Acute-on-Chronic Liver Failure

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Abbreviations

AARC	APASL ACLF research consortium
ACLF	Acute-on-chronic liver failure
AD	Acute decompensation
AIH	Autoimmune hepatitis
APACHE	Acute Physiology and Chronic Health Evaluation
APASL	Asian Pacific Association for the Study of the Liver
CANONIC-CLIF	Acute-on-chronic liver failure in cirrhosis
DAMPs	Damage-associated molecular patterns
EASL-CLIF	European Association for the Study of the Liver Chronic Liver Failure consortium
HE	Hepatic encephalopathy
MELD	Model for end-stage liver disease
ROS	Reactive oxygen species
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failures assessment

Key Points

- Acute-on-chronic liver failure (ACLF) is a distinct syndrome characterized by high 28-day mortality.
- ACLF is characterized by acute hepatic insult in a patient with diagnosed or undiagnosed chronic liver disease/cirrhosis.
- Acute insult can be inflicted by alcohol, virus (hepatitis B, hepatitis A or E, or a nonhepatotropic virus), drug, herbal supplement, autoimmune, or Wilson's flare.
- Postacute insult, pathogenesis of ACLF is based upon systemic inflammatory response, persistent inflammation, gut dysbiosis, and increased gut permeability, leading to cytokine storm in the portal and systemic circulation and organ failure.
- "Golden window" of 7 days usually precedes development of sepsis, organ failure providing opportunity for interventions, supportive care, organ support, and guiding management.
- Abstinence, steroids, and antivirals may be used as specific etiology-based therapies in ACLF, and GCSF as a nonspecific regenerative therapy.
- Plasma exchange or artificial liver support system such as MARS or Prometheus may help as adjunctive therapies.
- Liver transplant is the definitive therapy, and nearly 80% 1-year survival can be achieved with optimal selection and timing.

Acute-on-chronic liver failure (ACLF), as a term, first came into existence in 1995 when the Japanese review described alcoholic hepatitis, case of acute liver injury superimposed on cirrhosis, a condition different from acute liver failure [1]. Acute liver failure (without coexistent liver failure), acute-on-chronic liver failure (on background of underlying chronic liver failure), and acute worsening of decompensated cirrhosis denote the spectrum of liver failure and are usually associated with extrahepatic organ failure and high short-term mortality [2]. There are at least 13 definitions being propagated to define ACLF [3], owing to an overlap between the terminologies; however, the most commonly cited remain the Asian Pacific Association for the Study of the Liver (APASL) [4] and the European Association for the Study of the Liver (EASL) Chronic Liver Failure (EASL-CLIF) consortium (Fig. 32.1) [5, 6].

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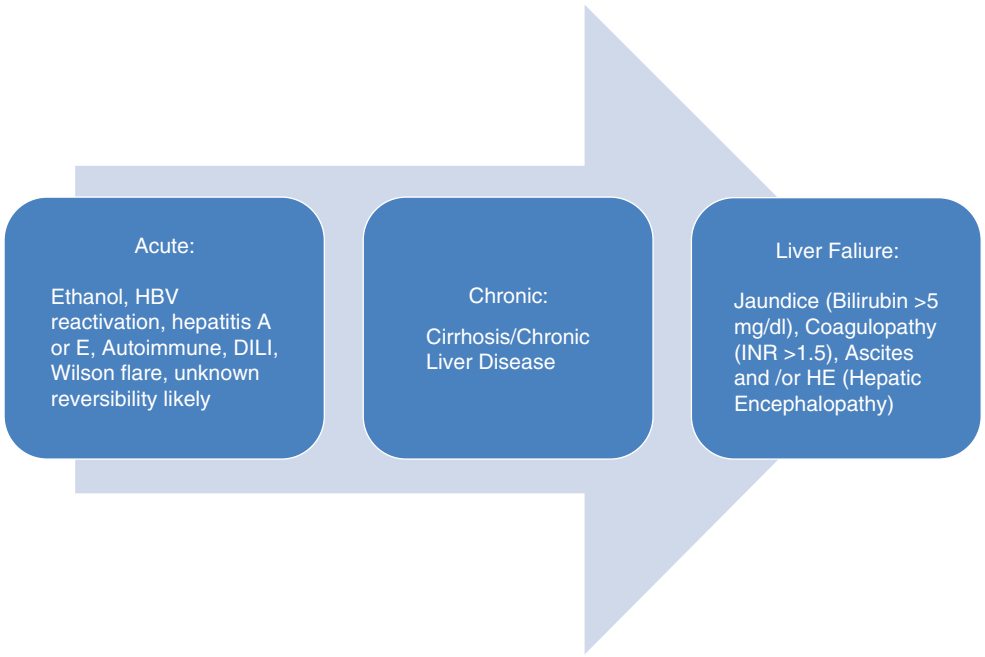

Fig. 32.1 Outline and concept of ACLF. Hepatic insult is the acute insult that leads to ACLF in patient with underlying chronic liver disease. Severity and extent of the acute insult and the stage of underlying chronic damage to liver helps in determining the outcome

Table 32.1 Comparison of the commonly accepted ACLF definition

	APASL	EASL/CLIF	NASCELD
Definition	Acute hepatic insult manifesting as jaundice and coagulopathy complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis associated with high mortality	An acute deterioration of preexisting chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure	A syndrome characterized by acute deterioration in a patient of cirrhosis due to infection presenting with two or more extrahepatic organ failure
Diagnosis	Early reversibility is likely and nontransplant interventions may affect outcome	Too late, reversibility is unlikely and nontransplant interventions may not affect outcome	Too late, reversibility is unlikely and nontransplant options may not affect outcome
Time frame	4 weeks	4–12 weeks (variable)	Not defined
Acute insult	Hepatic	Hepatic or extrahepatic (systemic)	Infection, i.e., systemic (extrahepatic)
Sepsis	Consequence/complication of liver failure	Cause/precipitant of liver failure	Cause/precipitant of liver failure
Golden window	Well defined for therapy, i.e., by 7 days SIRS or sepsis as well as for decision regarding liver transplant	No such concept	No such concept
Reversibility	Yes	Not described	Not described
Decompensated cirrhosis	Excluded	Included	Included

Defining Acute-on-Chronic Liver Failure

ACLF is defined as a clinical syndrome characterized by severe and acute hepatic dysfunction from varying insults and carries high short-term mortality [7]. The first consensus definition of ACLF was proposed by APASL in 2009 [8], and main distinguishing feature from rest of the definition remains the use of hepatic insults in defining liver failure. The APASL ACLF Research Consortium proposed a new definition in 2014 consensus statement, that is, "ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL (85 micromol/L) and coagulopathy (INR ≥ 1.5 or prothrombin activity <40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-day mortality" (see Fig. 32.1). Moreau et al. defined the ACLF on the basis of the CANONIC study as "an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure." Subsequently the duration of mortality has been reduced to 4 weeks in Western definition [9]. Main difference in various commonly used definitions has been highlighted in Table 32.1.

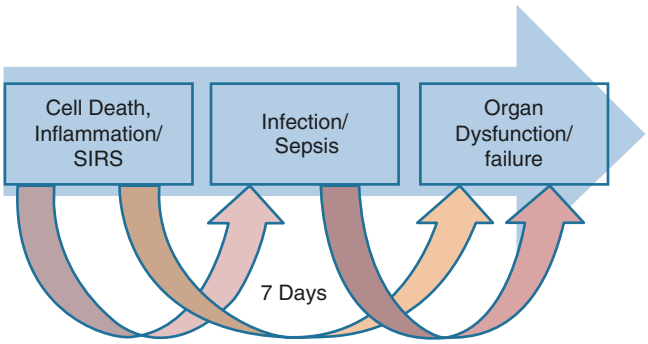

Fig. 32.2 Patients with ACLF within a period of 7 days develop SIRS, which can progress and lead to sepsis, organ failure, and mortality. This window of 7 days is known as the therapeutic window for antibiotics, organ supportive measures, nutrition, and prioritization for the liver transplantation should be done. (Modified from [2])

Concept of Functional Reserve or Critical Mass

Underlying functional reserve and severity of acute insult dictate the course of patient, that is, sudden acute insult on the healthy liver precipitates acute liver failure however, in the presence of underlying chronic liver disease; it may precipitate progressive liver failure (ACLF).

The "Golden Window" concept refers to the time in which acute insult, if removed, may lead to the reversal of the underlying liver failure, preventing extrahepatic organ failure and promoting hepatic regeneration (Fig. 32.2). This provides the window for introduction of therapies like steroids for alcoholic hepatitis and autoimmune hepatitis, antiviral therapies for HBV-related ACLF, and role of plasma exchange or other modalities that may help to tide over the acute insult and result in better transplant-free or short-term survival.

Differentiating ACLF From Acute Decompensation

Controversy remains between the East and the West in defining ACLF. As per the APASL Research Consortium (AARC) definition, when the ACLF is diagnosed, there is still significant hepatic reserve, so removing the acute insult may help in reserving the hepatic injury and improving survival. However, in prior decompensated cirrhotics, underlying functional reserve is poor, so even after removal of the acute injury, the transplant-free survival usually remains poor. Time frame for defining the acute decompensation is 3 months while ACLF is defined by a time period of 4 weeks. Acute decompensation has clumped together ACLF, hepatic, extrahepatic, sepsis-related ACLF creating confusion between the East and the West. Differentiating between the two groups will help in determining the homogenous group, guiding therapy, and prognosis of the disease (Table 32.2).

Table 32.2 Differentiating between acute-on-chronic liver failure and acute decompensation

Parameter(s)	Acute-on-chronic liver failure (ACLF)	Acute decompensation (AD)
Presentation	Hepatic insult Index	Hepatic or nonhepatic Can be index or subsequent
Identifiable precipitant	In up to 95% cases	In up to 70% cases
Time from insult to presentation	Within 4 weeks	Up to 12 weeks
Underlying cirrhosis	May or may not be present	Always present
Prior decompensation	No	With or without prior decompensation
Mortality at 1 and 3 months	33–51%	23–29%
Reversal or recovery	In half of cases	Uncommon
Clinical manifestations	Jaundice with ascites/HE/ coagulopathy	Ascites/HE/GI bleed/ sepsis/AKI, coagulopathy

What Constitutes an Acute Insult?

Origin of the acute insult forms the important difference between the two definitions. While in APASL definition it has to be hepatic insult that constitutes the acute insult, in EASL CLIF it can be hepatic or extrahepatic. Sepsis is the initial precipitating event or part of the liver failure still remains a controversial point between the two definitions. As the primary affected organ is liver, by default the insult should be directed to the primary organ, that is, the liver, such as acute exacerbation of COPD would not be called acute-on-chronic liver failure if it leads to worsening of liver functions. Similarly, patients with upper GI bleed developing renal failure, followed by jaundice or encephalopathy, would be difficult to be called ACLF.

Organ failures are an important component of ACLF; greater is the number of dysfunctional organs, poor is the outcome, and an overall increase in mortality is noted as shown by the CLIF sequential organ failures assessment (SOFA) score. Similarly, the chronology of the organ failures is also important, which may help in distinguishing between the two definitions. CLIF-SOFA score is being used in the West; however, it has been shown that simple organ failures may be helpful as simple bedside prognostication [10]. If we take the same patient, CANONIC definition will wait for the extrahepatic organ failure to set in before the diagnosis of ACLF. Since the rate or incidence of organ failure can be variable, diagnosis of ACLF could be delayed; hence, ACLF could be diagnosed with APASL definition earlier and prognostication and treatment options could be EASL CLIF definition.

Differentiating between the ACLF precipitated by the direct hepatic insult as by the extrahepatic source/sepsis is important as the cytoprotective therapy may be more relevant

in the direct insult, while anti-inflammatory therapy may be relevant in those accompanied by the extrahepatic organ failure [11]. In subgroup analysis in the CANONIC study, difference in survival was noted in the patients having hepatic insult as the precipitant compared to extrahepatic source, indicating difference in response to varying therapies [12]. In a study by Mahmud et al., of 80,383 patients with cirrhosis with a follow-up of 3.35 years, both EASL and APASL ACLF were seen in 783 patients while EASL ACLF in 4296 developed EASL ACLF alone, and APASL ACLF in 574 cases. Combined mortality was more in patients with both EASL and APASL ACLF, indicating severe disease. Median bilirubin was 2 mg/dL in EASL ACLF. It was stated that patients with APASL ACLF have higher short-term mortality, and have higher liver-related mortality, while nonhepatotrophic organ involvement was more common in EASL ACLF. This may lead to late diagnosis and can be clinically cumbersome to apply. Therefore, it was proposed that bilirubin should be reduced from >12 to ≥5 mg/dL, which may help in early diagnosis and liver-directed therapies can be assessed to reduce the mortality [13].

Etiology and Pathogenesis of the Acute Insult

Nature and severity of the acute insult determine the development and progression of the ACLF. Ascites and hepatic encephalopathy complicating liver failure are usually associated with a higher mortality (51% [Asian studies] [7] vs. 33.9% in the European counterparts [5]).

Alcohol-Related ACLF

Underlying chronicity is determined by the dose and duration of alcohol intake, which recent intake or binge usually accounts for the acute insult. Ethanol causes gut dysbiosis, causes hepatotoxicity, and promotes apoptosis secondary to an increase in reactive oxygen species, activation of the innate and adaptive immunity [14, 15]. There is an increase in the proinflammatory mediators (TNF, IL-1, IL-6, IL-17), which is noted with alcohol consumption, while a decrease in anti-inflammatory mediators (adiponectin and adenosine) is seen [16]. Impaired regeneration of liver is noted by limiting DNA synthesis. Chronic alcohol consumption leads to deranged proliferation of the liver progenitor cells as seen with low levels of tumor necrosis factor and IL-6 [17].

Hepatitis B Infection

Reactivation of hepatitis B on the background of underlying compensated cirrhosis or acute infection with hepatitis B in underlying CLD can precipitate ACLF. Eight percent of the patients with acute flare may develop decompensation [18]. Genetic heterogeneity plays an important role in response to acute insult; risk of HBV-related ACLF was increased with rs3129859 at human leukocyte antigen [19]. Similarly, presence of HBV basal core promoter/pre-core mutations, such as T1753V, A1762T, G1764A, A1846T, G1896A, and G899A, was related with an increased risk [20]. Changes in the immunological control and reconstitution of host response account for the reactivation of hepatitis B. An increase in the number of HBeAg and HBcAg specific T cells mediates the liver injury [21]. It can be seen spontaneously or secondary to intensive chemotherapy or immunosuppressive therapy [22] or following rituximab therapy [23].

Acute Viral Hepatitis

Hepatitis E virus (HEV) has been associated with ACLF and high mortality in India while cases from the West are usually sporadic [24]. Role of hepatitis E in precipitating ACLF in the West is not known. HEV induces cell-mediated immunity damage and increase in type I and II helper cells [25]. Increase in cytokines such as IFNγ, IL-2, and TNF is noted mediating the liver damage. Superinfection with hepatitis A and E has been associated with ACLF and hepatitis E has been associated with more severe form of ACLF and with higher mortality [26].

Drug-Induced Liver Injury

Hepatotoxic drugs and complementary and alternative medications have been implicated as a causative factor for drug-induced liver injury. Antitubercular remains an important cause for drug-induced liver injury. Up to 1.8–5.7% of the ACLF cases have been attributed to drug-induced liver injury. Owing to aberrant metabolism, reduced hepatic clearance, and altered excretion, patients with cirrhosis are prone to DILI [27]. High mortality has been attributed to DILI [28].

Sepsis and ACLF

Patients secondary to cirrhosis have deficient innate and adaptive immunity, which denotes inability to clear the infection [29]. Sepsis is a consequence or part of ACLF remains a controversial issue. Sepsis is defined as an extrahepatic insult in EASL CLIF definition. The term "infection-related ACLF" (I-ACLF) has been proposed; however, liver failure remains a late event and extrahepatic organ failures remain the major cause of mortality [30, 31]. Reduced HLD-DR expression, reduction in myeloid and plasmacytoid dendritic cells, and increased interferon production increase the risk of sepsis [32]. APASL defines sepsis as part or consequence of liver

failure and preventing sepsis by modulating the immune system should help in preventing organ failure.

Acute Variceal Bleed

Acute variceal bleed has been taken both as the precipitating event and as a defining event for acute decompensation. In CANONIC study, acute variceal bleed was the acute event in 13.8% of the patients [5]. However, if the acute variceal bleed results in jaundice and coagulopathy that fulfills the criteria of liver failure, the term ACLF can be used.

Autoimmune Hepatitis

Severe autoimmune hepatitis (AIH) can present as jaundice, encephalopathy, and coagulopathy, manifesting as ALF or ACLF. It is seen in up to 20% of the patients [33]. The spectrum of AIH as acute insult has not been clearly defined in Western studies. AIH is usually seronegative, with normal to high serum immunoglobulin G levels, and is characterized by parenchymal collapse, and advanced fibrosis (F3/F4), ductular reactions, and lymphoplasmacytic inflammation are predominant findings [34, 35].

Other Insults

Other nonhepatotrophic insults such as TIPS, TACE, or any surgery that can also lead to direct hepatic injury can account for ACLF.

Defining the Chronic Etiology

Diagnosis of underlying chronicity can be difficult in setting of the ACLF. Clinical History, physical examination to look for signs of portal hypertension, imaging (ultrasonography or CT), endoscopy can help in identifying underlying cirrhosis. If there is no conclusive evidence of cirrhosis, transjugular liver biopsy may be done to ascertain the cause [36]. There have been changing trends in etiologies of the chronic liver disease, that is, initially hepatitis B was the commonest etiology for the chronic liver disease; however, recent data suggest that etiology of the chronic etiology remains same in the West and the East [37, 38].

Pathophysiology of ACLF

Inflammation developing due to cell death remains the hallmark of ACLF, with an increase in white cell count, C-reactive protein, and cytokines, such as interleukins (IL)-6, IL-1β, and IL-8 [39]. Acute stress is an inducer that leads to tissue injury and releases DAMPs, and leads to damage via inflammation and immune-mediated mechanism. Increase in both pro- and anti-inflammatory cytokines is noted in ACLF, that is, TNF-a, sTNF-aR1, sTNF-aR2, IL-2, IL-2R, IL-6, IL-8, IL-10, and IFN-ϒ.

Inflammation

Inducers of the inflammation engage with the effectors, leading to the generation of the inflammatory response. Failed immune-tolerant mechanism, direct virulence of the microorganism, and excessive immune-mediated damage lead to tissue damage. Endogenous or exogenous inducers can initiate the immune response.

ACLF is usually complicated by the infections that are associated with significant mortality and morbidity.

Secondary to portal hypertension, altered bowel flora, and direct damage to the intestinal barrier, increased translocation of bacteria is noted. With the increase in severity of the liver dysfunction, increased migration of the bacteria is noted [40]. Increased cytokines like IL-6 and TNF-α and modulation of the cytokines with changing the gut bacteria, that is, Ruminococcaceae and Lachnospiraceae support the role of the cytokine in mediating the damage and altering the gut bacteria as means of therapeutic strategy [41] (Fig. 32.3).

Immunological Basis of ACLF

Dysfunctional immune system, over exaggerated immune response, altered in the processing of the antigen and altered effector response leads to increased systemic inflammatory response and sepsis like state in ACLF characterized by increased IL-6 and reduced HLA-DR expression [42]. Increased reactive oxygen species and oxidative burst are noted secondary to an increase in neutrophils, which are predominantly dysfunctional. A decrease in synthesis of TNF-α is noted secondary to HLA-DR expression, which is noted in ACLF patients [43]. MER receptor tyrosine is increased in the ACLF, and it is the negative regulator of immune cells and is expressed on the monocytes/macrophages, DCs, and epithelial cells. Increase in the former is associated with poor outcomes [44]. It has been correlated with levels of inflammatory cytokines and increased predisposition with infections. Increase in T-regulatory cells (T-reg) that cause inhibition of the monocyte and macrophages via an increase in interferon-ϒ production and higher ratio of T-reg to Th17 cells is correlated with survival. Ammonia levels and DAMPs have been shown to modulate the immune system, and high ammonia reduces the neutrophil activation, monocyte HLA DR expression, and migration capacities of the neutrophils [45]. Increased expression of the CXCR1/CXCR2 receptors

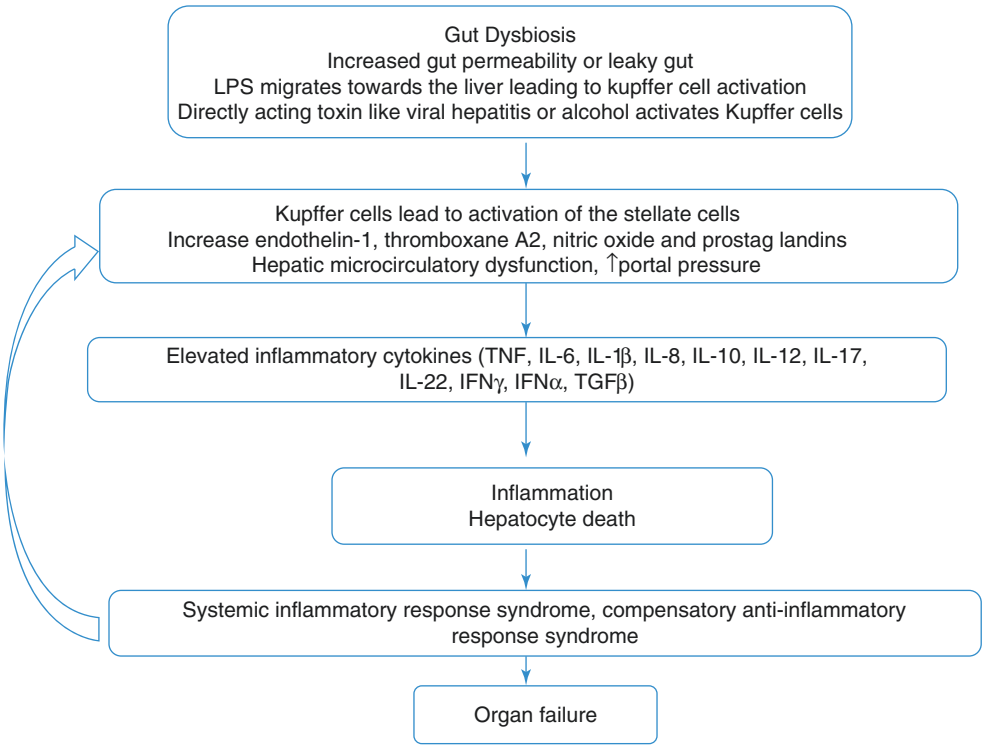

Fig. 32.3 Mechanism of injury in ACLF. Acute insult activates the Kupffer cells in hepatic sinusoids, leading to the release of the inflammatory mediators. Increase in gut permeability allows immune cells and endotoxin to migrate toward liver. An increase in endothelin-1, thromboxane *A2*, nitric oxide, and prostaglandins leads to hepatic microcirculatory dysfunction and increases portal pressure. An increase in hepatic necrosis and apoptosis is noted secondary to neutrophil infiltration and ROS species. These changes lead to injury, state of immunoparalysis, SIRS, and CARS and predispose to organ failure. (Modified from [7])

Table 32.3 Pathophysiology of sepsis in *ACLF* and immune changes (pro- and anti-inflammatory response

Sepsis in ACLF				
Mechanism of sepsis – bacterial translocation, bacterial infection	Proinflammatory response	Anti-inflammatory response	Upregulation of genes that regulate the innate immune response – Neutrophils: phagocytic defect, Monocytes: DR loss, NK cells	Downregulation of genes that regulate the adaptive immune response – T-cell exhaustion, Inability to proliferate, Increased apoptosis
Phases of sepsis	Early phase–hyper inflammation response (SIRS/sepsis)		Late phase: Immunosuppressive phase (CARS)	
Results of sepsis	Organ failure		Organ dysfunctions	

and reduction of the phagocytic capacity of the neutrophils in alcoholic hepatitis contribute to organ failure and high mortality [46].

There is a defect in the innate immunity also. There is activation of Kupffer cells via toll-like receptors and damage-associated molecular patterns (DAMPs) in response to the lipopolysaccharides (LPS). M2 variants of Kupffer cells are activated and cause anti-inflammatory effect via an increase in transforming growth factor-β (TGF-β) [47]. Stimulation of Kupffer cells induces activation of the hepatic stellate cells leading to release of endothelin-1 and thromoboxane-A2 causing disturbances of hepatic microcirculation and rapid aggravation of portal hypertension [48].

There is an immunological imbalance between pro- and anti-inflammatory responses and this leads to a sepsis-like state in ACLF. Activated immune cells in ACLF are dysfunctional and are in a state of immune paralysis leading to an increase in SIRS and increased predisposition to infections (Table 32.3).

Role of Histology in Predicting Outcome in ACLF

Biopsy in ACLF is done through the transjugular route owing to the presence of ascites and underlying coagulopathy. Poor prognostic markers on biopsy are marked ductular proliferation, coarse inspissated ductular bile plugs, eosinophilic degeneration of hepatocytes, foci of confluent/bridging necrosis, higher apoptosis, pericellular fibrosis, Mallory's hyaline, and advanced fibrosis [49]. In a cohort of 107 patients, a score derived from ballooning degeneration and Mallory-Denk bodies in the presteroid biopsies samples, helped in predicting the response to steroids. Area under the

curve for combined Mallory-Denk body and ballooning degeneration with a score >5 for predicting nonresponse was 0.731 [50]. Risk of infection is increased with a high degree of bilirubinostasis.

Disease Prognostication and Scoring Models

Severity of ACLF, underlying multiorgan failure, and progression of organ failure and ACLF should be taken into account while considering for early LT. MELD score ≥28 and APACHE ≥ 12 are associated with high mortality. Nonresponse to steroid at day 7 is associated with high mortality and early transplant is associated with high survival rate at 6 months (77 ± 8 vs. 8%, $p < 0.001$) [51]. In autoimmune hepatitis, MELD score >27 (83.3% sensitivity, 78.9% specificity, area under the receiver operating characteristic curve 0.86) and presence of hepatic encephalopathy, ≥F3 fibrosis (advanced fibrosis) were associated with poor response to steroids and should be referred to early transplantation [52].

Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II), model for end-stage liver disease (MELD), and CLIF-SOFA score have been used to assess disease severity and disease prognostication at the baseline [5]; however, they take into account mortality after the inclusion of the extrahepatic organ failure and are bit cumbersome. Simple organ failure is easy to recall and can be used as bedside assessment tool for predicting mortality [53].

APASL has established a more accurate *ACLF specific score*, *AARC score*, for prognostication of ACLF that has shown to provide better performance than other scores. It is a dynamic model consisting of bilirubin, creatinine, PT-INR, lactate, and hepatic encephalopathy and has been proposed on the basis of AARC database of 1402 patients. It is a dynamic score with an increase in score at day 4 and day 7 from 5 to 6 to 11 indicates high mortality, while persistent grade I or II organ failure indicates improved survival (Table 32.4). AARC score has good predictability with area under the curve of 0.81 and sensitivity and specificity of 75 and 81% negative predictive value for 28 and 90 days [54].

Similarly seen in the Western study, grade of ACLF at the time of diagnosis may help in guiding resolution of the disease, resolution of ACLF was noted in 55% of grade 1 ACLF while 15% of the grade 3 ACLF, and final grade is usually reached by the end of day 7; hence, calculation of the score at day 7 could help in predicting the 28- and 90-day mortality [55].

Baseline MELD > 28, AARC score > 10, advanced HE in the absence of overt sepsis, or multiorgan failure indicates poor prognosis.

Management of ACLF and Organ Failures

Bridge therapies, specific therapies, and definitive therapies along with general measures and nutrition form the basis of management of ACLF. Differentiating ACLF from decompensated cirrhosis is necessary as the two carry different prognosis. Acute insult should be evaluated, preventing inflammatory injury, and protecting organ failure should be hallmark of underlying management (Fig. 32.4).

Need for ICU Care

Patients with ACLF should be looked for presence of sepsis, organ failures, and underlying shock or hypotension. Presence of SIRS should be taken as a sign of occult sepsis. Antibiotics (prophylactic or therapeutic) should be guided by local hospital or community data, severity of infection, and nosocomial or community-acquired infections. Patients with ACLF and sepsis carry grave prognosis with mortality reaching up to 80% [56]. Terlipressin in combination is used in septic shock, which may help in reserving the shock and improving tissue microcirculation [57]. Patients with ACLF are predisposed to paracentesis-induced circulatory dysfunction (PICD) even with less than 5 L of paracentesis (modest volume paracentesis), and albumin has shown to reduce the

Table 32.4 AARC scoring and grading system

AARC score and ACLF grade						
Points	*Total bilirubin (mg/dL)*	*INR*	*Creatinine (mg/dL)*	*Lactate (mmol/L)*	*HE grade*	*Score maximum 15, minimum 5*
1	<15	<1.8	<0.7	<1.5	0	
2	15–25	1.8–2.5	0.7–1.5	1.5–2.5	I–II	
3	>25	>2.5	>1.5	>2.5	II–IV	
Grade	*Score*	*28-day mortality*	*Action required*			
I	5–7	12.7%	A potentially recoverable group			
II	8–10	44.5%	Needs special monitoring			
III	11–15	85.9%	Demands immediate interventions for improved outcome			

For a baseline AARC score of ≥10, with each one-unit increase, the day 7 mortality increased sharply compared to the patients who presented with a score of <10 at baseline (20% vs. 4%). The AARC score also predicts the day 28 and day 90 survival

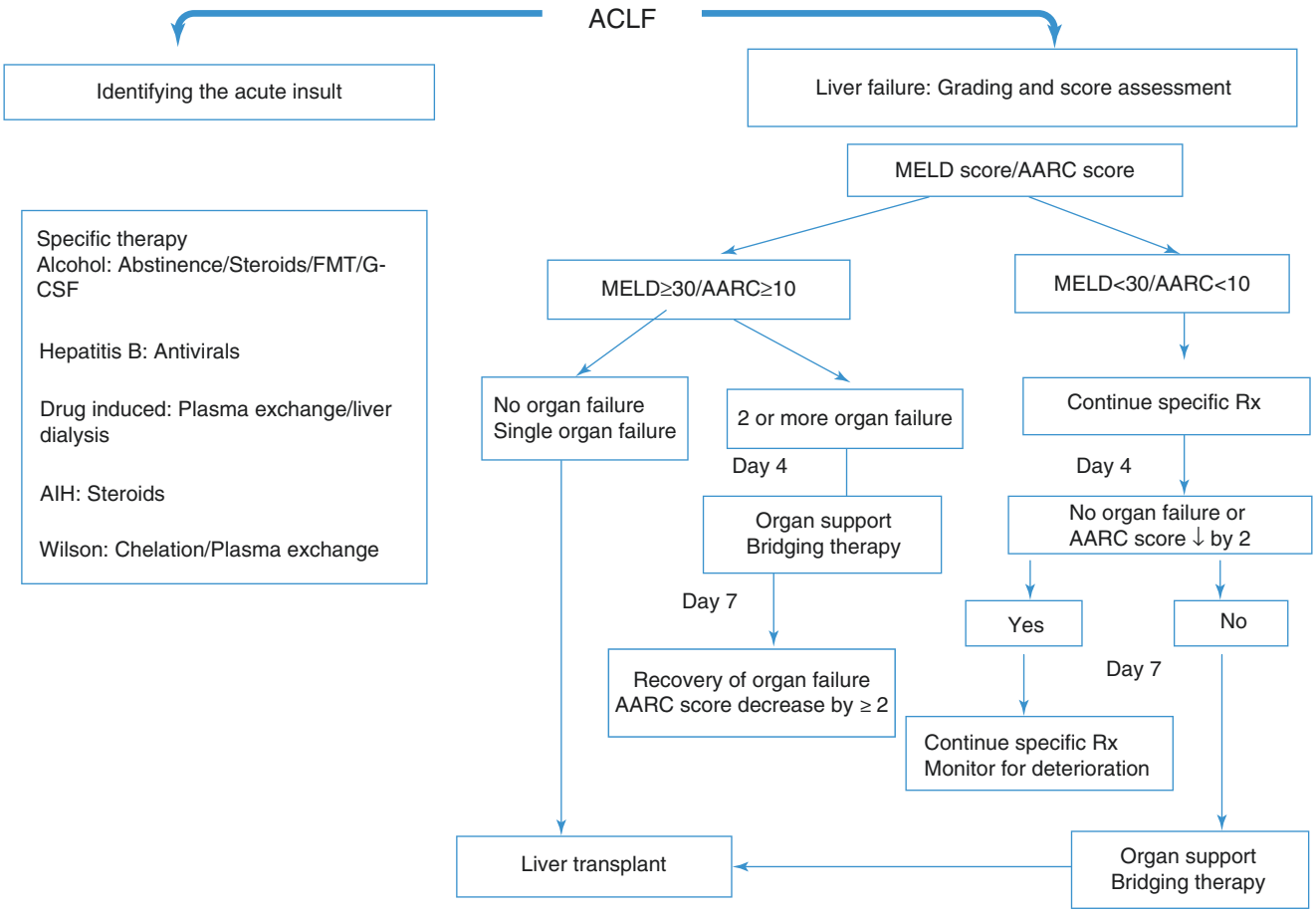

Fig. 32.4 Algorithmic management of patients with acute-on-chronic liver failure

incidence of PICD (70% vs. 30%, $p = 0.0010$) [58]. Besides being used as a plasma expander, albumin binds to prostaglandin E2 (PGE2), reduces the risk of infections, and has ROS scavenging activities, protecting endothelial integrity. Albumin has immune-modulatory effects, binding molecular patterns (i.e., lipopolysaccharide [LPS], DNA fragments), inflammatory mediators, DAMPs (hyaluronic acid, mitochondrial DNA), and reactive nitrogen species. Albumin has been shown to have effect on innate immune system. Guiding serum concentration of albumin could be a therapeutic target [59, 60].

Hepatic encephalopathy is noted in 40% of the patients and requires ICU care [4]. Increasing grade of encephalopathy indicates poor prognosis and higher mortality. Inflammation and impairment of brain energy kinetics play a part in pathophysiology of encephalopathy in ACLF. Baseline ammonia levels correlate with severity of encephalopathy and targeted reduction in ammonia may be given empirically.

Renal dysfunction is noted in 30% of the ACLF and causes include hepatorenal syndrome (HRS), acute tubular necrosis, sepsis, or hypokalemia and carries high mortality at day 7. Only one-third of the patients show response to terlipressin and albumin [61]. Terlipressin, given as continuous infusion, has been shown to be superior to noradrenaline in the management of ACLF AKI [62]. AARC score, severity of AKI, and MELD have been shown to be predictors of response [63].

Concept of Organ Failure and Dysfunction

Differentiating between dysfunction and organ failure is useful in determining the extent of organ damage, determining the progression or reversal of the organ damage, which may help in listing for the transplant or need for the palliative care. Organ dysfunction may be initial and reversible stage of the sepsis that may be reversible and progression to failure is predictive of increased mortality. They are not part of definition but may be used in prognostication of the patients. Liver, kidney, and brain are the organs of utility and involvement of circulatory and respiratory organs may be sign of futility, contraindicating liver transplant (Table 32.5).

Table 32.5 Defining the kidney and cerebral failure/dysfunction in ACLF

Organ	Organ dysfunction	Organ failure
Renal	Serum creatinine >1.5 mg/dL Early use of vasoconstrictors Targeting inflammation Combination of vasoconstrictors	Serum creatinine >1.1 mg/dL May benefit from anti-inflammatory strategies (albumin, *N*-acetylcysteine) and maintaining MAP Role of biomarkers (urine NGAL and IL-18) needs to be evaluated
Cerebral	Grade III/IV hepatic encephalopathy High-volume plasma exchange or albumin dialysis Decreasing systemic inflammation	Grade I/II hepatic encephalopathy Neuroinflammation plays a role Early detection of cerebral edema by DTI/DWI Ammonia-targeted therapy require more trials and validation

Specific Treatment

Alcoholic Hepatitis

Aggressive nutrition (1.5–2.0 g protein/kg per day and 35–40 kcal/kg), suppression of inflammation (corticosteroids, pentoxifylline, IL-1 receptor antagonist [Anakinra] is in phase II RCT, apoptosis signal regulating kinase-1 (ASK-1) inhibitor, modulating gut-liver axis, drug targeting regenerative pathways, that is, granulocyte colony-stimulating factor (G-CSF); antioxidants, that is, *N*-acetylcysteine are being used for management of alcoholic hepatitis.

HBV Treatment

With early reduction of hepatitis B DNA (reduction of 2-log of DNA achieved with 2 weeks), improved survival is noted [64]. Nucleos(t)ide should be started immediately at presentation in HbsAg-positive patients presenting with reactivation without waiting for HBV DNA report.

Autoimmune Hepatitis

Twenty percent of the patients with severe AIH can manifest as acute liver failure or ACLF [33]. As per the AARC cohort, AIH as etiology of ACLF is seen in 2.8% of the total ACLF cohort [65]. Steroids can be used in autoimmune hepatitis and have been shown to improve 90-day survival [47]. As mentioned before, advanced age, MELD > 27, fibrosis ($F \geq 3$), and hepatic encephalopathy are predictors of poor response to steroids [47].

Liver Support Devices

Removing the toxins and reducing the liver injury and promoting regeneration of the liver form the basis of artificial liver support devices. Liver injury is primarily driven by the cytokine burst [66]. The toxins, cytokines, and vasoactive substances accumulate secondary to the failing liver in addition to the toxins produced by the gut microbiota. These toxins promote inflammation, dysfunction of the innate, and adaptive immunity.

Data on the use of artificial liver support devices in ACLF are limited. There is no clarity regarding the use of liver support as per the APASL and EASL guidelines for ACLF. ALSS (the Molecular Adsorbent Recirculating System, MARS®; Gambro, Sweden) and the fractionated plasma separation and adsorption (FPSA; the Prometheus System®; Fresenius Medical Care, Germany) are the commonly used liver dialysis devices. These devices are based on albumin dialysis and are aimed at protecting the clinical and neurological status of individual. However, these devices, despite showing reduction in ammonia and bilirubin, have failed to show any survival benefit [67, 68] (Table 32.6).

Plasmapheresis has been used to aid the recovery of the failing liver, and as a bridge to transplant, and acts by removal of a wide range of toxins [69]. In a retrospective analysis by Wan Yue-Meng et al., a sicker cohort of patients in plasma exchange group has shown a better survival compared to those managed with the standard therapy [70]. In a study by Maiwall et al., plasma exchange was compared with Prometheus, which has shown to improve the hepatic encephalopathy and MELD score; however, no survival benefit or change in transplant free survival was noted [71] (see Table 32.6).

However, these treatment modalities require strict protocol and can be used in a selected group of patients. Further RCTs are required to prove the beneficial effect of the liver support systems.

Liver Transplantation in ACLF

Definite treatment for ACLF remains liver transplantation. In the absence of any obvious contraindications, patients should be counselled regarding the need of liver transplantation. ACLF is characterized by high short- and medium-term mortality, ranging from 34 to 50% [2, 5]. Patients develop infection, sepsis usually within first week, so before the patients are "too sick to transplant," serial assessment should be done for prioritization for liver transplantation [72]. Underlying sepsis, vasopressor requirement, psychological support, respiratory failure, or renal failure leads to high waitlist mortality. Recently one study showed mortality in the range of 67% in ACLF patients on waitlist for transplantation [73].

Table 32.6 Artificial liver support system in acute-on-chronic liver failure

Study	Population(n)	Device	Results
Ash et al. (1994) [79]	Mixed (some with ACLF and others with ALF) (56)	Liver dialysis vs. SMT	Improved HE and hemodynamic profile Increased bleeding in patients with DIC
Sen et al. (2004) [80]	ACLF—severe alcoholic hepatitis (18)	MARS + SMT vs. SMT (9 MARS; 9 controls)	Improvement of HE No hemodynamic changes No changes in plasma cytokines and ammonia levels
Laleman et al. (2006) [81]	ACLF—severe alcoholic hepatitis (18)	MARS + SMT vs. Prometheus + SMT or SMT alone (3d)	Better hemodynamic improvement in MARS with less bilirubin reduction than Prometheus or SMT alone
Banares et al. (2013) [65]	ACLF: bilirubin >20 mg/dL and/or HE greater than grade II and/or HRS (189)	MARS + SMT vs. SMT Up to 10 sessions (6–8 h)	No changes in survival Improvement in HE Improvement in HRS No differences in overall adverse event
Kribben et al. (2012) [66]	ACLF (145)	Prometheus + SMT vs. SMT Up to 8–11 sessions	No changes in overall survival Survival benefit in post hoc analysis in type I HRS and MELD score >30
Maiwall et al. (2017) [69]	ACLF (636)	Prometheus vs. plasma exchange vs. SMT	Improves HE and MELD No change in transplant free survival
Deshpande et al. (2018) [82]	ACLF (16)	Plasma exchange	No change in 28-day survival

HE hepatic encephalopathy, *HRS* hepatorenal syndrome, *SMT* standard medical therapy, *MARS* molecular adsorbent recirculating system, *MELD* model for end-stage liver disease

Patients with MELD more than 28, AARC score >10, and > grade 2 encephalopathy in the absence of any contraindication should be listed for early transplantation. Analysis of ACLF-AARC cohort of 1021 patients showed that MELD > 27 requires listing and presence of MELD > 30 and advanced stage of encephalopathy is associated with high mortality [74]. Dynamic scores such as AARC score can help in better prediction model for listing for liver transplant. Many studies have shown excellent outcomes with transplant in ACLF with 5-year survival more than 80% [75].

Newer Therapeutics in ACLF

The definitive therapy for ACLF, that is, liver transplant is often limited and newer options like regenerative therapy, stem cell mobilization, or immunomodulatory therapies have been proposed.

Garg et al. used G-CSF for ACLF patients. Forty-seven patients were randomized to G-CSF (n = 23) and standard (n = 24) and found that the 2-month survival was 66% compared to 26% (p = 0.001) [76]. Similarly, in the study by Duan et al., 3-month survival was 48% in G-CSF group vs. 21% in the standard treatment group [77]. Similarly, mesenchymal stem cell therapy was used by Shi et al. in hepatitis B-related ACLF, and 3-month mortality was 79.2% on the UC-MSC survived vs. 52.5% in the control group [78].

Prevention of ACLF

Identification of acute insult, universal immunization against hepatitis B, screening for hepatitis before starting immunosuppressants, mitigating the gut flora in NASH, alcoholic hepatitis, and obesity can help in preventing the ACLF. Educating the patients, attendants, the primary care physician about ALT level can help in preventing the DILI. Early referral can help the patient reach the tertiary care center in the "golden window," without sepsis or any organ failure, and can help in decreasing mortality and early referral for transplant.

Conclusion

ACLF is a serious and often a progressive form of liver failure with high short-term mortality. There are large studies from the East and the West, which may help in defining the homogeneity and having a universal acceptable definition. The aim of the management of ACLF patients should be to ameliorate the acute insult, achieve immune homeostasis by countering the systemic inflammatory response, and early diagnosis of organ dysfunction to prevent organ failure. Liver transplant remains the definitive option, and the role of bridge therapies and artificial liver support system remains to be evaluated in a greater detail.

References

1. Ohnishi H, Sugihara J, Moriwaki H, Muto Y. Acute-on-chronic liver failure. [in Japanese]. Ryoikibetsu Shokogun Shirizu. 1995;(7):217–9.
2. Sarin SK, Choudhury A. Management of acute-on-chronic liver failure: an algorithmic approach. Hepatol Int. 2018;12(5):402–16.
3. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. A systematic review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality. Liver Int. 2013;33(1):40–52.
4. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL): an update. Hepatol Int. 2019;13(4):353–90.
5. Moreau R, et al. Acute on chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426–37.
6. Choudhury A, Sarin SK. Letter to the editor: tale of two ACLF definitions: choices are getting clearer. Hepatology. 2019;70(6):2233–5.
7. Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. Nat Rev Gastroenterol Hepatol. 2016;13(3):131–49.
8. 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;3:269–82.
9. Arroyo V, Moreau R, Jalan R, Gines P, EASL-CLIF Consortium CANONIC Study. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. J Hepatol. 2015;62(Suppl):S131–43.
10. Agrawal S, Duseja A, Dhiman RK, Chawla Y. Simple organ failure count versus CANONIC grading system for predicting mortality in acute-on-chronic liver failure. J Gastroenterol Hepatol. 2015;30:575–81.
11. Garcia-Tsao G. Acute-on-chronic liver failure: an old entity in search of clarity. Hepatol Commun. 2018;2(12):1421–4.
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. Hepatology. 2015;62:232–42.
13. Mahmud N, Kaplan DE, Taddei TH, Goldberg DS. Incidence and mortality of acute-on-chronic liver failure using two definitions in patients with compensated cirrhosis. Hepatology. 2019;69:2150–63.
14. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011;141:1572–85.
15. Malhi H, Kaufman RJ. Endoplasmic reticulum stress in liver disease. J Hepatol. 2011;54:795–809.
16. Tilg H, Moschen AR, Kaneider NC. Pathways of liver injury in alcoholic liver disease. J Hepatol. 2011;55:1159–61.
17. Dubuquoy L, Louvet A, Bataller R, Mathurin P. Progenitor cell expansion and impaired hepatocyte regeneration in explanted livers from alcoholic hepatitis. Gut. 2015;64:1949–60.
18. Sheen IS, Liaw YF, Tai DI, Chu CM. Hepatic decompensation associated with hepatitis B E antigen clearance in chronic type B hepatitis. Gastroenterology. 1985;89:732–5.
19. Tan W, Xia J, Dan Y, et al. Genome-wide association study identifies HLA-DR variants conferring risk of HBV-related acute-on-chronic liver failure. Gut. 2018;67(4):757–66.
20. Xu Z, Ren X, Liu Y, et al. Association of hepatitis B virus mutations in basal core promoter and precore regions with severity of liver disease: an investigation of 793 Chinese patients with mild and severe chronic hepatitis B and acute-on-chronic liver failure. J Gastroenterol. 2011;46:391–400.
21. Aoki J, Kowazaki Y, Okamoto R, Kimura K. Kinetics of peripheral hepatitis B virus-specific CD8+ T cells in patients with onset of viral reactivation. J Gastroenterol. 2013;48:728–37.
22. Mikulska M, Nicolini L, Signori A, et al. Hepatitis B reactivation in HBsAg negative/HBcAb positive allogeneic hematopoietic stem cell transplant recipients: risk factors and outcome. Clin Microbiol Infect. 2014;15:8.
23. Martin ST, Cardwell SM, Nailor MD, Gabardi S. Hepatitis B reactivation and rituximab: a new boxed warning and considerations for solid organ transplantation. Am J Transplant. 2014;14(4):788–96.
24. Acharya SK, Kumar Sharma P, Singh R, Kumar Mohanty S, Madan K, Kumar Jha J, et al. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. J Hepatol. 2007;46(3):387–94.
25. Tripathy AS, Das R, Rathod SB, Gurav YK, Arankalle VA. Peripheral T regulatory cells and cytokines in hepatitis E infection. Eur J Clin Microbiol Infect Dis. 2012;31:179–84.
26. Zhang X, Ke W, Xie D, Gao Z. Comparison of effects of hepatitis E or A viral superinfection in patients with chronic hepatitis B. Hepatol Int. 2010;4:615–20.
27. Devarbhavi H, Dierkhising R, Sandeep MS, Adarsh CK. Single-center experience with drug induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol. 2010;105:2396–404.
28. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ, Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109:950–66.
29. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol. 2014;61:1385–96.
30. Bajaj JS, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology. 2014;60:250–6.
31. Jalan R, Stadlbauer V, Sen S, Mookerjee R. 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. 2012;16:R227.
32. Khanam A, Trehanpati N, Sharma BC, Sarin SK. Altered frequencies of dendritic cells and IFN-gamma-secreting T cells with granulocyte colony stimulating factor (G-CSF) therapy in acute-on-chronic liver failure. Liver Int. 2014;34:505–13.
33. Yeoman AD, O'Grady JG, Heneghan MA. Prognosis of acute severe autoimmune hepatitis (AS-AIH): the role of corticosteroids in modifying outcome. J Hepatol. 2014;61:876–82.
34. Stravitz RT, Lefkowitch JH, Fontana RJ, Gershwin ME, Leung PS, Sterling RK, et al. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology. 2011;53:517–26.
35. Anand L, Choudhury A, Bihari C, Sarin SK, for APASL ACLF (AARC) Working Party. Flare of Autoimmune Hepatitis causing acute on chronic liver failure (ACLF): diagnosis and response to corticosteroid therapy. Hepatology. 2019;70(2):587–96. https://doi.org/10.1002/hep.30205.
36. Rastogi A, Kumar A, Sakhuja P, Bihari C, Gondal R, Hissar S, et al. Liver histology as predictor of outcome in patients with acute-on-chronic liver failure (ACLF). Virchows Arch. 2011;459:121–7.
37. Jha AK, Nijhawan S, Rai RR, Nepalia S, Jain P, Suchismita A. Etiology, clinical profile and inhospital mortality of acute-on chronic liver failure: a prospective study. Indian J Gastroenterol. 2013;32(2):108–14.
38. Abbas Z, Shazi L. Pattern and profile of chronic liver disease in acute on chronic liver failure. Hepatol Int. 2015;9:366–72.
39. Sole C, Sola E, Morales-Ruiz M, Fernàndez G, Huelin P, Graupera I, et al. Systemic inflammatory response profile in acute-on-chronic liver failure and its relationship with prognosis. Sci Rep. 2016;6:32341.
40. Bellot P, García-Pagán JC, Francés R, Abraldes JG, Navasa M, Pérez-Mateo M, et al. Bacterial DNA translocation is associ-

ated with systemic circulatory abnormalities and intrahepatic endothelial dysfunction in patients with cirrhosis. Hepatology. 2010;52:2044–52.
41. Chen Y, Guo J, Shi D, Li L. Gut dysbiosis in acute-on-chronic liver failure and its predictive value for mortality. J Gastroenterol Hepatol. 2015;30:1429–37.
42. Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghöner A, Vidacek D, Siewert E, et al. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. J Hepatol. 2005;42:195–201.
43. Xing T, Li L, Cao H, Huang J. Altered immune function of monocytes in different stages of patients with acute on chronic liver failure. Clin Exp Immunol. 2007;147:184–8.
44. Bernsmeier C, Pop OT, Singanayagam A, Triantafyllou E, Patel VC, Weston CJ, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. Gastroenterology. 2015;148:603–615.e14.
45. Agrawal T, Maiwall R, Pande A, Jagdish R, Sarin SK, Trehanpati N, et al. Circulating DAMPs and ammonia levels modulate immune dysfunction in acute liver failure. Conference paper. AASLD 2018, San Francisco, CA, November 2018.
46. Khanam A, Trehanpati N, Riese P, Rastogi A, Guzman CA, Sarin SK. Blockade of neutrophil's chemokine receptors CXCR1/2 abrogate liver damage in acute-on-chronic liver failure. Front Immunol. 2017;8:464.
47. Wan J, Benkdane M, Teixeira-Clerc F, Bonnafous S, Louvet A, Lafdil F, et al. M2 Kupffer cells promote M1 Kupffer cell apoptosis: a protective mechanism against alcoholic and nonalcoholic fatty liver disease. Hepatology. 2014;59:130–42.
48. Keshavarzian A, Holmes EW, Patel M, Iber F, Fields JZ, Pethkar S. Leaky gut in alcoholic cirrhosis: a possible mechanism for alcohol-induced liver damage. Am J Gastroenterol. 1999;94:200–7.
49. Rastogi A, Kumar A, Sakhuja P, Bihari C, Gondal R, Sarin SK, et al. Liver histology as predictor of outcome in patients with acute-on-chronic liver failure (ACLF). Virchows Arch. 2011;459(2):121–7.
50. Shasthry SM, Rastogi A, Bihari C, Vijayaraghavan R, Arora V, Sarin SK. Histological activity score on baseline liver biopsy can predict non-response to steroids in patients with severe alcoholic hepatitis. Virchows Arch. 2018;472(4):667–75.
51. 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;365:1790–800.
52. Anand L, Choudhury A, Bihari C, Sharma BC, Kumar M. Flare of autoimmune hepatitis causing acute on chronic liver failure: diagnosis and response to corticosteroid therapy. Hepatology. 2019;70(2):587–96.
53. Agrawal S, Duseja A, Gupta T, Dhiman RK, Chawla Y. Simple organ failure count versus CANONIC grading system for predicting mortality in acute-on-chronic liver failure. J Gastroenterol Hepatol. 2015;30(3):575–81.
54. Choudhury A, Jindal A, Sarin SK, for the APASL ACLF Working Party, et al. Liver failure determines the outcome in patients of Acute-on-Chronic Liver Failure (ACLF)-comparison of APASLACLF Research Consortium (AARC) and CLIF-SOFA model. Hepatol Int. 2017;11(5):461–71.
55. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. Gut. 2017;66(3):541–53.
56. Choudhury A, Kumar M, Sharma BC, Maiwall R, Sarin SK, et al. Systemic inflammatory response syndrome in acute-on-chronic liver failure: relevance of "golden window": a prospective study (ACLF). J Gastroenterol Hepatol. 2017;32(12):1989–97.
57. Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Sarin SK, et al. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int. 2017;37(4):552–61.
58. Arora V, Vijayaraghavan R, Maiwall R, Sahney A, Kumar G, Sarin SK, et al. Paracentesis-induced circulatory dysfunction with modest-volume paracentesis is partly ameliorated by albumin infusion in ACLF. Hepatology. 2019; https://doi.org/10.1002/hep.31071.
59. Arroyo V, Clària J. Acute-on-chronic liver failure, human serum albumin, and immune modulation: the beginning of an exciting adventure. Clin Gastroenterol Hepatol. 2018;16(5):633–6.
60. China L, Maini A, Skene SS, et al. Albumin counteracts immunosuppressive effects of lipid mediators in patients with advanced liver disease. Clin Gastroenterol Hepatol. 2018;16:738–47.
61. Jindal A, Bhadoria AS, Maiwall R, Sarin SK. Evaluation of acute kidney injury and its response to terlipressin in patients with acute-on-chronic liver failure. Liver Int. 2016;36(1):59–67.
62. Arora V, Maiwall R, Vijayaraghavan R, et al. Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. Hepatology. 2020;71(2):600–10.
63. Maiwall R, Chandel SS, Wani Z, Kumar S, Sarin SK. SIRS at admission is a predictor of AKI development and mortality in hospitalized patients with severe alcoholic hepatitis. Dig Dis Sci. 2016;61(3):920–9.
64. Ma K, Guo W, Han M, et al. Entecavir treatment prevents disease progression in hepatitis B virus-related acute-on-chronic liver failure: establishment of a novel logistical regression model. Hepatol Int. 2012;6(4):735–43, (153n).
65. Gupta T, Dhiman RK, Rathi S, Agrawal S, Duseja A, Taneja S, et al. Impact of hepatic and extrahepatic insults on the outcome of acute-on-chronic liver failure. J Clin Exp Hepatol. 2017;7:9–15.
66. Artru F, Louvet A, Ruiz I, 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(4):708–15.
67. Banares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology. 2013;57:1153–62.
68. Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz C, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology. 2012;142:782–789.e3.
69. 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. 2015;64(1):69–78.
70. Yue-Meng W, Yang LH, Yang JH, Xu Y, Yang J, Song GB, et al. The effect of plasma exchange on entecavir-treated chronic hepatitis B patients with hepatic de-compensation and acute-on-chronic liver failure. Hepatol Int. 2016;10(3):462–9.
71. Maiwall R, Kumar G, Bajpai M, Chowdhury A, Sharma MK, Sarin SK, et al. Prometheus versus plasma exchange—a comparison of efficiency of two different modalities of liver detoxification in patients with acute on chronic liver failure. J Clin Exp Hepatol. 2017;7(Supplement 1):S72–3.
72. Pamecha V, Kumar S, Bharathy KG. Liver transplantation in acute on chronic liver failure: challenges and an algorithm for patient selection and management. Hepatol Int. 2015;9(4):534–42.
73. Gustot T, Fernandez J, Garcia E, for CANONIC Study Investigators of the EASL-CLIF Consortium, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62(1):243–52.
74. Bahirwani R, Shaked O, Bewtra M, Forde K, Reddy KR. Acuteon-chronic liver failure before liver transplantation: impact on post transplant outcomes. Transplantation. 2011;92(8):952–7.
75. Finkenstedt A, Nachbaur K, Zoller H, et al. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. Liver Transpl. 2013;19:879–86.

76. Garg V, Garg H, Khan A, et al. Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure. Gastroenterology. 2012;142:505–12.
77. Duan XZ, Liu FF, Tong JJ, 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;19:1104–10.
78. Shi M, Zhang Z, Xu R, 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;1:725–31.
79. Ash SR. Hemodiabsorption in treatment of acute hepatic failure and chronic cirrhosis with ascites. Artif Organs. 1994;18:355–62.
80. Sen S, Davies NA, Mookerjee RP, Cheshire LM, Hodges SJ, Williams R, et al. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver Transpl. 2004;10:1109–19.
81. Laleman W, Wilmer A, Evenepoel P, Elst IV, Zeegers M, Zaman Z, et al. Effect of the molecular adsorbent recirculating system and Prometheus devices on systemic haemodynamics and vasoactive agents in patients with acute-on-chronic alcoholic liver failure. Crit Care. 2006;10:R108.
82. Desphpande A, Kumbar S, Patil S, Jayprakash A, Menon P, Somu A, et al. Plasma exchange therapy in patients with ACLF, experience from a tertiary care centre. J Clin Exp Hepatol. 2018;8(Supplement 1):S3.