Acute on Chronic Liver Failure: An Update

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Abbreviations

ACLF	Acute on chronic liver failure
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ALF	Acute liver failure
AOPP	Advanced oxidative protein products
APASL	Asian Pacific Association for the study of liver
ATN	Acute tubular necrosis
ATP	Adenosine triphosphate
CAM	Complementary and alternative medicines
CK18	Caspase-cleaved keratin18
CLD	Chronic liver disease
CLIF	Chronic liver failure
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CysC	Cystatin C
DAMP	Damage associated molecular patterns
DDLT	Deceased donor liver transplant
EASL	European Association for the study of liver
eGFR	Estimated glomerular filtration rate
FPSA	Fractionated plasma separation and adsorption
G-CSF	Granulocyte colony stimulating factor
HBV	Hepatitis-B virus
HCC	Hepatocellular carcinoma
HE	Hepatic encephalopathy
HIV	Human immunodeficiency virus
HMGB1	High mobility group protein B1
HRS	Hepatorenal syndrome
iACLF	Infection related
ICA	International club of ascites
ICU	Intensive care unit
IL	Interleukin
IL-1RA	IL-1 receptor antagonist
INR	International normalized ratio
K18	Keratin 18
KCH	King's College Hospital criteria
KIM-1	Kidney-Injury molecule
LDLT	Living donor liver transplant
L-FABP	Liver fatty acid binding protein
LPS	Lipopolysaccharide
LT	Liver transplant
MAP	Mean arterial pressure
MARS	Molecular adsorbents recirculatory system
MELD	Model for end-stage liver disease
MERTK	Mer tyrosine-protein kinase
MHE	Minimal hepatic encephalopathy
NAC	N-acetyl cysteine

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NACSELD	North American consortium for the study of end-stage liver disease
NASH	Non alcoholic steatohepatitis
NGAL	Neutrophil gelatinase-associated lipocalin
OLT	Orthotopic liver transplantation
PAMPs	Pathogen-associated molecular patterns
PICD	Paracentesis induced circulatory dysfunction
PIRO	Predisposition, injury, response, organ failure
RAAS	Rennin–Angiotensin aldosterone
ROTEM	Rotational thromboelastometry
SBP	Spontaneous bacterial peritonitis
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
SPAD	Single-pass albumin dialysis
TEG	Thromboelastography
TNF-α	Tumor necrosis factor alpha

43.1 Introduction

The incidence of acute on chronic liver failure (ACLF) has been steadily increasing secondary to excessive alcohol use, usage of over-the-counter hepatotoxic drugs, complementary and alternative medicines, and the rising epidemic of non-alcoholic fatty liver disease [1–3]. Almost one in four outpatients with decompensated cirrhosis patients develop ACLF [4]. There are different definitions for ACLF but the two most widely accepted and validated are the one proposed by the Asian Pacific Association for the Study of Liver (APASL) [1–3] and the second by the European Association for the Study of Liver (EASL) Chronic Liver Failure (EASL-CLIF) consortium [5]. Following this, the world gastroenterology organization had combined the two definitions stratifying ACLF patients into three types [6] based on the underlying severity of chronic liver disease. It is challenging to have a unified definition of ACLF to develop treatment protocols, prognostic scores as well as stratifica-

tion for an emergency liver transplantation. Research exploring liver regenerative therapies, artificial liver support systems, strategies targeting systemic inflammation, and management of bacterial infections which are a key driver of extrahepatic organ failures is an unmet need [1]. Until, these therapies are able to conclusively improve transplant-free survival, liver transplant remains the only definitive treatment option for these patients [1–6].

43.2 Definitions of ACLF

The Asian pacific association for the study of liver (APASL) defines ACLF as an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5 or prothrombin activity <40%) complicating within 4 weeks by clinical ascites and or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease and is associated with high 28-day mortality [1–3]. Conceptually, the APASL definition of ACLF specifies the syndrome wherein there is liver failure precipitated by an acute hepatic insult in a patient with compensated chronic liver disease. The acute insults include hepatitis B reactivation as the commonest cause in the Asia Pacific, followed by alcohol and drugs [1, 7–9]. Alcohol is the most common cause of acute insult in several Asian countries for instance in the Indian subcontinent. Super-infection with hepatitis E virus is also an important cause in the Indian subcontinent [1–3, 9]. Hepatotoxic drugs and complementary and alternative medicines (CAM) are other important contributing causes of acute insult causing the syndrome of ACLF. Drugs used for treatment of tuberculosis are next most important cause of drug induced acute liver failure especially reported from the Indian subcontinent [7]. The definition of ACLF excludes non-hepatic causes as acute insult for instance acute variceal bleed and particularly sepsis. According to APASL, sepsis is a consequence and not a cause for liver failure. The common causes of underlying chronic liver disease include alcohol, NASH, and hepatitis B and C [1–3].

The second most popular definition of ACLF is that proposed by the Chronic Liver Failure (CLIF) acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) definition of ACLF [5, 10, 11]. According to this definition, ACLF is defined 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 multisystem organ failure." ACLF is defined and graded as ACLF grade 0 if patients had single non-kidney organ failure [5] or had no kidney dysfunction defined as serum creatinine level 1.5 mg/dL and absence of hepatic encephalopathy. Patients with ACLF grade 1 included patients with either single kidney failure (serum creatinine ≥2 mg/dL) or patients with single failure of either liver, coagulation, circulation, or respiration defined according to the CLIF-SOFA score. Patients with kidney dysfunction (serum creatinine between 1.5 and 1.9 mg/dL) and/or mild to moderate hepatic encephalopathy and patients with single cerebral failure (grade III or IV hepatic encephalopathy) and kidney dysfunction were classified as ACLF grade 1. ACLF grade 2 included patients with any two organ failures and ACLF grade 3 included patients with 3 organ failures. The 28-day and 90-day mortality rates increased with ACLF grades and were highest for ACLF grade 3, i.e., 76.7% and 79.1%, respectively. The 28-day and 90-day mortality rates of ACLF grade 1 were 22.1% and 40.7%, respectively and for ACLF grade 2 were 32.0% and 52.3%, respectively [5, 10, 11].

The North-American consortium has defined ACLF based on two or more organ failures. They define renal as requirement of dialysis, respiratory as requirement of mechanical ventilation, cerebral as grade III or IV hepatic encephalopathy and circulatory as requirement of vasopressors [12]. The way ACLF is defined based on these definitions is quite heterogenous and has generated confusion across the world. The context has become a bit more confused by inclusion of terms like hepatic and extrahepatic ACLF and infection related ACLF- iACLF. A unifying definition of ACLF is an unmet need to have a clarity for the syndrome and to differentiate it from patients with decompensated cirrhosis with organ failures. The APASL recommends for homogeneity by avoiding extrahepatic organ failures and sepsis in the definition of ACLF [1]. A comparison of the different definitions is given in Table 43.1 and a summary of existing studies on ACLF has been highlighted in Table 43.2.

Table 43.1 Comparison of different definitions of acute on chronic liver failure

	APASL	EASL-CLIF	NACSELD	WGO
Basis of definition	Consensus of international experts	CANONIC study	Prospective study	Consensus of international experts
Definition	Liver failure is defined as jaundice (a serum bilirubin level of ≥5 mg/dL) and coagulopathy (an INR of ≥1.5 or prothrombin activity of <40%). Liver failure is complicated within 4 weeks by clinical ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease (including cirrhosis)			ACLF is a syndrome characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset

Table 43.1 (continued)

	APASL	EASL-CLIF	NACSELD	WGO
Study population		1343 patients in 12 European countries	507 patients in USA and Canada	
Included population	Decompensation on existing CLD (including cirrhosis) of any etiology	1. Decompensation in cirrhosis	1. Infection at admission or during hospital stay	Existing CLD (including cirrhosis)
		2. Prior episodes of decompensation of cirrhosis	2. Prior episodes of decompensation of cirrhosis	
Excluded population	1. Bacterial infections	1. HCC	1. HIV	
	2. Prior episodes of decompensation of cirrhosis	2. Chronic medical illnesses unrelated to hepatic disease	2. Organ transplant	
		3. HIV infection	3. Disseminated malignancies	
		4. Immunosuppression treatment		
Organ failure defined as:				
Liver	Total bilirubin $\geq$5 mg/dL and INR $\geq$1.5	Bilirubin level of >12 mg/dL		
Kidney	Acute kidney injury network criteria	Creatinine level of $\geq$2.0 mg/dL or renal replacement	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 $\geq$1.5	INR $\geq$2.5		
Shock		Use of vasopressors	MAP <60 mm hg or a SBP reduction of 40 mm hg from baseline, despite adequate fluid resuscitation and cardiac output	
Lungs		PaO2/FiO2 of $\leq$200 or SpO2/FiO2 of $\leq$214 or need for mechanical ventilation	Need for mechanical ventilation	

Table 43.2 Different types of artificial liver support systems available

System	Components	Source of albumin	Albumin recycling	Toxin removed	Outcomes	Shortcomings	Anticoagulation	Advantages
Molecular adsorbent recirculating system (MARS)	Blood circuit	Exogenous albumin	Through CRRT	Albumin bound	Improvement in HE, no survival benefit	More sophisticated	UFH	Most widely studied
	Albumin circuit			Water bound				
	Classic hemodialysis circuit			Cytokines				
Single-pass albumin dialysis (SPAD)	Standard CRRT, no additional adsorbent columns or circuits	Exogenous albumin	Not done	Albumin bound	Improvement in HE, no survival benefit	No studies on ACLF patients, all existing data is from ALF patients	Local anticoagulation with citrate	Simplest to use
				Water bound		More expensive as albumin is not reused		
						Difficulty in determining optimal albumin dialyzate concentration, dialyzate flow rate and treatment regimen		
Fractionated plasma separation and adsorption–FPSA (Prometheus)	First circuit: Albumin enters through AlbuFlow® filter and is returned to circulation using a neutral resin adsorber (Prometh®01) and an anion-exchange column (Prometh® 02)	Patient's albumin	Through CRRT	Albumin bound (more efficiently than MARS)	Improvement in HE, no survival benefit	Newest and yet to be fully studied		Increase in hepatic growth factor (HGF)
	Second circuit: Hemodialysis			Water bound				
				Cytokines				

CRRT continuous renal replacement therapy, *UFH* ultrafiltration hemodialysis

43.3 Pathogenetic Basis of ACLF
(Fig. 43.1)

43.3.1 Systemic Inflammation

The presence of low-grade systemic inflammation in patients with stable or decompensated cirrhosis is considered to cause or augment relevant clinical signs and symptoms such as hyperdynamic circulation, fatigue, or minimal hepatic encephalopathy (MHE) [13, 14]. The etiology of cirrhosis could be chronic infections secondary to viruses, drugs, alcohol or autoimmune diseases. The progression of liver damage, fibro-
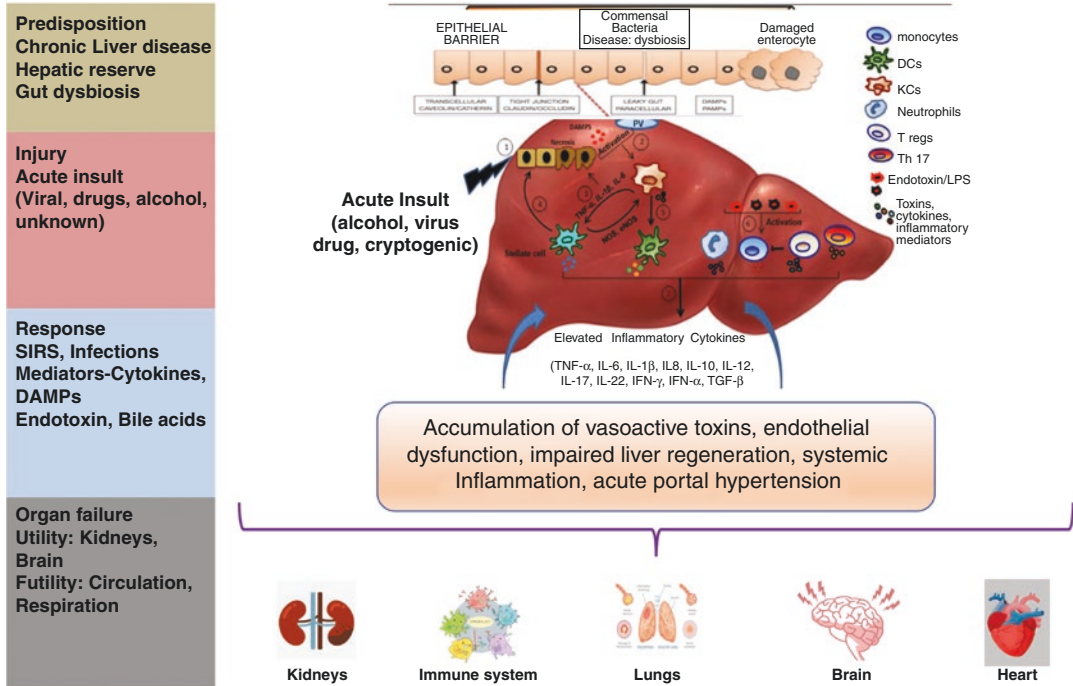

Fig. 43.1 The PIRO concept of ACLF. The PIRO concept i.e. (Predisposition, Injury, Response, Organ Failure) which has been used for stratifying patients of any acute illness can well be used for patients with ACLF. PIRO incorporates assessment of pre-morbid baseline susceptibility (predisposition) factors which includes the underlying hepatic reserve and gut dysbiosis which have an influence on the course of the disease. The injury includes the specific factor causing acute illness (insult) which includes viral, drugs, alcohol in patients with acute on chronic liver failure (ACLF). The acute insult in turn incites the host response. In patients with ACLF, the acute insult activates the Kupffer cells localized to the hepatic sinusoids, through toll-like receptor 4 (TLR4), complement receptors (C3R and C5R), and damage-associated-molecular-patterns (DAMPs) which results in increased release of proinflammatory and anti-inflammatory cytokines, endotoxin, prostaglandins, bile acids, lysosomal, and proteolytic enzymes. The activation of the hepatic stellate cells by the Kupffer cells produces vasoactive mediators like endothelin-1, thromboxane A2, nitric oxide, and prostaglandins which lead to a perturbed hepatic microcirculatory function, endothelial dysfunction, and an acute increase in the portal pressure. The response of the host to the inciting insult which is measured as systemic inflammatory response syndrome which is commonly assessed by the physiological variables and can progress to a compensatory anti-inflammatory response syndrome (CARS) causes infections and secondary organ failures. The last component of the PIRO incorporates organ failures which includes organs of utility, i.e. the brain and kidneys and organs of futility that is circulation and respiration which contraindicate a liver transplant. The PIRO concept is especially useful in diseases like ACLF where the clinicians have limited therapeutic options in their armamentarium and therefore a stratification system enables identification of a possible clinical trajectory, to predict outcome much early, allowing allocation of the best treatment options to the patients before the development of organ failure what is called as the "golden window" of therapeutic intervention. *ACLF* acute-on-chronic liver failure, *SIRS* systemic inflammatory response syndrome, *DAMP* damage-associated molecular pattern, *DCs* dendritic cells, *KC* kupffer cells, *eNOS* endothelial nitric oxide synthase, *LPS* lipopolysaccharide, *MODS* multiorgan dysfunction syndrome, *PV* portal vein, *TGFβ* transforming growth factor beta, *TH17 cell* type 17T helper cell, *TREG cell* regulatory T cell

genesis, and sinusoidal portal hypertension results in production of damage associated molecular patterns (DAMPS) which could be derived from the nucleus, i.e., high-mobility group protein B1 (HMGB1), histones, ATP, derived from cytoplasmic membrane, i.e. glypican and syndecan, from mitochondria or endoplasmic reticulum like calreticulin [15–17]. These DAMPs could initiate sterile inflammation and result in activation of the innate and adaptive immune system. At the same time, cirrhosis is characterized by gut dysbiosis, increase in gut permeability and enhancement of local intestinal inflammation with endogenous endotoxemia, and impairment of local intestinal defenses [15–17]. In animal models of liver cirrhosis, endotoxin-mediated tumor-necrosis-factor-alpha (TNF-α) is implicated in other organ dysfunction, worsening of systemic vasodilatation with impairment of cardiac contractility. All these effects could be abrogated by fecal microbial transplantation [18, 19]. In a study from EASL-CLIF consortium it was demonstrated that higher grades of systemic inflammation in

ACLF were associated with higher incidence of organ failures which also differentiated them from patients with acute decompensation of cirrhosis [20]. Trebicka et al. evaluated baseline plasma levels of 15 cytokines, chemokines, and oxidized albumin) in 161 patients with ACLF which were compared to 40 healthy controls, 39 patients with stable compensated cirrhosis, and 342 patients with acute decompensation of cirrhosis. They observed that these markers were significantly elevated in patients with ACLF and in those patients with acute decompensation who finally succumbed at 28 days of systemic inflammation [21]. Considering systemic inflammation as the key driver of organ failures, the concept of "golden-window" has been proposed by the APASL (Fig. 43.2). In a study by Chowdhury and colleagues the relevance of SIRS was shown in patients with ACLF [22]. It was seen that presence, persistence, and development of new SIRS was associated with worse outcomes in patients with ACLF while resolution was associated with improved outcomes. Therefore, dynamicity of SIRS has an important prognostic
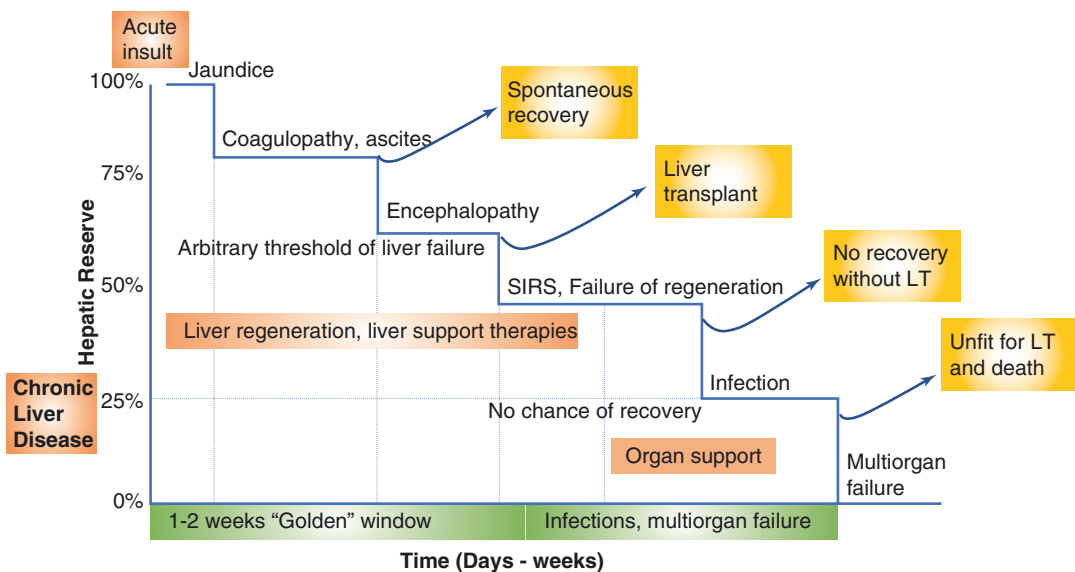

Fig. 43.2 The "Golden-Window" of therapeutic intervention in patients with ACLF. Systemic inflammation as the key driver of infection and multiorgan failure in patients with ACLF. The first 2 weeks provide the "golden-window" of targeted strategies for combating systemic inflammation using liver support therapies, immunomod-

ulation, and potentiation of liver regeneration using granulocyte colony stimulating factor (G-CSF) or modulation of gut dysbiosis using fecal microbial transplant for patients with ACLF as a possible bridge toward spontaneous recovery or liver transplant

implication in patients with ACLF. Altogether, SIRS in patients with ACLF can lead to a state of immunodysfunction which is a harbinger of sepsis and multiorgan failure. SIRS and or infection in these patients results in cell-death by causing deprivation of oxygen and energy from the tissues [23].

43.3.2 Immunodysfunction in Patients with ACLF

Patients with ACLF not only have state of systemic inflammation but at the same time a state of prolonged and suppressed state of immune exhaustion has been well-described in these patients. These patients characteristically have increased concentrations of ant-inflammatory cytokines, i.e., interleukin-10 (IL-10) or IL-1 receptor antagonist (IL-1RA) [24]. The cells of the innate immune system, for instance, the monocytes are even though increased in frequency and display an activated phenotype but have failure to respond to stimulation with bacterial lipopolysaccharide (LPS). An increase in the number of peripheral blood monocytes expressing the tyrosine-protein kinase Mer (encoded by *MERTK*) which has anti-phagocytic functions has also been shown [25]. Changes in the adaptive immune system i.e. a lower frequency of naïve helper and suppressor T-cells while the number of activated T-cells is inappropriately noted in patients with ACLF. The state of cirrhosis-associated immune dysfunction is further exaggerated in patients with ACLF which is characterized by defects in phagocytosis, complement presentation, defects in innate and adaptive immunity, and defects in clearance of intestinal and bacterial pathogens [26]. Continuous exposure of bacterial derived pathogen-associated molecular patterns (PAMPs) and DAMPs amidst a state of sustained inflammation results concomitantly to state of immunosuppression in these patients [27].

43.3.3 Intestinal Inflammation and Gut Dysbiosis

Patients with cirrhosis have loss of gut barrier integrity secondary to an increase in the inflammatory mediators which downregulate the tight junctions causing leaky gut and associated bacterial translocation. Intestinal dysbiosis is a hallmark of patients with ACLF [28–32]. There is alteration of the gut microbial environment which is characterized by a shift to pathogenic bacterial species (e.g. *Enterococcus* spp.) and a decrease in the number of beneficial bacterial species (e.g. *Bifidobacterium* spp.) Concomitant to this, these patients have alteration in the gut motility, a reduction in the antimicrobial proteins, altered composition of bile salts and reduction in the gastric acid which gets exacerbated by the use of proton pump inhibitors. All this results in an increase in the translocation of gut-derived pathogens, i.e. LPS, flagellin, etc. which exacerbates systemic inflammatory response syndrome and leads to the development of bacterial infections. Amongst all etiologies, patients with alcohol have the highest gut associated dysbiosis and altered permeability because of the direct effects of alcohol itself in these changes [18, 19, 28–32].

43.3.4 Infections

Patients with ACLF develop an increased frequency of infections which are both community-acquired and nosocomial infections. Spontaneous bacterial peritonitis, gastrointestinal hemorrhage or hepatic encephalopathy are known risk factors for development of infections in patients with ACLF [1–6]. Patients of ACLF frequently develop both bacterial and fungal infections [33, 34]. Prophylactic antibiotics are therefore recommended in these situations to lower the risk of bacterial infections. The diagnosis of bacterial infection, however, remains a challenge. Currently, there are no rapid diagnostic

methods for the diagnosis of occult infections and culture methods are the only definite proof of the presence of infections in these patients. Serum procalcitonin and C-reactive protein (CRP) in combination have a positive predictive value of more than 90% for the diagnosis of bacterial infection. A cut-off level of CRP of more than 24.7 ng/mL and serum procalcitonin of more than 0.47 μg/L is used for recommending prophylactic antibiotics [35]. The degree of systemic inflammation is could also be determined by the white cell counts and the use of neutrophil to lymphocyte ratio [5, 36]. A number of other pro-inflammatory markers, i.e. tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and IL-8 have been evaluated in these patients other markers, i.e., caspase-cleaved keratin18 (CK18) and keratin 18 (K18) are reflective of apoptotic and total cell death, respectively, and cK18: K18 ratio is known to increase with the severity of ACLF [37, 38]. However, currently none of the biomarkers can reliably differentiate sterile inflammation from infection. Infections are important triggers for the development of ACLF by causing organ failures which is associated with high mortality in the absence of liver transplantation. It is recommended to consider the site and acquisition of infection as well as the local microbiological profile to decide the choice of prophylactic antibiotics in patients with ACLF. In a large multicentric-multinational study global study performed to capture the data on bacterial infections across the globe regional differences were observed in the spectrum of infections in patients with cirrhosis. In the asian countries, particularly India a predominance of multidrug resistant infections was observed which was were associated with a higher incidence of organ failures, prolonged ICU stay, and higher mortality [39]. Choice of appropriate empirical antibiotics was associated with improved outcomes. As a protocol, the patients should be reassessed at 48–72 h for de-escalation of antibiotics after the culture report.

43.4 The Concept of Tolerance in ACLF

Sepsis is defined as the host response to a bacterial pathogen. Infections in patients with ACLF can directly impact or damage the tissues or cause stimulation of the immune system resulting in the release of pro-inflammatory cytokines which cause end-organ dysfunction or failure. The host response is related to the intrinsic tolerance. It has been well-documented that as compared to patients with decompensated cirrhosis, who are exposed to repeated prior episodes of bacterial infection and chronic endotoxemia, patients with ACLF respond poorly to containment of bacterial infections because of failure of protective mechanisms of tolerance [40].

43.4.1 Assessment of Liver and Extrahepatic Organs in Patients with ACLF

43.4.1.1 Liver Failure

According to the APASL definition the liver remains at the core of the entire syndrome of ACLF [1–3]. All patients therefore have liver failure which is manifested by jaundice, coagulopathy and/or ascites, and hepatic encephalopathy. Majority of patients with ACLF have ascites which is a consequence of underlying chronic liver disease, hemodynamic alterations secondary to systemic inflammation, and the development of acute portal hypertension. The severity of liver failure therefore is determined by the degree of jaundice, coagulation impairment, and the degree and severity of ascites [1–3]. Development of any grade of hepatic encephalopathy and its persistence is associated with worse clinical outcomes. Assessment of hepatic reserve would be worthwhile to determine the potential of spontaneous liver regeneration in patients with ACLF.

43.4.1.2 Coagulation Failure

Assessment of coagulation can be performed by standard tests, i.e., the international normalized ratio, platelet counts, and serum fibrinogen levels. In patients with decompensated cirrhosis, an intricate balance is noted between coagulation and fibrinolysis and is usually procoagulant [41]. The state of coagulation in patients with ACLF should be assessed by thromboelastography (TEG) or rotational thromboelastometry (ROTEM) [42, 43]. In a single-center prospective study consecutive patients of ACLF without sepsis were recruited and assessed by TEG and other specific assays (Factor VIII, von Willebrand factor, protein C and antithrombin III and followed for development of sepsis, bleeding events and overall outcomes [44]. A hypocoagulable TEG at baseline was an independent predictor of not only bleeding events but also mortality. The global coagulation index, lower levels of protein C, antithrombin III, and tissue plasminogen activator levels predicted 28-day mortality after adjusting for patient demographics and the MELD scores. Furthermore, during bleeding correction of coagulation using either ROTEM or TEG could also limit transfusion related adverse effects in patients with AC LF and may result in targeted coagulation correction.

43.4.1.3 Kidney Dysfunction or Failure

Kidneys are one of the most frequent extrahepatic organs that are affected in patients with ACLF. Acute kidney injury is reported in 22.8–34% of patients with ACLF [45]. Kidneys in patients with ACLF should be assessed using the relative changes in serum creatinine or by measuring urine output in hospitalized patients rather than relying on serum creatinine. This is because various factors influence the serum creatinine estimation which might result in underdiagnosis of renal dysfunction [45]. Use of biomarkers like serum cystatin C could be helpful in early detection of AKI in patients with ACLF. The AKI spectrum has also not been well-studied in patients with ACLF. These patients have predominance of structural AKI secondary to a higher prevalence of bacterial infections, systemic inflammation, high serum bilirubin, and predominance of circulatory dysfunction [46, 47].

43.4.1.4 Spectrum of AKI in ACLF

Patients with ACLF have acute portal hypertension, the main abnormality causing renal dysfunction in these patients is severe systemic and splanchnic vasodilatation which leads to decreased effective arterial blood volume and activation of the renin–angiotensin aldosterone (RAAS), the sympathetic nervous system and non-osmotic release of antidiuiuretic hormone which causes salt and water retention. The pathogenetic basis of renal dysfunction in ACLF is quite different from that of patients with decompensated cirrhosis. Majority of patients have structural kidney damage as assessed by microscopic urinalysis and renal biomarkers. Severity of systemic inflammation, bacterial infections, cholemic nephropathy are most common reasons for structural kidney damage [1–3, 45–48].

43.4.1.5 Prediction of AKI in ACLF

In a large multicenter multinational prospective study of patients with ACLF from the Asia Pacific, a predictive score was developed for identification of the development or progression of AKI in patients with ACLF. The score was developed on the concept of PIRO, i.e. predisposition, injury, response and organ failure which was initially developed for patients with sepsis. Components of the predisposition component included high urea, serum creatinine, potassium, and serum bilirubin. In the injury component, the use of nephrotoxic drugs was identified as an important predictor, response component included presence of systemic inflammatory response syndrome, and organ failure included presence of low mean arterial pressure. Patients of ACLF could be risk stratified for AKI using the PIRO score for additional therapeutic interventions targeting the components of PIRO [48].

43.4.1.6 Diagnosis of AKI in Patients with ACLF

Considering the limitations of serum creatinine in patients with ACLF and especially in context of intensive care unit stay retention of urine out-

put criteria may be relevant in the diagnosis of AKI in these patients [49]. However, this needs validation in patients with ACLF. The data from the AARC database suggested a lower value of serum creatinine is more relevant in patients with ACLF. Serum creatinine above 0.7 mg/dL (as derived from the AARC score) has a sensitivity of 78% and specificity of 36% for prediction of 30-day mortality in patients with ACLF. For the diagnosis of kidney failure, the conventional cut-off of 1.5 mg/dL even though had a low sensitivity of 48% but had a specificity of 99.8% for 30-day mortality [3]. The revised consensus criteria for AKI in patients with ACLF lead down by the international club of ascites suggest diagnosis of AKI using the AKIN criteria. In patients with stage 1 AKI or those with serum creatinine less than 1.5 mg/dL should be managed by removal of the precipitating cause and conservative measures. Patients who have stage 2 or 3 AKI and those with serum creatine above 1.5 mg/dL should undergo volume expansion with intravenous albumin. Kidney failure (serum creatinine $\geq$1.5 mg/dL) was seen in 22% of ACLF patients at baseline and developed in another 30% within a month [50]. The majority of patients of ACLF developed new episodes of AKI in the first 2 weeks (11%). Apart from the severity, the course of AKI was seen to be an important predictor of clinical outcomes. Patients with AKI resolution have improved outcomes while those with either AKI progression or persistence have worse outcomes [3].

43.5 Role of Biomarkers

43.5.1 Biomarkers of Glomerular Injury

43.5.1.1 Cystatin C
Cystatin C is a nonglycosylated protein with low molecular weight (13 kDa), has a constant rate of production and concentration of cystatin C is determined by glomerular filtration. It is, therefore, considered as an early marker of glomerular dysfunction. We have demonstrated the role of serum cystatin C in a large prospective cohort study in patients with cirrhosis, wherein it has been shown as a marker of renal reserve to predict development of new AKI episode and chronic kidney disease [47, 51]. In patients with hepatitis-B virus (HBV) related ACLF CysC was shown to accurately predict AKI even in patients with normal serum creatinine [52].

43.5.2 Biomarkers of Proximal Tubular Damage

43.5.2.1 Kidney Injury Molecule (KIM-1)
Kidney injury molecule-1 is a type 1 transmembrane glycoprotein which is comprised of an immunoglobulin and mucin domain. Under normal conditions, KIM-1 protein is only minimally expressed in kidney tissue or urine but is shed from the proximal tubules with tubular dysfunction wherein it can be detected in the urine by immunoassay. It is known to be upregulated in response to renal ischemia or nephrotoxic insult and is also believed to participate in the regeneration process after epithelial injury [53].

43.5.2.2 Liver Fatty Acid Binding Protein (L-FABP)
Fatty-acid protein bindings (FABPs) facilitate transfer of fatty acids between intra and extracellular membranes. They also have a role in the amelioration of cellular oxidative stress by inhibition of the toxic effects of oxidative intermediates on cellular membranes. In the normal healthy state, urinary L-FABP is undetectable; however, under states of renal ischemia there is decreased proximal tubular reabsorption of L-FABP which is detected as increased excretion in urine [53].

43.5.2.3 Interleukine-18
Interleukine-18 (IL-18) is a proinflammatory cytokine which is synthesized in renal proximal tubular epithelial cells as well as monocytes and macrophages. The concentrations of IL-18 have also been demonstrated to be increased in postischemic AKI following renal hypoxia. It can therefore be considered as an early biomarker of AKI in critically ill patients. It has also been

shown to correlate with poor clinical outcomes (death or requirement of renal replacement therapy) in patients with sepsis [53].

43.5.3 Biomarkers of Distal Tubular Damage

43.5.3.1 Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) NGAL belongs to the lipocalin superfamily (lipocalin 2, siderocalin). Both plasma and urine NGALs are increased after an episode of AKI. Elevated urine NGAL originates from both proximal and distal nephron after a nephrotoxic insult. Injury to proximal renal tubules precludes NGAL reabsorption and/or increase denovo NGAL synthesis secondary to upregulation of NGAL mRNA in the distal nephron segments (especially in the thick ascending limb of Henle's loop and the collecting ducts) [54].

43.5.4 Studies Assessing Markers of Tubular Injury in Patients with ACLF

The major challenge in patients with ACLF is to differentiate HRS associated with bacterial infections from ATN as it evolves through a continuous spectrum. In fact, HRS patients who are non-responders to vasoconstrictors are known to have tubular dysfunction requiring prolonged RRT [45]. In another prospective study in patients with cirrhosis and bacterial infections, measurement of urinary NGAL at infection diagnosis was reported to be useful in predicting clinical outcomes, persistent AKI and type of AKI [55]. Interestingly, N-GAL also accurately predicted development of a second infection and 3-month mortality. In this study significantly higher uNGAL was noted in patients who developed persistent AKI and amongst these patients was able to discriminate type-1 HRS from other causes of AKI with accuracy. In another study done in 55 patients with an acute decompensation of cirrhosis a panel of 12 biomarkers was

studied to differentiate ATN from other causes of AKI. In this study also, NGAL was identified as the best biomarker, others being IL-18, albumin, trefoil-factor-3 (TFF-3) and glutathione-S-transferase-π (GST-π) [53]. In a large prospective study performed in 716 patients with ACLF, urine and plasma NGAL levels were analyzed. The authors noted that the levels of urine NGAL were markedly elevated in patients with ACLF (108(35–400) vs. 29 (12–73) μg/g creatinine; $p < 0.001$) and independently predicted 28-day mortality [54]. The authors proposed urine NGAL as a biomarker for patients with ACLF. In another study performed in patients with HBV-ACLF 280 patients were compared to 132 patients with HBV-related decompensated cirrhosis (DC). The authors studied the levels of five urinary tubular injury including neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), liver-type fatty acid binding protein (L-FABP), cystatin C (CysC), and kidney injury molecule-1 (KIM-1). This was correlated to patient demographics, development and progression of AKI, and response to terlipressin therapy were recorded. The levels of urinary biomarkers (NGAL, CysC, L-FABP, IL-18) were significantly elevated in patients with HBV-ACLF and AKI (ACLF-AKI), compared with that in patients with HBV-DC and AKI (DC-AKI) or those without AKI [56].

43.5.4.1 Management of AKI
According to the new consensus by the ICA for AKI, a new algorithm for the management of AKI based on the revised criteria has been proposed. Based on this algorithm it is recommended that patients with initial AKI stage 1 should be managed by removal of all precipitants (careful review of medications, diuretics, nephrotoxic drugs, vasodilators or non-steroidal anti-inflammatory drugs). Second step is to consider plasma volume expansion in patients with hypovolemia (the choice of fluid could either be a crystalloid or albumin or even blood as indicated) along with identification and early treatment of bacterial infections. Patients who respond with a decrease in serum creatinine value of 0.3 mg/dL of the baseline value should be subsequently fol-

lowed up for any new episodes of AKI. Patients who have progression, should be managed as ICA-AKI stage 2 and 3. In this group of patients, along with the institution of all measures as recommended for patients with stage 1 AKI a work up for the differential diagnosis should be done on an immediate basis to identify whether it is HRS-AKI, intrinsic AKI or post-renal cause. It was further decided by the panel of experts that for patients with stage 1 AKI who do not improve but have no progression further management can be decided based on the absolute value of serum creatinine and if the serum creatinine is more than 1.5 mg/dL it was recommended to consider the same protocol as for management for stage 2 and 3 AKI. Patients with HRS-AKI are recommended to be managed with early use of vasoconstrictors based on the revised criteria for HRS-AKI (either with terlipressin or norepinephrine or midodrine plus octreotide). Management of non-responders to vasoconstrictors which constitute a large group of patients therefore still remains an ongoing challenge. There is paucity of data on dialysis in patients with cirrhosis therefore there are no specific recommendations regarding the dose, the intensity, duration and time of initiation of dialysis in these patients [45]. We propose different management algorithm with incorporation of antioxidants and anti-inflammatory strategies, early initiation of vasoconstrictors and extracorporeal support therapies considering a higher incidence of structural AKI and poor response to vasoconstrictors [45, 46, 48].

43.5.4.2 Cerebral Failure

Development and persistence of hepatic encephalopathy is associated with a grim prognosis in patients with ACLF. The pathophysiology of HE is multifactorial and complex important factors include hyperammonemia, systemic inflammation, gut dysbiosis, genetic factors, bacterial infection, and insulin resistance [1–3]. Alcohol use and hyponatremia are other factors implicated in brain dysfunction in patients with ACLF. Contrary to patients with acute liver failure, cerebral oedema is rare and is observed in 5% of the patients with hepatic encephalopathy as

reported in imaging studies [57]. Ammonia induces oxidative and cellular stress and in patients with ACLF. Whether higher levels of ammonia correlate with more severe grades of HE has not been studied in patients with ACLF [58]. Management involves identification and correction of precipitating factors should be identified and treated as required. Use of lactulose for bowel cleansing, non-absorbable antibiotics, novel ammonia lowering drugs, such as glycerol phenylbutyrate and ornithine phenylacetate, have shown some promise but are still experimental. Use of liver dialysis for refractory hepatic encephalopathy has shown some benefits. Abstinence of alcohol, strategies for systemic inflammation, use of antibiotics for infection, and treatment of diabetes may also improve hepatic encephalopathy by combating systemic inflammation [59].

43.5.4.3 Circulatory and Respiratory Failure

The revised consensus of APASL defined organs of utility and futility in patients with ACLF. Among the extrahepatic organ failures, brain and kidneys are considered as organs of utility because even though dysfunction or failure of these organs is associated with worse prognosis but these do contraindicate liver transplant. On the contrary, data from Europe and America has suggested that protocols of excluding patients with severe circulatory or respiratory failure. In patients wherein transplant is performed dysfunction or circulation or respiration is associated with worse outcomes as compared to patients who did not have these organ failures [60].

43.6 Management of Patients with ACLF (Fig. 43.3)

43.6.1 Albumin

Albumin has an important role in the treatment of ACLF. Normal liver synthesizes 11–15 g of albumin, however, this capacity is reduced by 60–80% in patients with ACLF. Albumin has colloid osmotic functions, is an important carrier of different substances, has anti-inflammatory and
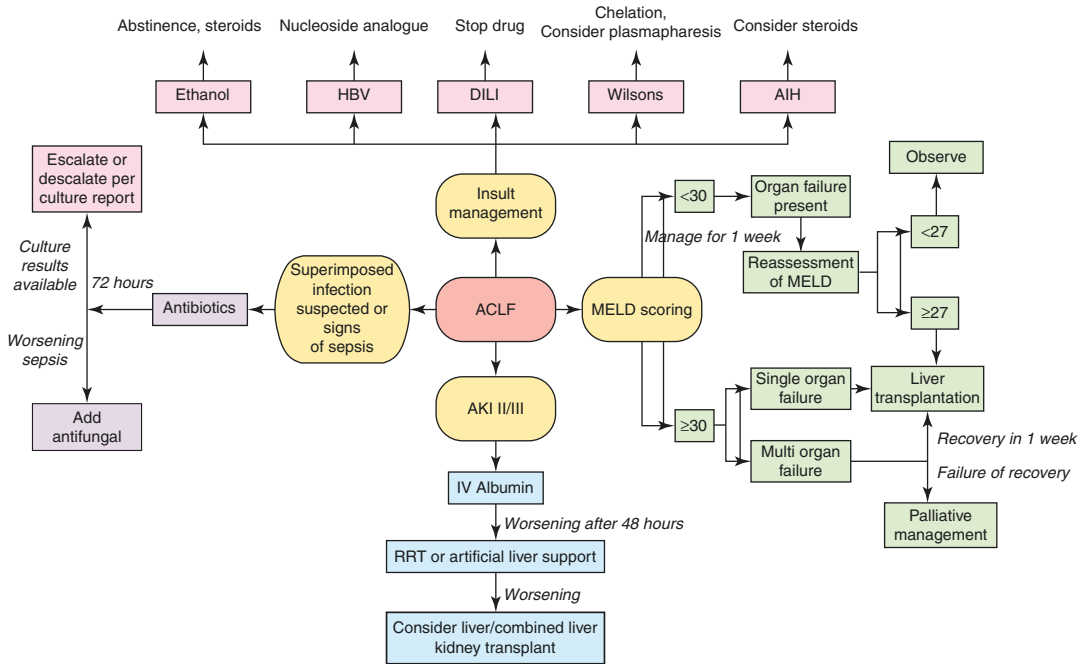
Fig. 43.3 Management algorithm for acute on chronic liver failure. *HBV* hepatitis B virus, *DILI* drug induced liver injury, *AIH* autoimmune hepatitis, *ACLF* acute on chronic liver failure, *AKI* acute kidney injury, *RRT* renal replacement therapy, *MELD* model of end-stage liver disease, *IV* intravenous

anti-oxidant property as well as maintenance of capillary permeability. Recent data has suggested utility of albumin in combating systemic inflammation and resolution of uncomplicated ascites [61–64]. Albumin is recommended for management for HRS-AKI, prevention of renal dysfunction in patients with spontaneous bacterial peritonitis (SBP), and prevention of paracentesis induced circulatory dysfunction (PICD). In a single-center randomized controlled trial in patients of ACLF who underwent modest-volume paracentesis the incidence of PICD and its associated complications was significantly reduced as compared to standard medical treatment [65].

43.6.2 Renal Replacement Therapy

The indications of renal replacement therapy are the same as those for other conditions, i.e. metabolic acidosis, volume overload, uremic complications, and electrolyte abnormalities. It should be considered in patients who are candidates for

orthotopic liver transplantation (OLT) or those with acute tubular necrosis (ATN), hypovolemia related renal failure or where renal functions are likely to be reversible. The leading indication identified in these patients has been volume overload. Continuous renal replacement therapy (CRRT) is better tolerated than intermittent hemodialysis because of improved cardiovascular stability, clear ammonia and pro-inflammatory cytokines, and improved cerebral oedema. Complications such as hypotension, bleeding secondary to coagulopathy, and catheter-related sepsis are commonly encountered with renal replacement therapy when used in patients with advanced liver disease. Hence, a multidisciplinary approach involving a hepatologist, a nephrologist, and an intensive care specialist is needed to decide the exact timing and modality of renal replacement therapy in patients with ACLF. Considering an extremely poor response to vasoconstrictors in only 35% of patients with HRS in patients with ACLF and higher prevalence of structural AKI in patients with ACLF,

the utility of RRT remains to be explored [66, 67]. There is paucity of data on dialysis in patients with ACLF and decompensated cirrhosis therefore there are no specific recommendations regarding the dose, the intensity, and the duration of dialysis in these patients. In a recent multicentric prospective study from North American Consortium for the Study of End-Stage Liver Disease (NACSELD) database for cirrhotic patients hospitalized with an infection (I-ACLF) where RRT was not identified as an independent predictor of survival when it was done as a bridging therapy to liver transplantation [12]. There is emerging data to suggest that initiation of RRT early may attenuate both kidney-specific and non-kidney specific organ dysfunction as well as counteract systemic inflammation in critically ill patients. However, unfortunately complications such as hypotension, coagulopathy-related bleeding, and catheter-related sepsis are frequently encountered with RRT in patients with cirrhosis and therefore in the absence of absolute indications it is a daunting task for the clinicians to decide initiation of early RRT in such a severely sick group of patients. Randomized controlled trials are therefore needed to decide the timing of initiation of RRT (that is, "early" versus "late") in patients of ACLF who have structural kidney damage or have non-response to vasoconstrictors awaiting liver transplantation.

43.6.3 Extracorporeal Liver Support Systems

These can be non-cell based or cell-based systems. Non-cell based systems do not incorporate tissue and provide only detoxification functions using membranes and adsorbents which allow removal of both water-soluble and protein bound substances as against conventional hemodialysis which removes only water-soluble toxins. These newer developing therapies have demonstrated benefits in biochemical parameters, hemodynamic, hepatic encephalopathy and also renal functions but are expensive and still considered experimental in patients with ACLF [68, 69]. Currently, they are considered as an option in

patients as a bridge to liver transplantation or clinical recovery. The Molecular Adsorbent Recirculatory System (MARS), single-pass albumin dialysis (SPAD), and the Fractionated Plasma Separation and Adsorption (FPSA or Prometheus) have shown limited efficacy in improving transplant-free survival in patients with ACLF. In the HELIOS trial survival of patients with type 1 HRS when treated with FPSA was better compared to SMT (28-day survival 62% vs. 39%, 90-day survival probability, 42% vs. 6%, respectively; log-rank test, $P = 0.04$). Similarly in the RELIEF trial with MARS it was seen that the proportion of patients with a serum creatinine below 1.5 mg/dL at day 4 in patients with HRS at baseline tended to be higher in patients who were treated with MARS ($p = 0.07$). Considering a higher prevalence of structural AKI and cholemic nephropathy in patients with ACLF, the utility of MARS remains to be explored [45, 70, 71]. Larger randomized controlled trials are required for patients with ACLF as the patient populations enrolled in the large trials in Europe were performed using heterogenous definitions of ACLF [68–71]. Case reports and series have suggested beneficial effects of plasma-exchange in patients with ACLF [72–75]. In the large European multicentric trial performed in patients with ALF, plasma-exchange was shown to improve survival by dampening the immune response [76]. The results from the AARC database suggested a beneficial role of plasma-exchange in patients with ACLF in preventing multiorgan failure and ameliorating SIRS. Currently, a specific device (DIALIVE) with an aim to remove dysfunctional albumin and endotoxin and replacing it with functional albumin is being evaluated in ACLF patients [35]. Table 43.2 summarizes the studies on artificial liver support therapies in patients with ACLF.

43.6.4 Therapeutic Strategies Targeting Liver Regeneration in ACLF

Initial randomized controlled clinical trials from India suggested encouraging data for G-CSF. An

impressive survival benefit was observed in these studies, however most of them were mono-centric [77–81]. Hence, the broad application of G-CSF in ACLF has not been routinely recommended outside clinical trials. The large multicentric trial performed in Europe, the. GRAFT-Study, did not Lreplicate the observed benefits observed in Asian trials. However, the differences in the definitions used to define ACLF may be a key factor explaining the observed differences [35].

43.6.5　Role of Anti-Oxidants in ACLF

Oxidative stress is hypothesized to play a crucial role in liver disease with the generation of advanced oxidative protein products (AOPP) playing a primary role in active inflammation. AOPP have been found to be in higher concentration in the serum in patients with viral hepatitis, diabetics, and advanced age. AOPP levels have also found to be higher in liver biopsies taken from severe ACLF secondary to alcohol compared to stable alcoholic cirrhosis, indicating role in ongoing damage [82].

Treatment with N-acetyl cysteine (NAC) in non-acetaminophen liver failure has been shown to improve survival in multiple studies. Nabi et al. showed that treatment of 40 patients with intravenous NAC for 72 h was associated with a decrease in mortality to 28% as compared to 53% in the control group [83]. These findings corroborated results of Mumtaz et al. study in 47 patients given oral NAC that showed a survival of 47% in treatment group and 27% in the non-treatment group [84]. Baniasadi et al. also showed benefit of NAC in antitubercular drug induced liver injury [85]. A meta-analysis of four prospective studies including 331 patients also showed that NAC was safe in non-acetaminophen liver disease and improved survival in both liver transplant and native liver patients [86]. However, studies are limited and NAC is not the standard of care for ACLF.

43.6.6　Liver Transplantation in ACLF

ACLF as a disease entity is characterized by dynamic course during hospital admission, with the course between day 3 and day 7 being the most integral in determining long-term management. An improvement in overall health opens the doors to other therapies such as bioartificial liver support (as summarized in Table 43.3), granulocyte colony stimulating factors, and stem cell transplant. These are in early phases of development and liver transplant is the only definite management option. Unlike acute liver failure (ALF), ACLF does not qualify for enlistment in the high urgency list. Furthermore, evaluation time is limited by the rapid evolution of disease with age, multiorgan failure, and recidivism forming key barriers to inclusion to the transplant list. Additionally, among those patients present on the waiting list, the incidence of mortality is high and exceeds that of ALF patients on the waiting list [87]. The key studies are summarized in Table 43.3.

Current data indicates that <50% ACLF patients are listed for transplant and < 20% ACLF patients actually successfully undergo transplantation. The 5-year survival in the patient that undergo successful transplantation is 74–90% [88]. This data highlights the necessity to validate prognostic tools to allow prioritization of patients with ACLF on the transplant list. Such patients should also be aggressively managed in the intensive care unit (ICU) with early management of known triggers of downward cascade such as infection and bleeding. The multiorgan failure seen as a defining feature of ACLF should be supported with vasopressors, mechanical ventilation, and continuous renal replacement as needed. It is notable that the highest quality of care can be provided with a well-balanced multidisciplinary team and early ICU admission [89].

The other options for these patients are living donor liver transplantation (LDLT) which has shown reasonable success, specifically with the

Table 43.3 Summary of studies on liver transplantation in patients with acute on chronic liver failure

Author, year	Sample size	Survival	Comments
Liu et al. (2003)	32	88% at 1 year	Hepatitis B patients
Wang et al. (2007)	42	83.3% at 1 year	Both DDLT and LDLT were done
Chan et al. (2009)	149	95.3% at 1 year 90% at 5 years	Both DDLT and LDLT were done
Bahirwani et al. (2011)	157	74.5% at 1 year	175 patients had no ACLF, post-transplant outcomes similar including eGFR
Ling et al. (2012)	126	73% at 1 year	Downgrading MELD improved survival, both DDLT and LDLT
Duan et al. (2013)	100	80% at 1 year 74% at 5 years	Both DDLT and LDLT
Xing et al. (2013)	133	78.1% at 1 year 72.8% at 5 years	Hepatorenal syndrome improved with LT, good outcome of combined liver kidney transplantation for patients with ESRD
Finkenstedt et al. (2013)	33	84.8% at 1 year 82% at 5 years	High wait list mortality in ACLF group, survival after LT comparable to non-ACLF
Gustot et al. (2014)	35	80.9% at 6 months	10% in those not transplanted for ACLF2–3
Levesque et al. (2017)	140	70% 1 year as compared to 92% in without ACLF	ACLF 3 poor than lower grades, 17/30 (56%) mortality at 1 year in this group
Artru et al. (2017)	73	83.9% at 1 year, baseline ACLF grade 3	7.9% survival in not LT, all patients had complications and longer hospital stay
Moon et al. (2017)	189 ACLF	76.8% at 1 year	ACLF longer stay in ICU as compared to without ACLF, survival worse than patients without ACLF (89.8% and 81.0%, respectively, at 1 and 5 years)
	136 (non-ACLF)	70.5% at 5 years	
Yadav et al. (2017)	52	88.5% at 90 days	Non-LT ($n = 68$) had 32.4% survival at 6 months
O'Leary et al. (2019)	768	93% each at 6 months	

use of right lobe liver grafts including the middle hepatic vein that ensures adequate venous drainage and speedy recovery. The 5-year survival rate with LDLT is also over 90% in patients with high MELD score at admission [90].

43.6.7 Assessing Futility in Patients with ACLF

In patients with deteriorating clinical course over the first week, a goals of care discussion should be undertaken. This patient population has shown to have the highest mortality in the second week of ICU admission. The CLIF-C ACLF score, designed to predict short-term mortality over 28 days in ACLF patients, has a 100% specificity in predicting mortality when the score is ≥70 has, despite all supportive treatment. The cumulative rate of survival in the ICU with MELD >28.2 is estimated to be 28.2% and SOFA greater than 10.5 is 10.5% [91]. Cirrhotic patients are prone to infection with higher risk of mortality as compared to non-cirrhotic, and the presence of septic shock is estimated to predict mortality independently (OR 50.3, 95% CI 8.99–281) [92].

Additionally, multiorgan failure involving >3 organs requiring support (i.e. ionotropic support, mechanical ventilation, and continuous renal replacement therapy) is independently associated with increased mortality [93].

43.6.8 Need of Dynamic Prognostic Models

Patients with ACLF rapidly develop infections, organ failures leading to high mortality in the absence of liver transplant. Currently, there is no universal prognostic model for deciding the liver transplant in patients with ACLF. The model for end stage liver disease score (MELD) is validated for patients with decompensated cirrhosis and King's College Hospital Criteria (KCH) for acute liver failure [94]. In patients with severe alcoholic hepatitis, the Lille's score has shown the need of an emergency liver transplant [95, 96]. In patients with autoimmune hepatitis, failure to improve the MELD scores at day 7 has been shown to be associated with worse outcomes and need for liver transplant [97, 98]. The AARC score has been developed from the large AARC database which is a composite of five variables [99]. The score includes bilirubin, creatinine, international normalized ratio (INR), arterial lactate, and hepatic encephalopathy. The score incorporates measures of liver failure (i.e., bilirubin, INR and lactate) and organs of utility, i.e., kidneys and brain. Kidneys are one of the most frequent extrahepatic organ failure in patients with ACLF and also have prognostic implication. Similarly, akin to ALF, brain involvement is an ominous sign and necessitates need of emergency liver transplantation. The AARC score additionally is dynamic and performed superior to other prognostic scores in predicting the outcome of ACLF patients. The score could therefore determine the need of emergency liver transplant in these patients, however, has not been validated in this context. Apart from these, the CLIF-C ACLF score developed by the EASL-CLIF consortium can be used in prognostication in ACLF patients admitted to the intensive care unit. A score above

70 has been shown to have a 100% specificity in predicting mortality in patients who are critically ill [100, 101]. However, considering the differences in the definitions, the score needs to be evaluated in ACLF patients defined according to the APASL.

43.7   Conclusion

ACLF is a distinct entity characterized by the development of liver failure on a background of chronic liver disease usually precipitated by an acute insult. Systemic inflammation is a key event in the pathogenesis of the syndrome. The management of the syndrome is a composite of identification and treatment of the etiological insult, systemic inflammation, and potentiation of liver regeneration. Development of infection and extrahepatic organ failure is a key event with a prognostic implication. The role of liver support therapies needs to be explored both as a bridge to transplant and to spontaneous recovery. Dynamic prognostic models for deciding transplant, reversibility, and futile ICU care are an unmet need in patients with ACLF.

Highlights
- Acute on Chronic Liver Failure (ACLF) is characterized by high 28-day mortality.
- Liver failure drives extrahepatic organ failures in patients with ACLF.
- ACLF occurs in the context of gut dysbiosis and systemic inflammation.
- The syndrome is characterized by a dynamic course and the rapidity of progression to organ failures providing the first 2 weeks as the "golden-window" for therapeutic interventions.
- Liver transplant is the ultimate savior in patients with ACLF.
- The syndrome of ACLF is a clinical challenge and an area of unwavering research for clinicians.

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