creatinine is a consistent predictor of response to vasoconstrictor therapy (45). A combination of albumin and vasoconstrictors (terlipressin or norepinephrine), is the mainstay of HRS1 treatment. Although midodrine, octreotide and albumin are inferior to terlipressin and albumin (46) for HRS1, a short course of the combination may be given if terlipressin is not available. The role of dialysis is debated, but in most practices, is only offered to potential LT candidates (6, 39).

Brain failure is defined as grade 3 or 4 HE. Two large studies determined that HE with ACLF conferred a worse prognosis compared to HE without ACLF (47, 48). In the North American study, grade 3-4 HE with >2 extra-hepatic organ failures had the highest 30-day mortality. Grade 3-4 HE was associated with 30-day mortality independent of other organ failures, indicating that brain failure is an important independent prognostic factor (48). HE in cirrhosis is caused by a multitude of factors associated with hyperammonemia and systemic inflammation (49). However, cirrhotic patients are also susceptible to mental status changes from several other causes including medications, alcohol intoxication/withdrawal, intra-cerebral bleeding, strokes, and sepsis-associated encephalopathy (50). Progression of HE from lower grades to grade 3-4 should be prevented, with a low threshold for instituting airway protection measures. The four prongs of treatment of suspected HE or altered mental status in cirrhosis are (i) confirmation of HE by ruling out other causes, (ii) standard of care of the unconscious patient with airway protection and early transfer to a monitored unit, (iii) management of precipitating factors, without which the mental status will not recover, and (iv) empiric HE treatment using first-line lactulose and other treatments as available (50). In patients who are not responding to the above measures (persistent HE), reconsideration of the diagnosis of HE, continuing to look for undiscovered precipitating factors and potentially embolizing spontaneous porto-systemic shunts in those with a low MELD score may be further options (51). Brain dysfunction impacts end-of-life decision-making and candidacy for LT (37, 52).

Management of Infection in an effort to prevent ACLF: Infections are one of the most important

precipitants of ACLF based on Western definitions (37, 53). With improving survival of variceal bleeding, HE and infections have become the leading reasons for hospitalization and readmission in cirrhotic patients (54). Recently, the bacteriology of infections has shifted, with the emergence of a greater proportion of gram-positive and drug-resistant organisms (21). In the absence of rapid infection control there is the risk of organ failure. Nosocomial and second infections are reliably associated with the development of ACLF and their prevention may avoid ACLF(21, 53). There is also an emergence of fungal infections, which most often arise as a result of antibiotic use and following bacterial infections (55). The role of infections in ACLF has been debated with the Asian-Pacific definition excluding infected patients, unlike the Western definitions (5, 6, 12). Regardless of the inclusion as a precipitant or a result of ACLF, infections are a prime target to improve the prognosis.

Gaps:

- *Differing definitions of organ failures*
- *Changing profile of infections*
- *Few treatments are directed towards the liver itself*

Changing face of cirrhosis, ACLF and outcome management

The role of extracorporeal liver support in the treatment of ACLF has been explored, despite heterogeneous definitions. Although an early study showed promise (56), studies with molecular adsorbent recirculating system (57) and PROMETHEUS (58) system failed to show any improvement in survival. Therefore, the status of these costly interventions for ACLF is unclear.

The status of LT in ACLF remains undefined (Table 4). Three studies from Europe reported an acceptable 1-year post-LT survival rate for ACLF patients ranging from 75 to 87% (37, 59, 60).

Post-OLT course of ACLF is currently not predictable. Small series question the value of transplanting these patients, with 1-year post-LT survival rate as low as 43-46% (61, 62).

Furthermore, post-LT complications of ACLF patients are associated with longer ICU and

hospital stays compared to patients without ACLF. Infectious, renal, pulmonary and neurological complications are the main post-LT events. The liver allocation process in the United States is based on MELD score and therefore not uncommonly, patients with ACLF are highly competitive, yet, associated respiratory and circulatory failures may contraindicate LT because of the known poor outcomes in such cases. In the multi-center study conducted by the NACSELD, infections were a major cause for delisting (52). Within 6 months, 42% of patients were de-listed with subsequent poor outcomes, while those transplanted did well. Those who were delisted or died had the highest proportion of 3 or 4 organ failures at hospitalization versus those listed or subsequently.

An analysis of United Network for Organ Sharing data from 2002 to 2013 noted a significant interaction between MELD score and hospitalization status on post-LT mortality(63). This interaction was most pronounced in patients with MELD score of <25 transplanted from an ICU, whose adjusted predicted 3-, 6-, and 12-month post-LT mortality approximated those of with a MELD of 30. Compared to hospitalized MELD 30–34 patients, those with a MELD \geq 35 in an ICU had significantly higher post-LT mortality, suggesting that transplanting patients in the ICU, as is the case for most ACLF patients, is associated with suboptimal outcomes and should be considered carefully. In another study which used an increase in MELD score by \geq 5 within a month as the definition of ACLF, the survival and renal outcomes in ACLF LT recipients were similar to those without ACLF(64).

One critical factor to be considered is that the aging cirrhosis population, which could worsen the prognosis with ACLF development because the combination of aging and aging-related comorbidities (e.g. diabetes, sarcopenia, coronary artery disease) may synergize with negative outcomes. Quantification of debility in these patients for LT eligibility is important. Researchers in the field of aging have operationalized older adults' physiologic reserve with a number of tools to measure the concept of *frailty* – the term referring to a state of decreased physiologic reserve and increased vulnerability to health stressors (65). Well-defined frailty tools such as the Fried

Frailty Index and Clinical Frailty Scale have been applied to non-geriatric cirrhotic patients, with strong associations between frailty and important outcomes including hospitalizations and mortality (66, 67). The development of the Liver Frailty Index, consisting of 3 performance-based measures – grip strength, chair stands, and balance testing – improves the ability of MELD-Na to predict mortality in patients awaiting LT (68). Objective assessment of frailty before transplant helps to anchor expectations for recovery of frailty post-LT, especially for older patients with ACLF.

The symptom burden in cirrhosis, especially in those with ACLF, is akin to advanced malignancy, making this an important population for palliative management (69). Although often misinterpreted as being end-of-life-care, palliative care has relevance at all stages of cirrhosis and undoubtedly in patients with ACLF who are not LT candidates. It includes advanced care planning and goals of care discussions, symptom control, psychosocial support, assessment of functional status and transitions to higher levels of care including hospice. In an ideal setting, palliative care principles would first be integrated alongside continued disease-modifying therapy, with the patient in a stable outpatient setting. A focus on transitions of care is also important to standardize care between levels of practitioners.

Gaps:

- *Role of liver assist devices in question*
- *High variability in offering transplant – are MELD driven criteria applicable in these patients?*
- *Selection of appropriate candidates and timing of liver transplant*
- *Criteria for delisting of patients, including cut-off for objective metrics of frailty*
- *Inadequate accounting for frailty and co-morbid conditions*
- *Limited uptake of palliative care,*

Future directions:

There are several steps that remain to make ACLF ready for prime time (Table 5). There is need for consensus criteria to define and diagnose ACLF, assess severity of liver and other organ failures, and initiate standard management protocols. Variability in management might result in variable outcomes in patients with identical severity of ACLF. Thus, there is a need for universally accepted management protocols. The final definition of ACLF will likely include an assessment of chronic liver disease, a marker of the inflammatory response, and a biomarker that is a surrogate for early onset of organ failure. Such a definition requires identification of a distinct pathophysiology that is likely to involve inflammation and the immune system. ACLF remains an entity, which has greatly increased in visibility and there has been substantial progress in characterizing and managing it. Its readiness for prime time has improved greatly and steps to make that a reality are being actively investigated.

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Figure Legends

Figure 1. Potential consequences of bacterial translocation in cirrhosis

Cirrhosis is associated with gut dysbiosis. Viable Gram-negative bacteria can translocate from the intestinal lumen to blood via a transcellular pathway which is poorly known. Translocated bacteria can reach ascites via systemic circulation and cause spontaneous bacterial peritonitis (SBP). Bacterial by-products such as pathogen-associated molecular patterns (PAMPs) can translocate via a paracellular route (a process that is favored by intestinal tight junction disruption). Then, PAMPs can reach the liver and here be recognized by pattern-recognition receptors (PRRs) resulting in liver inflammation.

Figure 2. A scenario for a role of liver necrosis and inflammation in extra-hepatic multi-organ failure, in the context of severe alcoholic hepatitis

Severe alcoholic hepatitis is associated with cell death and inflammation in the liver. Cell death can result in the release of damage-associated molecular patterns (DAMPs) that reach systemic circulation and cause remote inflammation in tissues that express their cognate receptors. Liver inflammation can result in cytokine/chemokine spillover to blood, which brings them to extrahepatic organs where they cause inflammation. Therefore, in severe alcoholic hepatitis, molecules produced by the liver can cause remote extrahepatic organ inflammation and subsequent dysfunction/failure. Pathogen-associated molecular patterns that have translocated from the intestinal lumen to blood (see Figure 1) may also contribute to inflammation of extra-hepatic organs (not shown).

Table 1: Comparison of the Definitions for Acute-on-Chronic Liver Failure (ACLF)

	Asian Pacific Association for the Study of Liver (APASL)	European Association for the Study of Liver-Chronic Failure (EASL-CLIF)	North American Consortium for Study of End-stage Liver Disease (NACSELD)	World Gastroenterology Organization (WGO Proposal)
Derivation	Consensus and observational	Prospective, observational study	Prospective study in patients with Cirrhosis and infection	Consensus
Patient Population Inclusion	Chronic liver disease Compensated cirrhosis	Compensated and decompensated cirrhosis	Decompensated cirrhosis by implication	Non-cirrhotic chronic liver disease; compensated and decompensated cirrhosis
Exclusion	Infection, prior hepatic decompensation	HCC outside Milan criteria HIV infection Significant comorbidity	HIV infection Prior organ transplantation Untreated malignancies	Not stated
Severity Score	Liver failure defined as jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (INR of ≥ 1.5 or prothrombin activity of $\leq 40\%$). Ascites or encephalopathy develops within 4 weeks.	Hepatic and extrahepatic organ failure.	Extrahepatic organ failure	Not Stated
Comments	Diagnosis can be made early enough for intervention to alter disease course. Diagnosis is sensitive but not specific for early mortality	Diagnosis of ACLF may be made too late to impact disease outcome.	Diagnosis of ACLF may be made too late to impact disease outcome.	Working definition for data collection to ultimately arrive at a validated definition

ACLF: Acute-on-chronic liver failure; HCC: hepatocellular carcinoma; HIV: human immunodeficiency virus; INR: International normalized ratio

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	Duration of Event	Underlying Liver Disease	Common Precipitating Events	Requirement for Diagnosis of ACLF
APASL	4 weeks	Non-cirrhotic chronic liver disease. Compensated cirrhosis	Reactivation hepatitis B Superimposed hepatitis E Alcoholic hepatitis	Ascites, hepatic encephalopathy
EASL-CLIF	4 weeks	Compensated and decompensated cirrhosis	Alcoholic hepatitis Bacterial infections Unknown in $\geq 40\%$	Organ failure (hepatic failure not essential for diagnosis)
NACSELD	30 days	Not specified, but by implication all patients had decompensated cirrhosis	Not specified, but only patients with infection included.	Extrahepatic organ failure
WGO	3 months	Chronic liver disease with or without cirrhosis. Both compensated cirrhosis and decompensated cirrhosis included	Alcoholic hepatitis Infection (West) Reactivation hepatitis B Superimposed hepatitis E Alcoholic hepatitis	Hepatic and extrahepatic organ failure

Asian Pacific Association for the Study of Liver (APASL), European Association for the Study of Liver-Chronic Failure (EASL-CLIF), North American Consortium for Study of End-stage Liver Disease (NACSELD), World Gastroenterology Organization (WGO Proposal)

Type of Organ Failure	APASL Organ Failure Definitions	EASL-CLIF Organ Failure Definitions	NACSELD Organ Failure Definition
Liver	Total bilirubin ≥ 5 mg/dL and INR ≥ 1.5	Bilirubin level >12 mg/dL	-
Kidney	Acute Kidney Injury Network criteria	Creatinine level of ≥ 2.0 mg/dL or renal replacement therapy	Need for dialysis or other forms of renal replacement therapy
Brain	West-Haven hepatic encephalopathy grade 3-4	West-Haven hepatic encephalopathy grade 3-4	West-Haven hepatic encephalopathy grade 3-4
Coagulation	INR ≥ 1.5	INR ≥ 2.5	-
Circulation		Use of vasopressor (terlipressin and/or catecholamines)	Presence of shock defined by mean arterial pressure <60 mm Hg or a reduction of 40 mm Hg in systolic blood pressure from baseline, despite adequate fluid resuscitation and cardiac output
Respiration		PaO ₂ /FiO ₂ of ≤ 200 or SpO ₂ /FiO ₂ of ≤ 214 or need for mechanical ventilation [Note: Accepted ratio is ≤ 300 for ALI or ≤ 200 for ARDS]	Need for mechanical ventilation

ALI, Acute Lung injury, ARDS, Adult respiratory distress syndrome, FiO₂, fraction of inspired oxygen; INR, international normalized ratio, PaO₂, partial pressure of arterial oxygen; SpO₂; pulse oximetric saturation. * WGO did not define organ failures

Asian Pacific Association for the Study of Liver (APASL), European Association for the Study of Liver-Chronic Liver Failure (EASL-CLIF), North American Consortium for Study of End-stage Liver Disease (NACSELD), World Gastroenterology Organization (WGO Proposal)

Table 4: Liver transplant and ACLF

First Author (reference number)	Experience	Criteria for ACLF	Survival	Notes
Gustot <i>et al.</i> (37)	CANONIC	CLIF criteria	80.9 v 10% (180 days)	Tx day 3-7, favors LT
Finkenstedt <i>et al.</i> (60)	Innsbruck	APASL criteria	87 and 82% (1 and 5 years)	Favors LT
Artru <i>et al.</i> (59)	Lille/P Brousse/Montpellier	CLIF-OF	83.9 vs 7.9% 1y survival	Favors LT, ACLF pts have high complication rates
Reddy <i>et al.</i> (52)	NACSELD	NACSELD criteria	95% vs <10% (compared with those delisted due to ACLF)	Favors LT
Bahirwani <i>et al.</i> (64)	University of Pennsylvania	MELD score increase >5 within 4 weeks	74.5% vs 83.4% unadjusted	After adjustment, ACLF did not appear to affect post-LT survival
Levesque <i>et al.</i> (62)	Montpellier/Henri Mondor	EASL-CLIF	90% 90 day survival	Does not favor LT
Umgelter <i>et al.</i> (61)	Munich	MELD/SOFA/APACHE	46% 1y survival	Shorter ICU stay and higher MELD at admit favored better survival

European Association for the Study of Liver-Chronic Failure (EASL-CLIF), North American Consortium for Study of End-stage Liver Disease (NACSELD), model for end-stage liver disease (MELD), treatment (Tx), liver transplant (LT), Intensive care unit (ICU), Acute Physiology And Chronic Health Evaluation II (APACHE), Sequential organ failure assessment (SOFA), Acute on chronic liver failure (ACLF).

Table 5: Future Directions for ACLF research

Areas of need in ACLF	Specific steps needed to address the gaps
Burden of ACLF	<ol style="list-style-type: none"> 1. Consortia that also include centers that are not transplant centers. 2. Education about ACLF beyond academic centers
Definition	<ol style="list-style-type: none"> 1. Focus on narrowing the differences, 2. Simplifying definitions to increase generalizability 3. Focus on separate diagnostic and prognostic markers 4. Could conventional prognostic scoring systems in ACLF patients perform better if markers of systemic inflammation and circulatory dysfunction are included?
Pathogenesis	<ol style="list-style-type: none"> 1. Research to identify PAMPs and DAMPs as diagnostic biomarkers of the mechanism of ACLF. 2. Excessive responses to DAMP(s) might also be under control of genetic factors and appropriate genome-wide association studies are required 3. No comprehensive description of the landscape of circulating immune-suppressed cells is available in patients with ACLF 4. Cytokine/chemokine signatures for identification and grading of systemic inflammation are required 5. Changes in microbiota in differing stages of ACLF

Organ failure management	<ol style="list-style-type: none"> 1. Biomarkers should be developed to identify early tissue dysfunction before failure sets in 2. Should the type of precipitating event (extrahepatic vs intrahepatic) be included in these prognostic scores? 3. Prevention of organ failures is critical 4. Changes in bacteriology and increasing importance of infections as modulators of ACLF are needed 5. Organ-specific therapies are required 6. Bridging therapies with liver-assist devices and elucidating the role of liver transplant 7. Which is the most appropriate time to decide prognosis in ACLF patients (given the dynamic course of ACLF)?
Non-medical approaches for ACLF	<ol style="list-style-type: none"> 1. Greater multi-disciplinary coordination between palliative care, transplant and inpatient hepatology services, 2. Improved education of trainees, professionals involved in ICU, Infectious disease, liver transplant care as well as palliative care professionals

ACLF: acute-on-chronic liver failure; DAMP: damage associated molecular pattern; ICU: intensive care unit; PAMP: pathogen associated molecular pattern

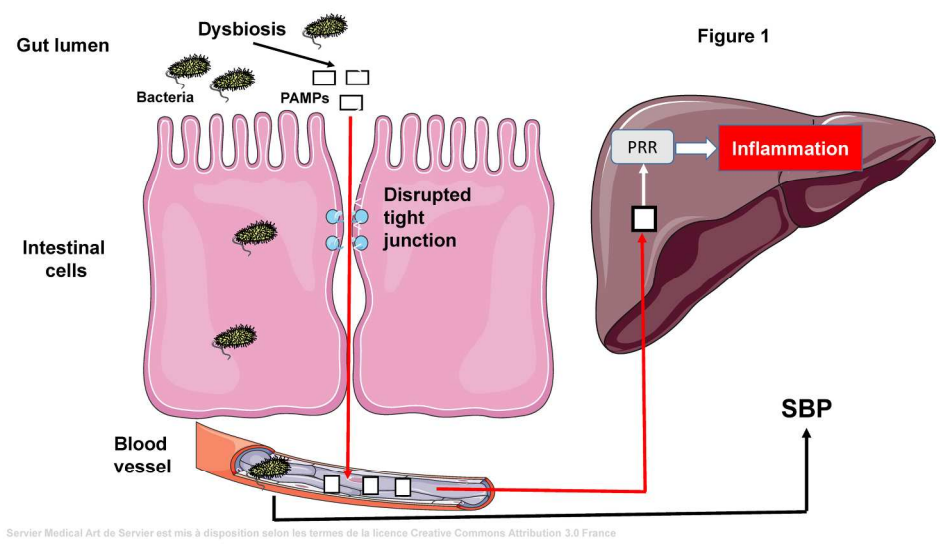
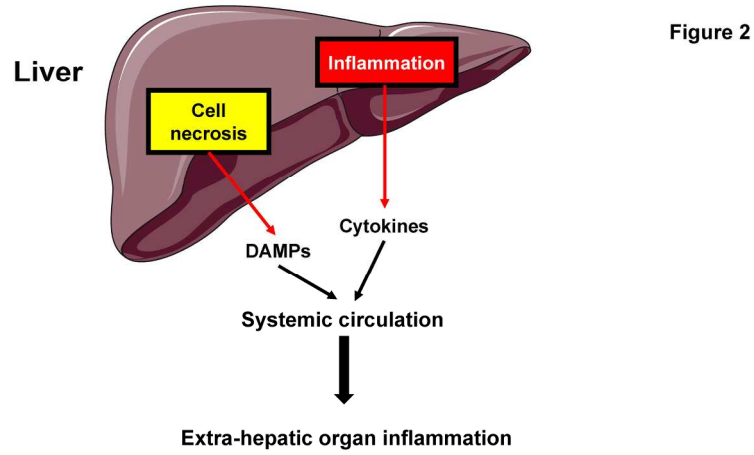


Figure 1

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Figure 2

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