Chapter

Acute on Chronic Liver Failure: Role of the Bacterial Infections

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Abstract

Acute-on-chronic liver failure (ACLF) refers to a syndrome characterized by acute deterioration of liver function of a pre-existing chronic liver disease with increased short-term mortality at 3 months due to multiorgan failure. Definition of ACLF has been refined, but differences between western and eastern areas still exist. Diagnosis of ACLF as recommended by the EASL-CLIF consortium is based on the assessment of organ dysfunction. The pathogenesis of this syndrome is attributable to an exaggerated host response to inflammation, responsible for the severe haemodynamic derangement leading to multiorgan failure. ACLF is triggered by precipitating events like acute hepatitis either viral, drug-induced, toxic, or alcoholic, variceal bleeding and sepsis. Bacterial infection is currently considered the most frequent trigger of ACLF in Western countries. Cirrhotic patients, particularly if decompensated are prone to develop bacterial infection because loss of integrity of the intestinal mucosal barrier and translocation of pathogen-associated molecular patterns (PAMPs). Bacterial translocation may develop into overt infection at different sites, along with sepsis and septic shock that may lead to ACLF. Epidemiology of bacterial infection in cirrhosis has been changing and this accounts for new antibiotic regimens as empirical therapy in critically ill cirrhotic patients with bacterial infection. In this chapter, we will discuss on definition, pathogenesis, clinical aspects and therapy of bacterial infection-related ACLF.

Keywords: acute-on-chronic liver failure (ACLF), bacterial infection, multi-drug-resistant bacteria, cirrhosis, sepsis, septic shock

1. Introduction

Acute-on-chronic liver failure (ACLF) is a recently recognized syndrome characterized by acute function deterioration on an underlying liver cirrhosis or chronic liver disease associated with a high short-term mortality and an immense health care expenditure. There is a worldwide agreement that ACLF represents an acute deterioration of pre-existing chronic liver disease, usually triggered by a precipitating event.

Although the pathogenesis of this syndrome is still under investigation, it seems to be largely attributable to an exaggerate host response to inflammation with release of circulatory proinflammatory cytokines and mediators which lead to hemodynamic and cellular dysfunction (cytokine storm). Bacterial infection represents the most important and frequent trigger cause of ACLF even though other trigger events like HBV reactivation or alcohol play a relevant role.

The prognosis of this syndrome remains dismal mainly because available therapeutic strategies, beside OLT, are ineffective and novel approaches are still lacking.

2. Acute-on-chronic liver failure

2.1 Definition

Definition of ACLF differs worldwide [1]. Three widely used definitions of ACLF are currently available from different geographic areas: the definition proposed by European ACLF consortium (EASL-CLIF) [2] and the North American Consortium (North American Consortium for the Study of End-Stage Liver Disease NACSELD) [3] mostly adopted in western countries and definition proposed by the APASL consortium (ACLF research Consortium: AARC) which is largely employed in eastern countries [4, 5]. All these definitions are derived from analysis of data obtained in large series of patients prospectively recruited in different centers [2, 3, 5]. These definitions share some common items such as high mortality, but also significant differences including precipitating events, underlying liver disease, diagnostic and prognostic criteria. In the western areas, bacterial infection plays the most important pathogenetic role [6, 7] followed by alcohol abuse [8], whereas in the East, both hepatitis B and alcoholic hepatitis are considered the most frequent precipitating events [5]. In the CANONIC study the following factors were considered as precipitating events for ACLF: infection, current alcohol drinking, acute reactivation of chronic viral hepatitis, gastrointestinal bleeding or a recent medical procedure like paracentesis or transjugular intrahepatic portosystemic shunt positioning [6]. It is important to note that others clinical conditions have joined the list of precipitating causes of ACLF as DILI-related injury (mainly antitubercular drugs, herbal medicine, anti-retroviral drugs and methotrexate) [9, 10], autoimmune hepatitis reactivation [11] and more recently NASH [12].

The definition of organ failures is also variable among different definitions suggesting that ACLF is not the same worldwide. Moreover, ACLF can occur not only in association with advanced cirrhosis but, as recently reported, even in chronic liver disease without cirrhosis and this issue is differently addressed in ACLF definitions [1]. However, ACLF should be distinguished from an acute liver failure in a pre-existing perfectly normal liver. The definition of short-term mortality is not uniform as well. For example, in APASL definition this time frame is settled at 28 days whereas in EASL definition is settled at 3 months. All these differences account for the difficulty in assessing the true prevalence of ACLF. In order to merge the different ACLF definitions, the World Gastroenterology Organization (WGO) tentatively proposed the following one: "ACLF is a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis, characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the international normalized ratio or INR) and one or more extrahepatic organ failures, associated with increased mortality up to 3 months [13]."

According to EASL-CLIF the definition of ACLF necessitates of extrahepatic organ failures (renal, brain, respiratory, and circulatory systems), being the sole liver failure insufficient for the diagnosis [3, 5, 6]. This specification is crucial to avoid to classify as ACLF an acute decompensation of an end-stage liver disease. Unfortunately, the definition of organ failure is not homogeneous among different regions being the agreement only on the definition of brain failure which should be graded as 3–4. Main issues showing agreement/disagreement among different definitions of ACLF are listed in **Table 1**.

	APASL	EASL-CLIF	NACSELD
Definition	Acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR ≥ 1.5 or prothrombin activity <40%) and complicated within 4 weeks by ascites and/or hepatic encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease associated with high mortality	An acute deterioration of a 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
Definition of liver failure	Bilirubin≥5 mg/dL, INR ≥ 1.5	Bilirubin >12 mg/dL	Not specified
Source of definition	Prospective cohort of 3300 patients	Prospective cohort of 1343 patients	Prospective cohort of 507 patients
Inclusion criteria	Compensated cirrhosis CLD without cirrhosis Acute insult to liver	Cirrhosis (compensated or decompensated) Renal failure (mandatory) Presentation not necessarily by liver failure Repeated episode of ACLF admitted	Cirrhosis (compensated or decompensated) Two extrahepatic organ failure Presentation not necessarily by liver failure Repeated episode of ACLF admitted
Exclusion criteria	Prior decompensation	HCC	Patients with infection but did not require hospitalization
	HCC		Cirrhosis without infection
			HIV
			Prior OLT
			Disseminated malignancies
Time frame	4 weeks	4–12 weeks (variable)	Not defined
Acute insult	Hepatic	Hepatic or systemic	Infection
Sepsis	Consequence/complication	Cause/precipitant	Cause/precipitant
Organ failure	Hepatic first, extrahepatic subsequently	Systemic inflammation leading to kidney failure as the primary with or without other organ failure	Systemic inflammation leading to extrahepatic organ failure
Disease severity score	AARC-score	CLIF-C OF	MELD
			NACSELD-ACLF
Syndrome reversibility	Yes	Not described	Not described

Table 1.
Agreement/disagreement among different ACLF definition.

In summary, the most important differences between east and west definition of ACLF is the time frame of syndrome recognition. The western paradigm of organ failure as a prerequisite for the diagnosis of ACLF delays de facto of 7–14 days the presentation/diagnosis of the syndrome as compared to the eastern paradigm which indeed put the acute hepatic insult and liver failure as the starting point. According to AACR consortium, organ failure should not be used for definition of the syndrome, but only for prognostication [14].

2.2 Pathogenesis of ACLF

AS previously stated, ACLF is characterized by an excessive inflammatory response to different insults leading to a severe circulatory dysfunction involving several organs and ending to multiorgan failure. Bacterial infection is a well-recognized cause of ACLF worldwide and it is the prevalent precipitating event according to the western definitions. Gut bacterial translocation is the initiating pathogenic mechanism. Infection by viable bacteria can induce inflammation through two classes of molecules: pathogen-associated molecular patterns (PAMPs) and virulence-related factors [15]. Both PAMPS and virulence-related factors interact with the innate immunity through innate pattern recognition receptors (PRRs), and this results in production of several proinflammatory cytokines. If this response becomes excessive, the inflamed organism is exposed to a sort of "cytokine storm" responsible for tissue damage, which, in turn, causes the release of additional molecules: the damage-associated molecular patterns (DAMPs) which accentuate and perpetuate inflammation [15]. This inflammatory cascade is the driven force leading to a full-blown ACLF.

However, not all cirrhotic patients exposed to bacterial infection will develop an ACLF. This would suggest that an individual susceptibility to inflammation does exist, the explaining mechanisms of which are still poorly understood. Furthermore, many patients developing ACLF do not have any identifiable precipitating event [6]. In these cases, it is hypothesized that ACLF might be initiated and sustained by undetected bacterial or fungal infection with subclinical intestinal translocation of bacterial PAMPs and succeeding increase of DAMP release. Targets of the "cytokine storm" are circulatory system, heart, lung, kidney, adrenal glands and brain [16]. The severity of dysfunction and the number of organ/systems involved are the main determinants of ACLF prognosis [13]. Circulatory dysfunction is characterized by a progressive peripheral arteriolar vasodilation (PAV) due to reduced vascular resistance responsible of reduced effective volemia and organ hypo-perfusion with consequent tissue damage. Heart failure is another hallmark of ACLF. Cardiac dysfunction is typically found in advanced cirrhosis and contributes to the reduction of effective volemia since the hyperdynamic state as a compensatory response to hypovolemia, becomes no longer able to compensate arterial vasodilation [17, 18]. By worsening of inflammation, hyper-dynamic state becomes even more pronounced and may shift into the so called "cirrhotic cardiomyopathy" found in 40–50% of cirrhotic patients [19]. Damaged heart becomes no longer responsive to vasoactive compounds and this causes further tissue damage perpetuating the vicious circle.

Renal failure is particularly frequent in ACLF. Acute kidney injury (AKI) defined as an increase in serum creatinine by ≥0.3 mg/dL in <48 hours or a 50% increase from a stable baseline within the past 3 months, occurs in about 20% of all hospitalized patients with cirrhosis [20]. AKI represents the most frequent organ failure in ACLF patients with a worse prognosis, hepatorenal syndrome type 1 being the most frequent prototype [21]. Hemodynamic instability and systemic inflammation both concur to renal failure. AKI in ACLF is frequently associated with organic damage of kidney which should be ruled out as soon as possible in order to set the proper therapeutic approach (plasma volume expansion with albumin plus vasoconstriction therapy or renal replacement) [22].

Brain failure, defined as grade 3 or 4 hepatic encephalopaty (HE), is part for the EASL-CLIF definition of ACLF and it is a strong prognostic predictor. In a large North American study, HE predicted short-term mortality independently of other organ failure [23, 24].

Relative adrenal insufficiency (RAI) is another complication detectable in almost half of cirrhotic patient with acute liver decompensation and should be regarded as part of multiorgan failure. It has been found to be associated with poor in-hospital survival, refractory shock, and renal failure [25]. In a prospective observational study, Piano et al. reported that cirrhotic patients with RAI have a high risk of developing sepsis, septic shock, organ failure, and death within 90 days. The authors concluded that RAI has similar prognostic value as non-renal organ failures and it should be included in the EASL-CLIF classification of ACLF [26].

2.3 Prognostic scores

The prognosis of ACLF is universally considered dismal with a mortality at 4 weeks as high as 39%. Quantitation of short- and long-term mortality risk is of paramount importance to correctly planning therapeutic measures. This quantitation is quite difficult owing to the fact that ACLF patients differ as to precipitating events, grade of cirrhosis decompensation, number of organs involved and comorbidities.

Among single easily available laboratory parameters as predictors of outcome, lactate seems to be the most accurate one. In a cooperative European study [27] serum lactate on admission was directly related to the number of organs failing and to 28-day mortality (AUROC 0.72). In addition, both baseline lactate ≥5 mmol/L and 12-hour lactate clearance emerged as independent predictors of 1-year mortality [27].

Multiple predictive scores have been proposed in the last few years. Classical scores as Child-Pugh score (CP), or the model for end-stage liver disease (MELD) and MELD-Na revealed to be inaccurate to correctly predict short-term mortality in ACLF patients. Therefore, several other multiparametric score systems have been proposed in the last few years, from western and eastern areas [14, 28, 29].

Recently, the EASL-CLIF consortium proposed the CLIF-SOFA score (Chronic Liver Failure-Sequential Organ Failure) [6] (**Table 2**). This score includes biochemical and clinical parameters indicative of organ function and stratifies ACLF patients into three grades of severity [6, 30–32]. This score was constructed over the assumption, borrowed from the point of view of intensivists, that with increasing number of organ dysfunction or failure, the mortality would cumulatively increase. The CLIF-SOFAs, however, is complex, based on consensus and expert opinion rather than data, and did not significantly improve the prediction accuracy of other scores

Organ system	Score = 1	Score = 2	Score = 3
Liver: bilirubin (mg/dL)	<6	6–12	>12
Kidney: creatinine(mg/dL)	<2	2–3.5	>3.5 or renal replacement therapy
Brain: grade (West Haven)	0	1–2	3–4
Coagulation: INR	<2.0	2.0 to <3.5	≥3.5
Circulation: MAP (mmHg)	≥70	<70	Vasopressors
Respiratory (PaO2/FiO2)	>300	≤300 to > 200	≤200
or SpO2/FiO2	>357	>214 to ≤ 357	≤214

Column 3 defines organ failure.

Table 2.
CLIF-C OF score and parameters to define organ failure.

like Child-Pugh and MELD. For these reasons, in 2014 the CLIF Consortium, using CANONIC database, developed a simplified score named CLIF-C OF score (Organ Failure) derived from CLIF-SOFA one. Patients are stratified into three-point range and scored 6–18. This score confirmed to perform better than CP and MELD. A further refinement was obtained by adding to CLIF-C OF score age and white blood cells count. This refined version, named CLIF-C ACLF, was the result of a mathematical model constructed by logistic analysis carried out upon CANONIC database and validated on a validation set of ACLF patients. Patients are scored 1–100 by a bedside easy-to-use tool which is now available at the CLIF Consortium website: http://www.clifconsortium.com/ [28]. Both CLIF-C OF and CLIF-C ACLF scores showed better prognostic performance than the conventional prognostic scores [2, 28, 33]. In a recent retrospective study carried out on a cohort of 343 consecutive cirrhotic patients with ACLF diagnosed according to the EASL-CLIF definition and aimed at comparing eight different prognostic scores, emerged that CLIF-SOFA and CLIF-C OF scores displayed the highest predictive accuracy [34]. In this study a CLIF-C OF score of 8 or lower had a 92.0% NPV and 97.8% sensitivity, while a score of 17 or higher allowed for a 95.0% PPV and 99.4% specificity for the prediction of 28-day mortality.

The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) in 2014 built a predictive score of short-term mortality named NACSELD-score further refined in 2018 [3]. According to NACSELD-ACLF score the presence of at least two organ failures such as shock, grade 3 or 4 encephalopathy, renal failure requiring hemodialysis, or respiratory failure requiring mechanical ventilation, accurately predicted 30-day survival. This score has been further validated in a population-based study on over 100,000 patients included in a large, North America representative database of hospital discharges (NIS). In this study, NACSELD-ACLF predicted survival with an area under the ROC curve 0.77 [35].

APASL consortium proposed a prognostic score named AARC with an elevated accuracy to predict early and late mortality (AUROC >80%) in patients with ACLF. Variables included in AARC score are bilirubin, INR, lactate, ascites and HE [14] (**Table 3**). According to this score patients are stratified as Grade I for a score of 5–7, Grade II for 8–10 and Grade III for 11–15 with 28-day mortality of 12.7, 44.5 and 85.9%, respectively. The score also predicted well 28 and 90-day survival.

In summary, beyond which is the best available predictive score of ACLF to be adopted, early diagnosis and rapid prognostication are essential to positively impact on outcome of this severe complication.

2.4 Treatment

Treatment of ACLF demands for a multi-disciplinary approach involving hepatologist, intensivist, infection control team, nutritionist and transplant team. The target of treatment is to cure the precipitating event on one side and liver, kidney, heart and brain failure and circulatory dysfunction on the other.

Points	Total bilirubin (mg/dL)	HE grade	PT-INR	Lactate (mml/L)	Creatinine (mg/dL)
1	<15	0	<1.8	<1.5	<0.7
2	15–25	I–II	1.8–2.5	1.5–2.5	0.7–1.5
3	>25	III–IV	>2.5	>2.5	>1.5

Grade1: score 5–7, Grade 2: score 8–10, Grade 3: score 11–15.

Table 3.
AACR-ACLF score.

2.4.1 Treatment of liver failure

In the setting of ACLF, liver transplant (OLT) is the only potentially curative option. However survival benefit shows great variability ranging from 43 to 75% in European series [36–38] and above 90% in Asia-Pacific regions [39]. The decision whether or not to list a patient for OLT has to cope with two relevant issues: urgency and futility. Urgency is motivated by the finding of around 67% mortality on waiting list for ACLF patients. This high rate of mortality is mainly due to sepsis, respiratory failure with mechanical ventilation, high vasopressor requirement and need of renal replacement treatment (RRT).

On the other hands futile transplants must be avoided. Indeed, post-transplant course in too sick patients if often characterized by severe prognosis. Many authors agree that OLT should not be offered when cardiac or pulmonary support is needed or there is rapidly progressive organ failure since, in these instances, OLT is unlike to offer survival benefit [40]. A recent observational study by Sundaram et al. [41] revealed that in patients with impairment of ACLF-3 grade score at listing to a lower grade at transplantation, post-transplant mortality was significantly lower than in patients without this impairment (12% vs. 18%). Improvement in circulatory failure, brain failure, or removal from mechanical ventilation has the strongest impact on post-transplant survival. These data further reinforce the paradigm that early selection of good candidates for OLT (realistically within the first week from admission) is mandatory to avoid futility. To maximize survival benefit through a correct selection of good candidate to OLT, some algorithms have been proposed but they are still waiting an external validation [42, 43].

Besides OLT, other therapies for liver failure have been tempted in the last few years with discordant results. This is due, at least in part, to the different criteria employed to define ACLF from different geographic areas, making hard drawing definite conclusions. Based on the assumption that ACLF may result from an exaggerated response to inflammation with high levels of circulating pro- and antiinflammation substances, extracorporeal depurating devices such as molecular adsorbent recirculating system (MARS) [44] and the PROMETHEUS [45] could have a role as a bridging therapy to OLT. Unfortunately, data on efficacy of these instruments are disappointing. In a meta-analysis and systematic review by Kiaergard et al., no benefit of MARS treatment in reducing mortality as compared to standard medical therapy was noted [46]. These conclusions were further confirmed by two recently published European randomized multicentric controlled trials, that is, HELIOS (for Prometheus) [45] and RELIEF trial (for MARS) [44] showing no benefit with these modalities on short-term transplant-free survival. Hence, their use is currently not recommended by international guidelines. Bioartificial liver (BAL) support devices such as AMC-BAL Bioreactor, HepatAssist device (employing porcine hepatocytes attached to collagen-coated micro carriers and charcoal columns) and extracorporeal liver assist device (ELAD)-C3A employing human hepatoblastoma cells provided inconsistent results on survival [47].

Thus, besides OLT, treatment of liver failure still remains largely disappointing.

An interesting issue is the use of non-selective beta-blockers in ACLF patients. In a retrospective study by Mookerjee et al. carried out on a subgroup of patients enrolled in the CANONIC study, those patients on carvedilol treatment (47%) had lower 28-day mortality (24% vs. 34%, $p = 0.048$), a less severe ACLF and a slower progression of ACLF during the study period than those not on NSBB. Moreover, patients who discontinued NSBBs ($n = 78$) after development of ACLF had a higher mortality (37% vs. 13%) [48]. These data prompted a randomized controlled trial by Kumar et al. [49] on carvedilol administration to ACLF patients without esophageal varices and moderately increased HVPG. The authors reported that carvedilol leaded to improved survival and lowered the risk of developing AKI and SBP up

to 28 days. However, these preliminary data need to be further confirmed, before carvedilol can enter the medical armamentarium of hepatologists to cure ACLF.

2.4.2 Treatment of renal failure

Acute kidney injury (AKI) is the most common organ failure in patients with ACLF, being type1 hepatorenal syndrome (HRS1) the more severe prototype. It has been demonstrated that AKI complicating ACLF is more severe than AKI complicating cirrhosis and lesser responsive to treatment [22]. The correct approach to AKI in cirrhosis has been specifically addressed in the last few years. Early diagnosis of AKI is crucial to adopt the correct treatment. A multidisciplinary panel of experts recently proposed a useful diagnostic algorithm based on serum creatinine (Scr) monitoring [50]. It should be remembered that serum creatinine tends to overestimate kidney function in cirrhotic patients. For hospitalized patients, the International Ascites Club suggests referring to the Scr determined in the last 3 months as a baseline value to monitor and stage AKI while GFR assessment is not recommended [20]. Oliguria is a useful tool for diagnostic purposes and even a useful clinical parameter in determining the severity of renal dysfunction as well. Worsening oliguria or development of anuria should be considered as AKI until proven otherwise, regardless of any rise in Scr [20]. Volume expansion is the mainstay step for management of AKI. Albumin should be preferred over crystalloids owing to its oncotic and non-oncotic properties and it must be the first choice plasmaexpander in case of bacterial infection, suspected type-1 HRS or when the cause of AKI is unclear. The recommend regimen is infusion of 25% albumin 1 g/kg day 1 followed by 20–40 g/day until renal function improves [20]. The goal of albumin infusion is to counteract the dramatic renal hypoperfusion and intrarenal vasoconstriction. Albumin plus vasoconstrictors infusion as terlipressin is the recommended combined therapy for HRS1 and it should be started as soon as possible. The earlier we start vasoconstrictor therapy the greater the chance of survival [51].

Renal replacement is the only reasonable approach when renal damage supervenes. RRT is recommended in case of worsening AKI, worsening fluid overload despite diuretic therapy or worsening acid-base status [52]. The role of dialysis however, is still under evaluation and in clinical practice; it is mostly reserved to patients candidate for OLT [50, 53].

2.4.3 Treatment of circulatory and cardiac dysfunction

As previously outlined, circulatory dysfunction due to vascular vasodilation and consequent hypotension is a severe complication of ACLF. Cirrhotic patients with hyperdynamic and hypodynamic circulatory state have a higher risk of fatal ACLF [54]. It has been shown that arterial hypotension is an independent risk factor for ACLF development [55]. In particular, cirrhotic patients with hyperdynamic state as expressed by increased cardiac index, (>CI4.2 L/min/m2) have increased levels of circulating IL-6/8 and PCR and are at major risk to develop fatal ACLF [54]. Pharmacologic support including the amine infusion, inotropic substances and fluid administration are the recommended approach [53]. In critically ill patients, a mean arterial pressure of 60 mmHg or more should be the target [56]. Repeated serum lactate determination is the best way to monitor circulatory dysfunction and repeated lactate determination is more informative than the absolute value due to the impaired lactate clearance in patients with cirrhosis [57].

Careful attention to fluid supplementation is mandatory since, in cirrhosis, an aggressive fluid administration may lead to tissue edema and to an increased total body water retention which may adversely affect the outcome [58–62]. It is well

known that cirrhotic patients are particularly prone to develop extracellular edema, ascites and pulmonary edema as a consequence of too aggressive fluid administration. In volume depleted patients, normal 0.9% saline solution at an initial dose of 10–20 ml/kg or balanced salt solutions such as PlasmaLyte are recommended [63, 64]. Albumin infusion as plasmaexpander is highly recommended. The benefits of albumin infusion in patients with cirrhosis go beyond simple volume expansion and rely on its numerous biological properties [65, 66]. Albumin infusion is strongly recommended in three specific situations: SBP, large volume paracentesis and type-1 HRS [67–72]. In addition, albumin infusion prevents AKI in patients with infections other than SBP [73, 74]. As to the amine choice, norepinephrine should be the first line agent being associated to fewer adverse events [75]. Vasopressin and terlipressin may be used as second line agents able to achieve hemodynamic improvement [76–79]. Corticosteroids in critically ill patients may be beneficial in reducing vasopressor doses and increasing the rate of shock reversal [25, 80, 81]. The rationale of corticosteroids administration lies on the relative adrenal insufficiency (RAI) that commonly comes along with circulatory dysfunction in critically ill cirrhotic patients. Corticosteroids have demonstrated a survival benefit in some [25, 82] but not in all studies [80, 81]. Hydrocortisone 200–300 mg/day in divided doses should be administered to patients partially responsive to vasopressor agents [83, 84].

2.4.4 Treatment of neurologic dysfunction

Brain dysfunction is part of multiorgan failure complicating ACLF and HE grade 3 or 4 is required for diagnosis of ACLF according to EASL-CLIF definition. The correct interpretation and differential diagnosis of brain dysfunction is challenging since several conditions may be in cause. EEG changes are of limited value in the diagnosis of HE, even though EEG may help excluding other causes of altered mental status. Brain imaging could be useful to exclude other causes of altered mental status and, in particular, to exclude intra-cerebral hemorrhage in critically ill cirrhotic patients with coagulative disorders [85].

Measurement of fasting ammonia is routinely performed in clinical practice to differentiate HE from other conditions. Nevertheless, high ammonia levels alone are not recommended for diagnosis of HE since false positive results are frequent. West-Haven criteria (WHC) are useful for HE staging and managing [50] and advanced grade [3, 4] indicate those patients needing airways protection. Glasgow coma scale (GCS) is another simple clinical tool widely employed in HE patients and a threshold <8 is a useful parameter to decided airway protection [86].

Lactulose is the recommended initial therapy for HE. Other options such as rifaximine, LOLA, intravenous albumin, or other laxatives are currently not recommended for HE treatment [50].

3. Multidrug-resistant bacterial infections in patients with acute-on- chronic liver failure

3.1 Epidemiologic considerations

Cirrhotic patients are particularly prone to develop bacterial infection [87] and bacterial infection may trigger an ACLF in up to 50% of cases in western countries [3, 6, 88–90]. On the other hand, patients with ACLF are likely to develop spontaneous and secondary bacterial infections. [6, 88, 91]. Bacterial infections increase short-term mortality by 2–4 fold, [7, 91, 92] and it is the most important prognostic predictor of bad outcome [88, 93–95].

Epidemiologic characteristics of bacterial infection have changed in the last decades. Until the 90s, Gram-negative bacteria were by far the main organisms detected in patients with cirrhosis and spontaneous bacterial peritonitis (SBP) and pneumonia were the most frequent sites of infection [9, 96–98]. In the last two decades we witnessed a steady increase of gram-positive isolates. In a recent international cooperative study (Global Study) by Piano et al. including 1302 patients with bacterial infections (43% from Europe,32% from Asia and 25% from America), the prevalence of positive bacteria was up to 38% [99]. As to the site of infection, more recent studies, confirmed SBP, urinary tract infection, and pneumonia as the most frequent sites [99–106]. Fungal infection is an emerging problem as well, particularly in cirrhotic patients needing ICU stay [107]. Noticeably, in the multi-center study of Galbois et al. [108], including 31.251 patients in ICU for septic shock, the fungal infections were more frequent in cirrhotic than non-cirrhotic patients (9.9% vs. 6.3%, $P < 0.05$). Unfortunately, in most instances fungal infection is not recognized and this could cause delayed diagnosis, treatment failure and high mortality rates [109–111]. Thinking to prophylactic antifungal treatment in severely ill patients without improvement after 48 hours of antibiotics, or in those in dialysis, corticosteroid treatment or carrying central devices is highly warranted and could also help improving the otherwise poor outcome.

Experts agree that early diagnosis is critical in determining the course of infection in cirrhotic patients [88, 112]. The acute phase proteins, such as C-reactive protein and procalcitonin, were reliable and early biomarkers for bacterial infection and are currently recommended as screening tools for the presence of bacterial infections along with routine cultural examination. Biomarkers such as galactomannan or B–D glucan are recommended for supporting the diagnosis of invasive fungal infection.

In the last 20 years, however, we record an increasing rate of bacterial infections sustained by multidrug-resistant (MDR) bacteria, and resistance to antibiotics is becoming a major global public health problem [113–118]. Recurrent hospitalizations, invasive procedures and repeated exposures to prophylactic or therapeutic antibiotics constitute known risk factors for drug-resistant organisms, in patients with decompensated cirrhosis [115]. According to internationally accepted definition, resistant bacteria can be divided into three different groups, depending on susceptibility to different class of antibiotics. Multidrug resistant bacteria (MDR) are isolates non-susceptible to at least one agent in three or more antimicrobial categories, extensively-drug resistant (XDR) are those non-susceptible to at least one agent in all but 2 or fewer antimicrobial categories and pandrug-resistant (PDR) are those non-susceptible to all currently available agents [119].

Data on prevalence and type of MDR derive mainly from single-center studies [89, 90, 96–98, 120, 113, 115–117, 121, 122] or from multicenter studies performed in specific countries [102] or assessing specific infections [123]. Canonic Study database represents an important source of information on the prevalence of MDR bacterial infections in cirrhosis across Europe, potential epidemiological differences among regions and centers, the characteristics of these infections, their impact on prognosis, risk factors for MDR and type and efficacy of empirical antibiotic treatment employed [6, 106]. According to CANONIC data, prevalence of MDR bacterial infections in Europe varies in different countries being higher in Northern and Western Europe [106].

In the Global study [99], the overall prevalence of MDR bacterial infections varies among series from a minimum of 8% in Turkey to 27–46% in Italy peaking in Korea and India (87 and 69%, respectively). This high rate of MDR bacteria found in India may be, at least in part, explained by non-prescriptional access to antibiotics in this country [124].

In Europe and USA, the highest prevalence of MDR is registered in nosocomial and health-care associated infections [91, 100, 103, 104, 116, 117, 121, 122, 125–129].

All these data unequivocally confirm that the rate of MDR bacterial infections has increased almost 10%, in the last 10 years and it is becoming a problem of growing clinical relevance in decompensated cirrhosis and ACLF. As to the type of MDR, ESBL-producing Enterobacteriaceae, VSE and MRSA are those most frequently isolated [28, 89, 102, 122, 123, 130]. However, the type of resistant strain significantly differs across countries and centers [91, 99, 106]. The Canonic study revealed that ESBL and Amp-C producing Enterobacteriaceae were more frequently isolated in France, Italy, the UK and the Netherlands; VSE predominated in France and Austria and MRSA in infections occurring in the Netherlands, the UK and Ireland. This continuous change in isolated strains among countries demands to develop surveillance programs aimed at investigating the prevalence and epidemiological pattern of MDROs at each hospital [131].

XDR bacteria must be considered extremely dangerous in cirrhosis (as in other settings), and their prevalence is far from being negligible. In the study of Piano et al., the rate of XDR was 16% in Asia,4% in America and 5% in Europe [99].

The problem of multi-drug resistance is particularly evident in ACLF or acute liver decompensation. In a study by Fernandez et al., prevalence of overall infection and, in particular, of nosocomial infections (53% vs. 22%, $p < 0.001$) caused by MDRs (16% vs. 3%, $p = 0.01$) was significantly higher in ACLF than AD [91]. In CANONIC database [106], ESBL-producing *Escherichia coli*, VSE, MRSA and ESBL-producing *Klebsiella pneumoniae* were the most frequent strands. The overall prevalence of MDR bacterial infections was 14.8% and 29.2% in culture-positive episodes and were more frequently isolated in bacteremia (28.6%), pneumonia (23.5%), and UTI (20.7%). MDR bacteria were also more frequently isolated in the ICU (23.8% vs. 12.2%, $p = 0.005$) and in nosocomial infections (21.3% vs. 8.3% and 6.6% in CA and HCA infections, respectively, $p < 0.001$). Finally, MDRs were more prevalent in infections causing severe sepsis/shock (30.3% vs. 12.2%, $p < 0.001$) or ACLF (20.5% vs. 9.4%, $p < 0.001$).

3.2 Therapeutic considerations

Due to the urgency to treat suspected bacterial infection in critically ill cirrhotic patients before susceptibility tests are available, an empirical approach is the rule. Two types of empirical antibiotic strategies are usually employed: "classical" strategies based on third-generation cephalosporins, amoxicillin-clavulanic-acid/cloxacillin or quinolones and "MDR covering strategies" including piperacillin-tazobactam, carbapenems, ceftazidime/cefepime ± glycopeptides or linezolid/daptomycin. The latter is generally considered when we face to healthcare-associated (HCA) or nosocomial infections [91, 113].

The initial empirical antibiotic therapy is considered appropriate when the antibiotic has activity in vitro adequate for the isolated pathogen in culture positive infections or when it solves the infection without need for further escalation, in culture-negative infections. Otherwise, the initial therapy is considered inappropriate [91]. When the first-line empiric antibiotic therapy failed, patients experienced a higher rate of renal failure and death during hospitalization [102, 132] as confirmed by the study by Umgelter et al. [127] who found an association between failure of antibiotic first line regimen and mortality in SBP patients. Even, Fernandez et al. [113] reported a frequent inefficacy of the empiric antibiotic therapy in patients with high risk of death, especially in nosocomial infections. All these observations reinforce the relevance of an appropriate first line antibiotic administration in ACLF [88].

3.3 Type and efficacy of first line antibiotic strategies

The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria has led to a decrease in the efficacy of classical empirical strategies

based on the administration of third-generation cephalosporins. The resistance to classical empirical antibiotic regimens is associated with a higher mortality rate, an increased duration of in-hospital stays and higher healthcare related costs when compared to infections caused by susceptible strains [89, 91, 98, 99, 116, 133, 134]. To date, it is recommended to treated nosocomial and HCA infections with empirical MDR covering strategies, whether a classical empirical approach is recommended for CA infections (**Table 4**). Empirical MDR covering strategies are usually more effective than empiric classical schemes in nosocomial infections (81.7% vs. 68%, respectively, $p = 0.01$) with a positive impact on short-term survival. A trend towards statistical significance is also observed in severe sepsis/shock (81.3% vs. 60.9%, $p = 0.06$). Inadequacy of first line antibiotic strategies increased 28-day mortality in both AD (33.3% vs. 7.7%, $p < 0.001$) and ACLF patients (50% vs. 25.8%, $p = 0.002$).

Thus, broad schemes covering all potential pathogens should be empirically used in the nosocomial setting and in severe sepsis/shock, followed by rapid de-escalation strategies to avoid a further spread of antibiotic resistance [88, 106, 114, 135]. In a recent retrospective study from Germany [136] the authors evaluated the efficacy of different first line empirical antibiotic therapies in ACLF patients with SBP. From this study emerged that meropenem-daptomycin (99.5%), meropenem-linezolid, (98.5%) and meropenem-vancomycin (96.8%) combination scheme had the highest antimicrobial susceptibility rates and piperacillin/tazobactam had the highest antimicrobial susceptibility rates among the monotherapies/fixed combinations considering all of the Gram-negative and Gram-positive bacteria. On the contrary, classical empiric therapy based on cefotaxime or ceftriaxone showed a sensibility as low as 60%. Susceptibility of bacteria to these combination regimens positively impacted on inpatient mortality and complications. However, some pharmacologic and pharmacokinetic properties of these antibiotics should be considered when empirical MDR covering therapy has to be started. Linezolid achieves rapid penetration in peritoneum and rapidly reaches high concentration in tissue [137]. However, in patients with concomitant sepsis, it might not be the best option because the effect is more towards the bacteriostatic side, and thus might be too weak to ideally treat the bacteremia component [137]. Contrarily to linezolid, vancomycin has a lower tissue concentration and weak penetrability [138]. It is therefore should be preferred for sepsis [138]. Daptomycin has a very low concentration in the peritoneal cavity (only 6% of that in serum) [139]. Thus, daptomycin should be the first-choice antibiotic to treat bacteremia and sepsis being safer than vancomycin. As to gram-negative infection, thanks to their moderate volume of distribution and excellent penetrability both piperacillin/tazobactam and meropenem could be used for infection of peritoneum as well as bacteremia/sepsis [140, 141].

As in other settings, there is a cogent need to evaluate new strategies for preventing the spread of antibiotic resistance in cirrhotic population. Many studies are investigating epidemiological surveillance through regular assessment of potential carriers of MDRs through rectal and nasal swabs during hospitalization [142, 143], rapid microbiological tests [144, 145] and antibiotic stewardship programs [112, 146, 147].

As previously stated, fungal infection is an emerging problem in cirrhotic patients, particularly in those with ACLF hospitalized in ICU. An early diagnosis of fungal infection and antifungal treatment is prognostically crucial and it has been associated with improved outcome [148]. Triazoles (fluconazole, itraconazole, voriconazole, and posaconazole) are the most frequently employed antifungal agents. However, due to reported emergence of azole resistant non-albicans spp., the first line treatment recommended in critically ill patients shifted toward a new antifungal class: the echinocandins (caspofungin, anidulafungin, and micafungin). Echinocandins are indeed, the recommended first-line treatment for patients with cirrhosis and nosocomial spontaneous fungal peritonitis. The usual intravenous

	Type of infection		Suspected MDR		
	Community acquired	**Nosocomial health-care associated**	**ESBL-P**	**MRSA VSE**	**VRE**
SBP	Cefotaxime or ceftriaxone	Piperacilline/tazobactam	Carbapenems/meropen em	Vancomicin or teicoplanin	Linezolid or Daptomycin
Spontaneous bacteremia	Cefotaxime or ceftriaxone	Piperacilline/tazobactam	Carbapenems/meropen em	Vancomicin or teicoplanin	Linezolid or Daptomycin
UTI Uncomplicated	ciprofloxacin	Nitrofurantoin or fosfomycin	Carbapenems/meropen em	Vancomicin or teicoplanin	Linezolid or Daptomycin
With sepsis	Cefotaxime or ceftriaxone	Piperacilline/tazobactam			
Pneumonia	Ciprofloxacin or moxifloxacin or	Ceftazidime	Carbapenems + ciprofloxacin	Vancomicin or teicoplanin	Linezolid or Daptomycin
	Cefotaxime or ceftriaxone		Meropenem + ciprofloxacin		

SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection; ESBL-P, extended spectrum beta-lactamase producers; MRSA, methicillin-resistent Staphylococcus aureus; VSE, vancomycin susceptible; VRE, vancomycin resistant.

Table 4.
Empirical antibiotic treatment of infection in cirrhosis (adapted from Allaire et al.) [149].

dosing regimens for invasive candidiasis are as follows: caspofungin: loading dose 70 mg, then 50 mg daily. No dose adjustement are recommended in case of moderate and severe liver disease except for caspofungin (loading dose 70 mg, then 35 mg daily) [148, 150]. De-escalation from echinocandins to fluconazole is advised in those cirrhotic patients when their condition becomes stable.

4. Conclusions

Acute-on-chronic liver failure (ACLF) is a clinical independent entity capturing the interest of hepatologists from the East and the West in the past 2 decades. Although universal definition does not exist, there is a substantial agreement that this syndrome should refer to liver failure, usually after an acute event, in a patient with chronic liver disease and characterized by an elevated short-term mortality. It should be distinguished from an ordinary decompensation of chronic liver disease and from acute liver failure of a normal liver. Although the pathophysiological mechanisms leading to this syndrome are only partly understood, systemic inflammation seems to play a crucial role. Exaggerated inflammatory response, the so-called "cytokine storm" is the main driving event leading to multiorgan failure. In most cases, bacterial infection is the initiating event of ACLF and early identification and treatment is mandatory to stop SIRS-sepsis cascade and to prevent multiorgan failure. An emerging clinical problem is represented by infection sustained by of MDR bacteria. This new epidemiologic reality has completely changed antibiotic strategies for empirical approach in decompensated cirrhosis. Control and prevention of MDR infection widespread, in particular in the nosocomial setting, as well as to make available new treatment opportunities, beside OLT, to manage liver failure are the challenge of the near future.

Conflict of interest

None to be declared.

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