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Review

Cirrhosis

Acute-on-chronic liver failure: an update

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Abstract

Introduction

Acute-on-chronic liver failure occurs in patients with cirrhosis, either spontaneously or after a precipitating event. It is characterised by high short-term mortality, resulting from the development of organ failures, infections and immune system dysfunction. New diagnostic criteria have recently been proposed, which will probably redefine this syndrome. Specific therapeutic guidelines have not yet been created. It is the main challenge to do so in the following years. For the moment, prevention and early detection of patients at risk are crucial in the management of acute-on-chronic liver failure. This review discusses all aspects of acute-on-chronic liver failure.

Conclusion

Specific guidelines to treat patients with ACLF have not been created. With a more accepted definition of the syndrome, the conduction of prospective and randomised studies to assess different interventions will be possible. Preventive measures in ACLF also play an important role in the susceptible population.

Introduction

Chronic liver failure is the most frequent and better characterised type of liver failure. It occurs in patients with cirrhosis, in which a slow and progressive deterioration of the liver function, associated with the development of portal hypertension is observed. This usually evolves over years, and culminates with the development of ascites, jaundice, variceal haemorrhage, encephalopathy and bacterial infections[1].

Another well characterised type of liver failure is acute liver failure. In this case, a rapid deterioration of the liver function is observed, which occurs after an acute hepatic insult. It is manifested by the development of coagulopathy, jaundice and encephalopathy, which develop in a period of up to 26 weeks. By definition, this type of liver failure develops in the absence of a pre-existing hepatopathy (except in the case of patients with Wilson disease, chronic hepatitis B or autoimmune hepatitis)[2].

Acute-on-chronic liver failure (ACLF) was first described in 1995[3]. Since then, many definitions have been proposed.

The Asian Pacific Association for the Study of the Liver (APASL) was the first multidisciplinary group dedicated to ACLF who proposed the following definition:

'Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease[4].'

In 2009, the Chronic Liver Failure Consortium (CLIF), together with the American Association for the Study of Liver Diseases (AASLD), provided an alternative definition:

'Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure[5].'

Unfortunately, both definitions were inaccurate. From the practical standpoint, taking those definitions, ACLF could be diagnosed in any of the following cases:

– A 45-year-old woman with a history of non-alcoholic steatohepatitis with mild liver fibrosis, that as a consequence of a toxic hepatic insult, develops jaundice, coagulopathy, encephalopathy and renal failure in a 3-week period. This patient will also fit the definition of acute liver failure.

– A 64-year-old man, with an alcoholic cirrhosis (child pugh (CTP): B-8; model for end-stage liver disease (MELD): 18) with recurrent episodes of encephalopathy and hepatocellular carcinoma within Milan criteria. After an episode of variceal bleeding, he progressed to grade III encephalopathy, developed renal failure and worsening of the prognostic scores (CTP: C-11, MELD: 25) in a 3-week period. Traditionally, we would have said that this patient is experiencing acute decompensation of the cirrhosis induced by a variceal bleeding.

Recognising the limitations of the proposed definitions, a multicentre study was created with the purpose of defining ACLF with more clear and precise criteria. The CLIF Acute-on-chronic liver failure in cirrhosis (CANONIC) study is discussed below. The aim of this review was to give an update on ACLF.

Discussion

Defining a new syndrome

Different groups have been working in the field of ACLF for many years. However, specific therapeutic guidelines, different from those already existing for the management of

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decompensated cirrhosis, have not been provided. This makes us wonder whether it is really necessary to define ACLF as a different syndrome.

There is no doubt that from the health economics point of view, this is a group of patients with high costs.

In the United Kingdom, the Intensive Care National Audit and Research Centre (ICNARC, UK) reported an increase in the proportion of patients with cirrhosis admitted to intensive care units from 2.8% to 5.4% between 2003–2005 and 2006–2008[6].

In a study that involved 23,600 patients with cirrhosis that required mechanical ventilator support and/or invasive haemodynamic monitoring, the estimated cost was of USD116,200 corresponding to every day that each patient stayed in the intensive care unit[7]. Even if not all the patients fulfilled ACLF criteria, the study represents this population who frequently develop respiratory, neurological and/or haemodynamic failure, requiring organ support therapy. Organ failure, as we will explain hereafter, is one of the essential components of patients with ACLF.

Another aspect why it is important to distinguish patients with cirrhosis and ACLF from patients with decompensated cirrhosis but without ACLF is because the prognostic is significantly different, being worse in patients with ACLF.

It is also important to determine whether a patient with cirrhosis has ACLF to select the proper tools to predict outcomes such as mortality. The most used scores to predict mortality in patients with cirrhosis are the CTP and MELD[8,9]. However, when organ failures develop, the performance of these scores is worse than the scores used in patients in the critical care units. The sequential organ failure assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) scores, designed to identify organ failures, might be more adequate to predict mortality of patients with cirrhosis and organ failures[10,11]. As discussed below, organ failures are key components of patients with ACLF.

Finally, physiopathological mechanisms for patients with ACLF have been proposed, which would define it as a different entity[5].

A new definition of ACLF: the CANONIC study results

This multicentre and prospective study was designed with the main purpose of defining ACLF with strict criteria. The study enrolled 1343 patients hospitalised with acute complications of cirrhosis. Development of organ failures and mortality within 28 days was assessed. In this study, "acute complication" was defined as any of the following: grade II–III ascites which developed in a period of 2 weeks (excluding patients with refractory ascites), acute encephalopathy, gastrointestinal bleeding or bacterial infections. In order to define organ failures, the following systems were evaluated: respiratory, haemodynamic, haematological, neurological, renal and hepatic. Each of these systems were evaluated by a modified SOFA score (CLIF-SOFA) (Table 1). By determining the mortality rate according to the presence or absence of organ failures, the following groups of patients were established:

Patients without ACLF: Represented 77.5% of the enrolled patients. This group comprises three subgroups:

1. Patients with no organ failures.
2. Patients with a single non renal organ failure who had serum creatinine < 1.5 mg/dL and no neurological failure.
3. Patients with single neurological failure who had serum creatinine < 1.5 mg/dL.

The mortality at 28 and 90 days in this group was low: 5% and 14%, respectively.

Patients with ACLF: Three subgroups were defined, with different mortality rates according to the development of organ failures.

ACLF I: Represented 11% of the enrolled patients and includes three sub-groups:

1. Patients with single renal failure.
2. Patients with single liver, coagulation, hemodynamic or respiratory failure, who had serum creatinine raging from 1.5 to 1.9 mg/dL and/or mild to moderate hepatic encephalopathy (Grade I or II).
3. Patients with single neurological failure who had serum creatinine ranging from 1.5 to 1.9 mg/dL.

The mortality at 28 and 90 days in this group was 22% and 41%, respectively.

ACLF II**:** Represented 8% of the enrolled patients. This group included patients with 2 organ failures.

The mortality at 28 and 90 days in this group was 32% and 52%, respectively.

ACLF III: Represented 3.5% of the enrolled patients. It included those patients with three or more organ failures.

The mortality at 28 and 90 days in this group was 77% and 79%, respectively.

With the results of this study, the authors proposed the following definition: '*acute decompensation of cirrhosis (ascites, encephalopathy, gastrointestinal bleeding or bacterial infection) that as a result of the development of organ failures, presents high short term mortality'.*

Depending on which organs fails, mortality rates vary, as previously explained[12].

The precipitating event

Most of the ACLF cases occur after a precipitating event, which may occur up to 4 weeks before the diagnostic is established. Since the definitions of ACLF varied significantly over the last years, different triggers have been reported. Traditionally, the precipitating events were classified as hepatic (alcoholic hepatitis, hepatotoxicity, viral hepatitis, ischemic hepatitis, etc.) or extra-

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Table 1 CLIF-SOFA. Organ failure is defined by this score when at least one of the highlighted criteria is met

Variable	0	1	2	3	4
Respiratory PaO_2/FIO_2, or SPO_2/FIO_2*	>400 >512	≤400 357–512	≤300 214–375	**≤200** **89–214**	**≤100** **≤89**
Coagulation INR** Platelets (μL)	<1.1 –	1.1**<1.25** –	1.26**<1.5** –	1.51**<2.5** –	**≥2.5** <20.000
Liver Bilirubin (mg/dL)	<1.2	≥1.2 to <1.9	≥2 to <5.9	≥6 to <12	**≥12**
Cardiovascular MAP*** (mmHg)	70	70	**Dopamine ≤ 5†** **Dobutamine††** **Terlipressin††**	**Dopamine 5 to ≤15†** **Adrenaline ≤ 0.1†** **Noradrenaline ≤ 0.1†**	**Dopamine > 15†** **Adrenaline > 0.1†** **Noradrenaline > 0.1†**
Neurological encephalopathy grade	No EPS	I	II	**III**	**IV**
Renal creatinine (mg/dL)	<1.2	≥1.2 to <1.9	**≥2 to <3.5**	**≥3.5 to 5**	**≥5**

*PaO_2/FIO_2, relation between oxygen pressure and inspired fraction of oxygen; SPO_2/FIO_2, relation between oxygen saturation of oxygen and inspired fraction of oxygen.
**INR
***Mean arterial pressure
†μg/kg/min
††Any dose

hepatic (bacterial infections, variceal bleeding, surgery, etc.). Geographical differences seem to exist regarding the prevalence of the different triggers. Bacterial infections and alcoholism are among the main causes in Europe[5]. Reactivation of HBV in patients with cirrhosis is one of the main causes in Asia. Hepatitis E is a frequent trigger of ACLF in India[4].

Given that the precipitating events are heterogeneous, the initial clinical picture of patients with ACLF may vary. As an example, patients with compensated cirrhosis who present an acute hepatitis A infection may, most of the time, be treated as an outpatient and do not require specific treatments. On the contrary, patients with cirrhosis who develop spontaneous bacterial peritonitis or variceal bleeding require hospitalisation and immediate treatment. However, over the days or weeks, no matter what the trigger was, patients who develop ACLF acquire similar clinical characteristics as a result of organ failures.

In the CANONIC study, it was not possible to determine the precipitating event in 54% of the patients. Twenty-four per cent were related to infections, 17% to alcoholism and 16% to variceal bleeding[12].

Inflammatory response and infections

One of the main functions of the immune response is to control infections. Depending on the characteristics of the patient (genetic and acquired) and the pathogen, different grades of inflammatory response may be generated. The systemic inflammatory response (SIRS) is one of the ways in which the inflammatory response manifests. In favourable conditions, the inflammatory response is controlled by anti-inflammatory mechanisms which return the patient to its basal immune status. However, occasionally, the inflammatory response may be harmful, due to an excess in the pro-inflammatory phase or in the anti-inflammatory phase.

An excessive pro-inflammatory response produces organ damage through the reduction of tissue perfusion. This is induced by endothelial dysfunction which is mediated by the formation of vascular microthrombus, capillary leak and mitochondrial dysfunction, among other mechanisms (all the direct consequences of the inflammatory response).

On the other hand, an excessive anti-inflammatory phase increases the risk of infection, which is the main complication of patients with ACLF[13].

Bacterial infections are frequent complications in cirrhosis, and are associated with poor prognosis and high mortality rates. Thirty per cent of the infected patients die within 1 month of the infection and another 30% die within one year[14].

Moreover, 20%–40% of cirrhotic patients hospitalised will develop an infection. Overall in-hospital mortality rate of cirrhotic patients with bacterial infections is around 15%, which is significantly higher than of those without infection. The mortality rate of cirrhotic patients with severe bacterial infection or with septic shock is about 60%–100%[15,16].

As mentioned, bacterial infection is a frequent trigger of ACLF. However,

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they can also complicate the evolution of patients who already developed ACLF. In this way, a vicious cycle is created. The relationship between the inflammatory response and infection may lead to immune dysfunction that may predispose to new infection or prevent the control of the already existing ones[17].

An interesting finding of the CANONIC study is that patients who had a previous history of decompensation presented lower mortality rates than patients without prior episodes of decompensation. For the moment, the most accepted explanation for this phenomenon is to consider that patients with a history of previous decompensation develop an ability to adapt the immune response, probably though desensitisation to future insults[12].

Organ failures

As we mentioned, the CLIF-SOFA allows assessing, in a simple way, the function of the most important systems (Table 1). A limitation of this score is the overlapping of the criteria used to define organ failures. For example, the liver function is defined by the level of bilirubin, whereas coagulation is defined by the international normalised ratio (INR) and the neurological failure by the encephalopathy grade. In patients with cirrhosis, the increase in the INR or bilirubin, and the development of encephalopathy could be explained by liver failure and portal hypertension, or it could also reflect a neurological and haematological failure.

Another limitation of the CLIF-SOFA is the way in which renal failure is assessed, which is through creatinine. Numerous studies have proved the limitation of creatinine to estimate the renal function in patients with cirrhosis[18].

Nevertheless, it is a valuable tool to evaluate organ function and it has prospectively been used in the CANONIC study[12].

Neurological failure (encephalopathy)

Neurological failure is defined by CLIF-SOFA by the development of encephalopathy grade III or IV.

Neurological dysfunction is very frequent in patients with ACLF. In patients with ACLF, other neurological injures are added to the classic mechanisms of hepatic encephalopathy. For example, disturbances induced by different organ failures (renal failure, haemodynamic instability, hypoxemia, etc.) and by SIRS[19] might worsen the hepatic encephalopathy.

Cerebral oedema has been proposed as a cause of encephalopathy in patients with ACLF. It is known that hepatic encephalopathy in patients with acute liver failure occurs mainly due to hepatic insufficiency and the development of cerebral oedema and intracranial hypertension[20].

On the other hand, patients with cirrhosis may present severe grades of encephalopathy but will not develop intracranial hypertension, being the hepatic insufficiency and the porto-systemic shunts the main physiopathological mechanisms involved. It has been suggested that some patients with ACLF may develop cerebral oedema and significant intracranial hypertension, in addition to the proper mechanisms of cirrhosis-related encephalopathy[21,22].

Renal failure

Renal failure is defined by the CLIF -SOFA as a creatinine ≥2 mg/dL. There are many aetiologies of renal failure in patients with cirrhosis. Undoubtedly, the circulatory dysfunction plays an important role. This is the consequence of the splanchnic vasodilatation, low blood pressure, intensive renal vasoconstriction, deteriorated cardiac function and activation of the sympathetic neurohormonal system which are present in patients with cirrhosis.

In a study that included 562 hospitalised cirrhotic patients, the most frequent causes of renal failure were related to bacterial infections (46%), hypovolaemia (32%), hepato-renal syndrome (13%) and intrinsic renal failure (9%)[23–25].

Attributing the renal failure to a single mechanism in patients with multiorgan failure is usually difficult, and generally more than one mechanism is implicated. The SIRS that characterises patients with ACLF may have a central role in the development of renal failure, accompanying and aggravating the mechanisms mentioned before.

The benefit of the anti-inflammatory or immunomodulatory agents such as corticosteroids or pentoxifylline in the prevention of renal failure in patients with acute alcoholic hepatitis might support this observation[26,27].

The administration of albumin is known to prevent renal failure in patients with spontaneous bacterial peritonitis (SBP). The most likely mechanism underlying this effect is by improving the circulatory dysfunction. However, the anti-inflammatory properties of the albumin might contribute to the nephroprotective effect[28,29].

Haemodynamic failure

Patients requiring vasopressors are considered to present haemodynamic failure in the CLIF-SOFA.

As mentioned, patients with decompensated cirrhosis present a hyperdynamic state manifested by low peripheral resistance, high heart rate and increased cardiac output, which is triggered by the vasodilatation of the splanchnic bed[30].

Moreover, it is known that some patients develop cirrhotic cardiomyopathy, which is usually manifested after some stimulus, for example, after liver transplant or after the placement of a transjugular intra hepatic porto-systemic shunt (TIPS)[31].

The inflammatory response of ACLF may worsen this hyperdynamic

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state and, occasionally, induce some degree of heart failure[32].

It is important to evaluate these patients with the proper tools in order to guide the vasopressor support and fluid replacement adequately. It is not clear which vasopressor is better for patients with ACLF. Even though terlipressin may improve the haemodynamics of patients with cirrhosis, it could also induce a reduction of the heart rate and the cardiac output[33].

Studies are required in this field to define the possible benefits or risks of the different vasopressors in ACLF.

Liver failure

Liver failure is defined by the CLIF-SOFA as a total bilirubin ≥12 mg/dL. From the physiopathological point of view, it is proposed that, besides the already existing liver structural changes, dynamic mechanisms are added which worsen tissue perfusion. The proposed mechanisms are activation of stellate cells, increase in the endothelial smooth muscle contractility and endothelial dysfunction, among others[5].

Inflammation and infection are also responsible for the progressive jaundice frequently observed in ACLF[34].

Haematologic failure

Failure in the coagulation system has been defined as an INR of 2.5 or more, or a platelet count of <20,000/μL.

Patients with cirrhosis are known to present several alterations in the coagulation. As pro-thrombotic and anti-thrombotic systems are altered, a neutral state or, more likely, a pro-thrombotic state, is generated. The most significant anti-thrombotic alterations are: deficiency in the coagulation factors (except for Factor VIII), thrombocytopenia, abnormal platelet functions and a state of hyperfibrinolytic state related to an increase of the tissue plasminogen activator (tPA) and a decrease of thrombin activatable fibrinolysis inhibitor (TAFI).

At the same time, an acquired pro-thrombotic state exists, which is manifested as a decrease of anti-coagulation proteins (protein C, protein S and antithrombin III) and plasminogen, associated with an increase in factor VIII, von Willebrand factor and the plasminogen activator inhibitor (PAI)[35,36].

The inflammatory response observed in ACLF may trigger a misbalance between these two states and its consequent manifestations in both extremes.

Other organ failures

Respiratory failure is defined in CLIF SOFA by gasometric parameters: a relation between the pressure of oxygen and the inspired fraction of oxygen (PaO_2/FiO_2) of ≤200 or by a relation between the oxygen saturation and the inspired fraction of oxygen of ≤214. In general terms, a significant proportion of the patients that complies with these criteria would require assisted mechanical ventilation.

Finally, other organ failures, such as the adrenal insufficiency, are at the moment, not considered in the definition of ACLF. Particularly, adrenal function is difficult to evaluate in cirrhotic patients. However, adrenal insufficiency was reported in 51%–68% of the cirrhotic patients with severe sepsis, especially in patients with high CTP and MELD scores, and in patients with haemodynamic instability. In these patients, an increased mortality was reported[37,38].

Clinical manifestations

In general terms, patients with ACLF are seriously ill patients, often hospitalised in critical care units and usually present ascites, encephalopathy and/or jaundice.

In patients with underlying decompensated cirrhosis before the development of ACLF, malnutrition is usually severe and progressive from the beginning. Conversely, in those patients with compensated cirrhosis before the development of ACLF, malnutrition is usually mild at the beginning but rapidly worsens.

The trigger of the ACLF and the organ failures involved will also determine the clinical characteristics of each case.

Treatment

Usually patients with ACLF are managed in intensive care units, where the management of patients with multi-organ failure is protocolised. However, patients with ACLF present some unique characteristics that may differentiate them from the non-cirrhotic patients; for example, the high susceptibility to infections, the development of specific infections (spontaneous bacterial peritonitis, spontaneous bacteraemia), the possible concomitant hepato-renal syndrome, hepato-pulmonary syndrome, porto-pulmonary hypertension, cirrhotic cardiomyopathy, haemodynamic alterations, hepatic encephalopathy and the specific coagulation disorders, among others. This is why a multidisciplinary approach is essential.

Artificial liver support

The best studied artificial liver support methods in patients with ACLF are the molecular adsorbents recirculating system (MARS) and the Prometheus.

Both devices have proved to be able to achieve detoxification functions and to remove inflammatory mediators in patients with ACLF. However, its impact regarding survival improvement has not been proved. The development of prospective and randomised studies in a complex and heterogeneous population like ACLF is challenging.

The RELIEF Study Group compared treatment with MARS vs. conventional therapy in 189 patients with ACLF and failed to show any survival benefit[39].

The HELIOS Study Group performed a prospective study that randomised

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145 patients to Prometheus or conventional therapy. The study suggested a survival benefit for patients with MELD >30 for hepato-renal syndrome. However, this should be assessed and confirmed in a new study with a suitable design to prove it in this particular sub-group of patients[40].

Until today, given that there was not a strict definition of ACLF, assessing these treatments, or others, in prospective studies was difficult. The new definition of ACLF might help develop new trials in the following years.

Liver transplant

Liver transplant in patients with ACLF raises difficulties. On the one hand, these are patients with indication for transplant and with high short-term mortality. On the other hand, the clinical conditions of patients with ACLF may present absolute contraindications for the transplant. Liver transplant has not been systematically evaluated in patients with ACLF, according to the current diagnostic criteria. Some studies, with different definitions, suggest that ACLF would not determine a worse prognosis in the post transplant period[41].

However, there is evidence to contraindicate liver transplant in patients with significant haemodynamic instability, severe hypoxemia and/or uncontrolled infections.

For the particular case of renal failure, reversion possibility after liver transplant should be predicted, and in cases where it is improbable, an alternatively simultaneous liver–kidney transplant should be considered. Finally, liver transplant in patients with advanced encephalopathy has also been associated with worse post-transplant outcomes[42].

For the moment, the timing and applicability of liver transplantation in ACLF must be individualised and assessed by a liver transplant team.

New therapeutic targets

Several lines of therapies aimed to decrease bacterial translocation have been evaluated. Rifaximin in patients with cirrhosis and ascites seems to decrease bacterial translocation and prevent SBP. Moreover, it might reduce endotoxin levels and improve systemic haemodynamics and renal function after 4 weeks of treatment[43,44].

Recently, the role of granulocyte colony Stimulating Factors (G-CSF) in ACLF was assessed. This study included 47 patients with ACLF randomised to GCSF or placebo. A survival benefit, together with an improvement of CTP, MELD and SOFA scores, was observed in the treated group[45].

Prevention

Any effort to prevent decompensation in cirrhotic patients must be applied, including:

-Immunisation: Hepatitis A, Hepatitis B, Influenza and *Pneumococcus*.
- Hygienic measures for HEV, in endemic areas.
- Alcohol abstinence.
- Avoid toxic exposures.
- Primary and secondary prophylaxis of variceal bleeding.
- Primary and secondary prophylaxis of bacterial infections.

Even if these measures are simple, in practice, they are not always performed. A clear example is the rate of immunisation in patients with chronic hepatopathy. A study that evaluated the vaccination rate in patients with risk factors between 2007 and 2011 showed a low rate of immunisation in patients with liver diseases: influenza 57%, HAV 35%, HBV 40.5% and pneumococcus 35%[46].

Conclusion

Acute-on-chronic liver failure has been redefined. Even if it may be modified in the future, this new definition allows a precise characterisation of this heterogeneous group of patients.

The most accepted definition at the moment is: '*acute decompensation of cirrhosis (ascites, encephalopathy, gastrointestinal bleeding or bacterial infection) that as a result of the development of organ failures, presents high short term mortality'.*

Probably, over the time, the present definition will be modified, particularly, regarding the definition of 'acute decompensation' and organ failures.

The CLIF-SOFA objectively defines the severity of the organ failures, and proved to be the score that best correlates with in-hospital mortality in this group of patients.

Mortality within 28 and 90 days of patients with ACLF is very high and it is related to the number of organ failures and the organs involved.

Specific guidelines to treat patients with ACLF have not been created. With a more accepted definition of the syndrome, the conduction of prospective and randomised studies to assess different interventions will be possible. Prevention measures in ACLF also play an important role in the susceptible population.

The most ambitious goal is, probably, to detect which patients are at risk of developing ACLF, in order to implement strategies to avoid the development of organ failures.

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