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REVIEW

Acute on chronic liver failure: From pathophysiology to clinical management

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SUMMARY

Acute on chronic liver failure (ACLF) is currently recognized as a specific entity characterized by acute deterioration of liver function in the context of compensated or even decompensated, but hitherto stable, cirrhosis. Worsening of liver function and subsequently of other end-organs occurs rapidly and follows a precipitating event that directly or indirectly affects liver function. Available data indicate that ICU mortality for ACLF ranges from 35% to 89% and in-hospital mortality ranges from 43% to 88%. Patient outcome is not simply determined by the severity of liver disease. Indeed, the development and degree of end-stage organ failure represents the main determinant of outcome in ACLF patients. The pathophysiology of ACLF may be approached with the PIRO concept employed for sepsis (Predisposition, Infection/Inflammation, Response, Organ Failure). According to this approach, Predisposition is indicated by the severity of cirrhosis, Injury by nature/severity of the precipitating event(s), and the severity of inflammation and risk of infection express the patient's Response to injury. Finally, the extent of Organ failure is responsible for prognosis of ACLF patients. Current medical therapy involves management of the precipitating event, support end-organs and prevention/treatment of complications, until the eventual recovery of liver function. If medical treatment fails, transplantation is the only option in eligible patients. Characterization of the syndrome, definition of pathophysiological mechanisms, and improvement of patient management, currently call for ample efforts.

1. Introduction

Liver failure can develop acutely in the absence of pre-existing liver disease (acute liver failure, ALF), in the presence of known or unknown chronic liver disease (acute on chronic liver failure, ACLF), or chronically, as decompensation of pre-existing end-stage liver disease (Table 1). In recent years, ACLF has been increasingly recognized as a specific entity characterized by acute deterioration of liver function in the context of compensated or even decompensated, but hitherto stable, cirrhosis. Worsening of liver function and subsequently of other organs occurs over a period of a few weeks and follows a precipitating event. This event may directly (e.g. drug- or alcohol-induced liver injury) or indirectly (e.g. sepsis, portal hypertension-related bleeding) affect liver function. The clinical features of ACLF imply rapid disease progression, the need for multiple organ support and poor short- and medium-term prognosis.[1] However, a clear definition of ACLF is currently lacking, and some uncertainties emerge, as this term is being used by clinicians to define different conditions. Two consensus conferences elaborated a definition for this syndrome. The first definition of ACLF was provided by the Asia–Pacific Association for the Study of Liver Disease (APASL), as an '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'.[2] Subsequently a second definition emerged from an EASL-AASLD single topic symposium, where ACLF was 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 multi-system organ failure'.[3] The second definition, if not stated

Abbreviations: ALF, acute liver failure; ACLF, acute on chronic liver failure; ADMA, asymmetric dimethyl-L-arginine; APACHE, acute physiology, age and chronic health evaluation; APASL, Asia–Pacific association for the study of liver disease; ASA, American Society of Anesthesiologists; cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; FABPS, fatty acid binding proteins; HBV, hepatitis B virus; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic vein pressure gradient; ICU, intensive care unit; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; INR, international normalized ratio; MARS, molecular adsorbent recirculating system; MELD, model of end stage liver disease; NAG, N-acetyl-β-(D)-glucosaminidase activity; NGAL, neutrophil gelatinase-associated lipocalin; NO, nitric oxide; PIRO, predisposition, infection/inflammation, response, organ failure; SIRS, systemic inflammatory response; SOFA, sequential organ failure assessment; TIPS, transjugular intrahepatic portosystemic shunt; TNF, tumour necrosis factor.

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Table 1
Comparison of end-stage liver disease and ACLF.

Present in both conditions	Unique to ACLF
Multi-organ failure	Potential reversibility
Deranged systemic inflammatory response	Precipitating event
	High mortality compared to cirrhotic patients with similar MELD scores

Abbreviations: ACLF, acute on chronic liver failure; MELD, model of end stage liver disease.

otherwise, will be employed in the present review. Characterization of the syndrome, definition of pathophysiological mechanisms, and improvement of patient management, currently call for ample efforts. This review focuses on recently acquired concepts related to these various aspects. The pathophysiology of ACLF may be approached with the PIRO concept employed for sepsis (predisposition, infection/inflammation, response, organ failure).[4] According to this approach, predisposition is indicated by the severity of cirrhosis, injury by nature/severity of the precipitating event(s), and the severity of inflammation and risk of infection expressed in the patient's response to injury. Finally, the extent of organ failure is responsible for the prognosis of ACLF patients. Categorization of patients with PIRO allows for a definition of therapeutic intervention and prognosis at different levels.

2. Epidemiology, clinical scenario and prognosis (P)

Limited data are available concerning ACLF epidemiology. Data obtained in a US patient sample, analysed in a EASL-AASLD single topic symposium on the management of critically ill cirrhotic patients in the intensive care unit (ICU),[3] reported in-hospital mortality of 53% and mean hospitalization length of 14 days for ACLF. Prognostic factors predicting the outcome in patients with ACLF are currently under evaluation. In ACLF, two simultaneous insults are operating, acute and chronic. The degree of each injury is variable, with a prominent role for either type. Whether the prognosis of the patient depends on the degree of acute or chronic injury, or both, is still not well defined (Table 2). Accumulating evidence indicates that scoring systems simply addressing the severity of liver disease, such as the Child-Pugh[5] or the Model of End Stage Liver Disease (MELD) scores,[6] are not adequate in comparison to systems also evaluating extra-hepatic organ dysfunction such as the Sequential Organ Failure Assessment (SOFA) (Table 3)[7] or the Acute Physiology, Age and Chronic Health Evaluation (APACHE)[8] scores.[9] Available data indicate that ICU mortality for ACLF ranges from 35% to 89% and in-hospital mortality ranges from 43% to 88%,[10–29] (for a comprehensive list of references see Ref. [9]). Although different criteria were employed in patient selection and follow-up, a careful evaluation of these data demonstrates that patient outcome is not merely determined by the severity of liver disease as expressed by conventional scoring systems (such as the Child-Pugh score), while the development and degree of end-stage organ failure represents the main determinant of outcome in ACLF patients.

Table 2
Grades of ACLF.

ACLF-1: Renal failure or a non-renal organ failure associated with creatinine 1.5 −2 mg/dL and/or grade I–II encephalopathy;
ACLF-2: 2 organ failures
ACLF-3: 3 organ failures
ACLF-4: 4–6 organ failures

From R. Moreau et al., Diagnosis, prevalence, and prognosis of acute-on-chronic liver failure (ACLF): results of the EASL-chronic liver failure (CLIF) consortium CANONIC study. Abstract 1404, International Liver Congress 2012.
ACLF, acute on chronic liver failure.

Table 3
End organs failure according to SOFA score.

Liver failure will be defined by a SOFA sub-score of 4
Respiratory failure by a sub-SOFA score ≥3 or requirement for mechanical ventilation
Haematologic failure by a sub-SOFA sub-score of 4 and/or INR >2.5
Cardiovascular failure by a sub-SOFA score ≥2 (i.e. the use of vasopressors)
Neurologic failure by a sub-score ≥3 (based upon the West Haven criteria) or requirement for endotracheal intubation to prevent aspiration pneumonia
Renal failure by a sub-SOFA score ≥2 or requirement for renal-replacement therapy

Abbreviations: SOFA, sequential organ failure assessment; INR, international normalized ratio.

3. Pathophysiology

3.1. Injury (I)

The precipitating event may directly affect and worsen liver function such as in the case of drug-induced liver injury, alcoholic hepatitis, superimposed viral hepatitis, vascular diseases (mainly portal vein thrombosis or Budd-Chiari syndrome) and ischaemic hepatitis. Alternatively an extra-hepatic event may indirectly induce decompensation (portal hypertension-related bleeding, surgery, infection or trauma). Nonetheless, in a substantial proportion of patients no precipitating event can be identified. Survival of patients with bleeding related to portal hypertension can be improved by early administration of antibiotics or by insertion of a transjugular intrahepatic portosystemic shunt (TIPS), which is indicated in actively bleeding Child Pugh class B patients and in patients with advanced liver disease[30,31] because cardiopulmonary events and the decline in hepatocellular function that follows failure to control bleeding and/or early rebleeding were prevented. Early antiviral therapy in patients acutely infected with HBV in the setting of pre-existing chronic liver disease prevents decompensation and improves survival.[32]

In patients undergoing surgery, the most relevant predictors of post-operative mortality were severity of liver disease as indicated by the MELD score, age, and the American Society of Anesthesiologists (ASA) score.[33] It is conceivable that an altered patient response to direct or indirect injury implies an unregulated inflammatory response and immune dysfunction leading to increased susceptibility to infection and ultimately causing ACLF. This sequence of events defines a stereotyped common cascade unifying diverse precipitating injuries/events.[34]

3.2. Inflammation and infection (R)

The pivotal role of a systemic inflammatory response (SIRS) in ACLF emerges by its association with more severe encephalopathy, infections, renal failure and poor outcome.[34–36] Elevated levels of multiple pro- and anti-inflammatory cytokines have been reported in patients with ACLF, including tumour necrosis factor (TNF)-α, sTNFαR1, sTNFαR2, interleukin (IL)-2, IL-2R, IL-6, IL-8, IL-10, and interferon (IFN)-γ.[37,38] Although interference with these or other cytokine systems could be considered an appealing therapeutic strategy, only limited data are available. Moreover, the use of anti-TNF-α in patients with alcoholic hepatitis has been associated with an increased risk of infection and greater mortality rates.[39,40] Moreover, mortality associated with renal failure in cirrhotic

patients is significantly higher in those with SIRS,[41,42] emphasizing the possible pathogenic role of this condition.

Bacterial infections in cirrhosis are common, particularly in decompensated patients, and their occurrence increases mortality by two- to four-fold.[43] About 40–50% of patients with ACLF present an infection at hospital admission and an additional 20–40% will develop nosocomial infections. The mortality rate for severe bacterial infection in cirrhotic patients is about 60–100%.[43–47] Therefore, strict surveillance and repeated cultures are mandatory. Careful use of indwelling devices, including urinary catheters, and prompt prophylaxis or treatment of infections remain the cornerstones of patient management.

Several causes account for the increased susceptibility of these patients to bacterial infections. Liver dysfunction leads to several abnormalities of defence mechanisms, as both humoral and cell-mediated immunity are depressed. Therefore SIRS may lead to immune dysregulation, predisposing to bacterial translocation and infection, that in turn will further aggravate a pro-inflammatory response.[48] This vicious cycle ultimately results in sepsis, renal failure, bleeding or rebleeding, hepatic encephalopathy and death.[49–53] Identification of biomarkers that predict susceptibility to infections could in the future allow for the stratification of patients in clinical categories with different risks, and therapy could be individualized. Along these lines, neutrophil dysfunction in ACLF seems reversible and probably due to circulating endotoxin.[50] Interestingly preliminary data support a role for modulation of enteric microflora in the recovery of neutrophil phagocytic capacity[52] (Fig. 1).

3.3. Liver and other end-organs in ACLF (O)

Although liver damage is the initiating event in ACLF, its occurrence triggers an involvement of other extrahepatic systems that eventually condition the prognosis of the patient (Fig. 2).

3.4. Liver

Jaundice is considered an essential sign for the diagnosis of ACLF. Various authors have used different cutoff levels of bilirubin, varying from a serum concentration of 6–20 mg/dL.[54–57] A cut-off

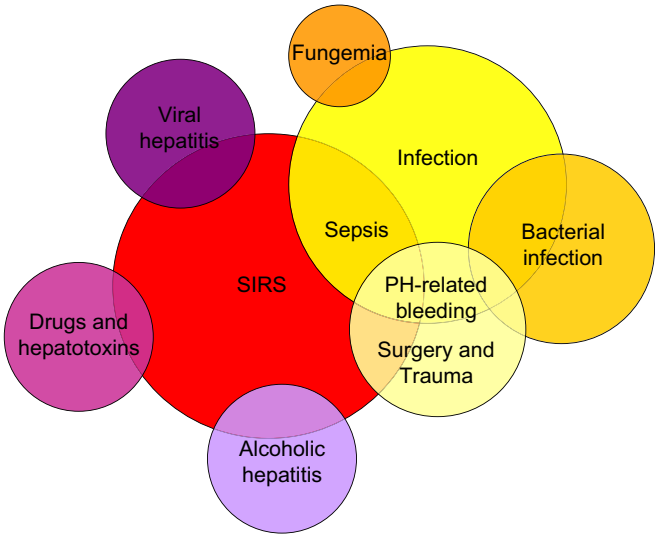

Fig. 1. Precipitating events in ACLF. Note that SIRS may even occur in the absence of injury. Infection and sepsis are mainly related to spontaneous bacterial peritonitis, pneumonia, urinary tract infection and skin infection. SIRS, systemic inflammatory response syndrome; PH, portal hypertension. Modified from Olson & Kamath Curr Opin Crit care 2011,17:165.

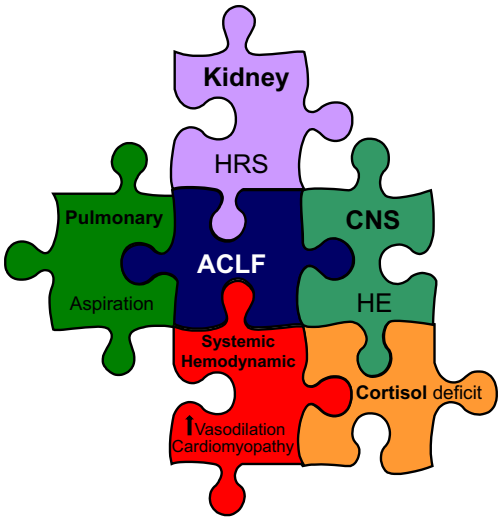

Fig. 2. The liver and other organs in acute on chronic liver failure (ACLF). CNS, central nervous system; HE, hepatic encephalopathy; HRS, hepatorenal syndrome.

level greater than 5 mg/dL of serum bilirubin was suggested in the APASL consensus recommendations.[2] Coagulopathy was defined by APASL as a INR >1.5 or prothrombin activity less than 40%.

An early biopsy may help in understanding the mechanisms involved and improve patient management (see liver histology in ACLF). Indeed, ACLF due to a non-specific injury such as variceal bleeding or bacterial infection is thought to cause different effects other than direct injury such as the ones caused by drugs, toxins or superimposed hepatitis. Recent evidence has highlighted the importance of bilirubinostasis and SIRS as early markers to allow identification of high-risk patients among those with acute deterioration of alcoholic cirrhosis and resultant ACLF. Moreover, bilirubin levels were strongly associated with an increased risk of subsequent infection.[58,59]

Liver inflammation markedly influences portal pressure, a major complication of cirrhosis and a critical determinant of prognosis, and superimposed alcoholic hepatitis in patients with alcoholic cirrhosis is a prototypical example of ACLF. In this context, experimental studies indicate that TNF-α could play an important role in the development of portal hypertension in alcoholic hepatitis. Indeed, anti TNF-α therapy has been reported to reduce portal pressure in patients with severe alcoholic hepatitis and cirrhosis.[60] Several lines of evidence suggest that gut-derived endotoxaemia plays a pivotal role in the pathogenesis of portal hypertension, and therefore have a role in the pathogenesis of ACLF.[61] In fact, modulation of gut flora by antibiotics administration[62,63] or endotoxin neutralization with high density lipoproteins[64] have been associated with the reduction of portal pressure. Moreover, reactive oxygen species also contribute to increase portal pressure, reducing the availability of intra-hepatic nitric oxide (NO),[65] and resulting in increased intra-hepatic resistance to blood flow. Along these lines, hepatic eNOS activity has been shown to be reduced in the context of cirrhosis with superimposed inflammation.[66,67] The liver also plays a prominent role in the metabolism of asymmetric dimethyl-L-arginine (ADMA), an endogenous inhibitor of nitric oxide synthase. Hepatocellular damage is a main determinant of elevated ADMA concentrations.[68–72] Moreover, dysfunction of the cyclic GMP system has been indicated as an additional mechanism leading to reduced response to nitric oxide in cirrhotic livers. Interestingly, phosphodiesterase-5 inhibitors such as sildenafil, which increase cGMP, have been shown to have a beneficial effect on intra-hepatic resistance.[73]

3.5. Kidney

Acute kidney injury is a frequent and important feature of ACLF, as it is associated with poor prognosis.[11–13,17,42,58,74,75] In general, changes in renal haemodynamics occur early in cirrhosis and culminate in a circulatory dysfunction that characterizes hepatorenal syndrome (HRS). HRS is characterized by a massive splanchnic vasodilatation, which reduces arterial blood pressure and leads to extreme renal vasoconstriction, impaired cardiac function and marked activation of the main vasoconstrictive systems[76–78] (Table 4).

Hyperdynamic circulation is essential to maintain central blood volume and renal perfusion in cirrhosis. When cardiac output decreases, effective hypovolaemia is further enhanced, leading to additional recruitment of endogenous vasopressor systems followed by worsening of renal hypoperfusion and HRS. The mechanisms leading to decreasing cardiac output remain largely unknown, but SIRS has been suggested to be involved (see systemic haemodynamics and cardiac dysfunction). Gold standard treatments for HRS, which are directed to the restoration of arterial effective blood volume, are unsuccessful in 54% of patients,[79] suggesting that in these patients different factors contribute to the development of renal dysfunction. Moreover, in 30–40% of cirrhotic patients with renal failure bacterial infection, e.g. spontaneous bacterial peritonitis, is the leading cause.[77]

The role of inflammation and/or oxidative stress in renal failure associated with ACLF is highlighted by the benefit of anti-inflammatory agents such as albumin, pentoxifylline or N-acetylcyteine, which decreased the risk of renal dysfunction in patients with alcoholic hepatitis.[80,81] In ACLF, both prerenal and renal causes are involved in the pathogenesis of acute renal failure. Prerenal factors are generally associated with renal hypoperfusion, which may be associated with intravascular volume depletion (haemorrhage, renal and gastro-intestinal fluid loss). In other cases, a full-blown HRS express the type of kidney damage in the presence of marked deterioration of effective arterial blood volume. Most intrarenal causes are related to ischaemic acute tubular necrosis due to renal hypoperfusion.

Availability of urinary biomarkers in clinical practise may allow early diagnosis of renal impairment and the discrimination between functional and inflammatory causes. Markers of tubular injury such as kidney injury molecule-1 and alpha glutathione S-transferase or markers of inflammation such as NAG, NGAL, FABP, and IL-18[82] appear to be promising and will deserve further evaluation.

3.6. Brain

Metabolic encephalopathies refer to alterations of the brain's integrated activity in the absence of structural abnormalities.[83] Clinical manifestations vary from mild executive dysfunction or agitated delirium to deep coma with decerebration. Encephalopathy may represent a manifestation as well as a precipitating factor of ACLF. From a pathophysiological perspective, brain swelling is an important feature of ACLF.[84–87] Ammonia is thought to play a key role in the development of hepatic encephalopathy (HE) but no direct relationship between the severity of hyperammonaemia and HE has been demonstrated.[88] The current view is that a synergy between chronic increase in ammonia and inflammation related to an acute hepatic insult facilitate the development of brain oedema. The mechanism is likely related to generation of cytokines in the brain, increased iNOS expression, oxidative stress and formation of nitrated protein adducts.[87,89]

The most common clinical entities observed in decompensated cirrhotic patients are hepatic and hyponatraemic encephalopathy and they may even co-exist.[90] Mortality rate in ICU was 10% in patients with isolated encephalopathy and 80% in those with failure of other organs.[91] In these patients airway protection represents a priority, and aspiration pneumonia and acute respiratory failure are major complications of encephalopathy.

Table 4
Diagnostic criteria for the hepatorenal syndrome.

- Cirrhosis with ascites
- Serum creatinine above 1.5 mg% (>1.33 mM)
- No improvement of serum creatinine (decrease to a level of 133 mmol/L) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/Kg of bodyweight per day up to a maximum of 100 mg/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography

3.7. Systemic haemodynamics and cardiac dysfunction

Portal hypertension associated with cirrhosis is initiated by an increase in intrahepatic vascular resistance, related both to fibrosis and to increased intrahepatic vascular tone. The resulting increase in splanchnic blood flow in turn gives rise to a hyperdynamic systemic state. The increased cardiac output observed in this situation is mainly due to a vasodilated splanchnic bed but paradoxically, the blood flow in other organs, such as kidneys or the brain is decreased.[92]

Circulatory failure in ACLF resembles severe sepsis and is typically characterized by an exacerbated hyperdynamic state with the inability to obtain adequate perfusion pressure despite volume expansion and large doses of inotropes, with subsequent appearance of lactic acidosis.[93–97] Indeed, unlike decompensated cirrhosis, where cardiac output remains elevated, in ACLF a drop in cardiac output may be observed despite splanchnic vasodilation and both systolic and diastolic function may become affected. Cardiac dysfunction in ACLF, as well as in sepsis, is related to increased TNF-α and nitric oxide, and decreased cortisol levels,[98] resulting in further vascular dilatation and decreased sensitivity to vasoconstrictors. Cortisol (see hepato-adrenal axis) is reduced in more than 50% of patients affected by chronic liver disease and concomitant sepsis, resulting in adrenal insufficiency.[98–100] Cardiovascular collapse in ACLF is associated with increased mortality, especially in patients who present with other end-organ dysfunction and particularly renal failure.[94] Therefore, is crucial to properly follow cardiac function to guide fluid replacement and inotropic support.

3.8. Coagulation

Regardless of abnormal routine coagulation tests, thrombin generation is normal in compensated or "stable decompensated" cirrhotic patients, due to a rebalancing of pro- and anti-coagulant factors that seldom leads to hypercoagulation, providing that platelet count is 'adequate', i.e. >50,000/uL. The prophylactic use of blood products, even in the context of variceal bleeding is no evidence-based and therefore empirical, and no effect of recombinant factor VIIa has been shown.[101] Moreover, normalization of coagulation parameters is difficult to achieve and this practise could provoke transfusion-related acute lung injury, volume excess and other transfusion-associated reactions. However, endogenous low-molecular weight heparinoids are detected in cirrhotic patients with sepsis, and disappear with resolution of infection.[46] Along these lines, administration of antibiotics in

variceal bleeding is reported to reduce early rebleeding rate and mortality.[102] Major coagulation abnormalities described in ACLF include increased fibrinolysis and defective platelet function.[103] There is an unmet need for more comprehensive coagulation tests to guide correction of coagulation dysfunction on an individual basis.

3.9. Hepato-adrenal axis

Development of adrenal insufficiency worsens the prognosis of cirrhotic patients with severe sepsis. As stated above, this disorder has been reported in a considerable fraction (51–68%) of patients with cirrhosis and severe sepsis, and particularly in those with haemodynamic instability and more advanced liver disease as expressed by MELD or Child-Pugh scores. Preliminary data indicate that administration of hydrocortisone in this setting may improve circulatory function.[98]

4. Portal pressure measurement in ACLF

ACLF is an acute event on an underlying liver disease and hence portal pressure is thought to differ from that in patients with compensated and even decompensated cirrhosis. Kumar et al.[104] demonstrated that patients with small varices and lower hepatic vein pressure gradient (HVPG) have a higher chance of recovery after the acute insult settles down. Conversely, patients with large varices or high HVPG have a poor prognosis following ACLF.

5. Liver histology in ACLF

Histologic data in ACLF are scarce, since it is not easy to obtain a liver specimen in these often very sick patients, and thus the need for a liver biopsy should be individualized. The transjugular approach is relatively safe in these patients and allows simultaneous evaluation of systemic haemodynamic and HVPG. Liver biopsy may provide information on the severity of the underlying liver disease, and may also be useful in identifying the etiology of the acute injury.

No histologic features are considered pathognomonic of ACLF. Single centre data[105] discriminate two patterns with different prognosis: pattern I, characterized by hepatocyte ballooning, rosette formation, cellular cholestasis, variable interface activity and fibrosis; pattern II, with marked ductular proliferation, coarse, inspissated bile plugs, foci of confluent/bridging necrosis, eosinophilic degeneration of hepatocytes, higher stage of fibrosis and variable activity. Pattern II was associated with a much worse prognosis.

6. Management of ACLF

Current medical therapy involves management of the precipitating event, support end-organs and prevention/treatment of complications, until the eventual recovery of liver function. If medical treatment fails, transplantation is the only option in eligible patients. However, cadaveric organ shortage strongly limits this possibility, and alternative methods to support liver function are currently being investigated. Intensive care management of patients with ACLF is beyond the scope of this review. Otherwise, the main principles of multiple organ support have to be employed to allow treatment of acute injury and liver function recovery.

6.1. Liver transplantation

There is a paucity of data on liver transplantation in ACLF, even if this represents the only definitive therapy for patients who do not improve with supportive measures to multiple organs. Haemodynamic instability and the need for high-dose inotropes, raised intracranial pressure and reduction in cerebral perfusion pressure, and the presence of severe bacterial and/or fungal infections make patients often unsuitable to undergo transplantation. Therefore the timing is crucial as patients with ACLF may have a narrow window of opportunity. Following this line, living-donor transplantation may be an attractive option. Encouraging results are reported from South-East Asia in patients with ACLF due to re-activation of hepatitis B virus infection. Indeed, an 80% survival at 5 years was reported in these patients.[106] Bahirwani et al.[107] also showed that ACLF was not an independent predictor of post-transplant mortality, arguing that this may be a good indication for transplantation. Nevertheless, in many centres there is no prioritized organ allocation for ACLF patients, due to scarcity of data and a supposedly higher short-term mortality. A better understanding of pathogenesis and natural history, and improvement in multiple organ support and in the prevention of complications will allow ACLF to be incorporated as a possible new indication for high urgency allocation.

6.2. Liver support devices

The role of hepatotoxins in the development of ACLF provides a rationale for the use of extracorporeal liver support systems. In principle, liver-assisting devices aim to provide detoxification functions to patients with ACLF, until liver function eventually recovers. Nonetheless, even if this approach is safe and well tolerated, devices failed to demonstrate any survival benefit in randomized studies.[108–110] Two major types of liver support systems have been investigated, acellular devices such as albumin dialysis and plasma-exchange/diafiltration (mainly MARS and Prometheus), and bio-artificial livers, which incorporate cells from human or animal sources, or immortalized cells. Preliminary data indicate a possible beneficial effect in ACLF induced by HBV reactivation.[111] The best studied liver support devices are the Molecular Adsorbent Recirculating System (MARS) and Prometheus devices, which are based on the principle of albumin dialysis.[112] Indeed, albumin exerts a number of functions besides its oncotic properties. These devices may remove inflammatory molecules, reduce NO and improve systemic and hepatic haemodynamics.[109,113,114] Interestingly Prometheus showed a possible benefit in the sub-group of patients with a MELD score of >30 and in those with hepatorenal syndrome.[109]

6.3. Cell-based therapies

The therapeutic use of several types of cells has been hypothesized to improve ACLF. In a recent study, Garg et al. tested the possibility that mobilization of bone marrow-derived stem cells with granulocyte colony-stimulating factor could promote hepatic regeneration.[115] Treatment with this cytokine resulted in a significantly higher survival and improvement of liver function parameters. These intriguing results await confirmation from different groups and different geographical areas.

6.4. Use of antivirals in ACLF

Spontaneous or iatrogenic (immunosuppression) flares of inflammation are frequently observed in chronic hepatitis B. Antiviral therapy should be immediately initiated in patients with ACLF related to re-activation of hepatitis B or acute infection in the context of a different chronic liver disease. In general, drugs with high potency and a high genetic barrier such as entecavir or tenofovir should be preferred in view of the long term need for viral suppression.[2]

7. Conclusions

ACLF is a devastating independent clinical syndrome with high mortality. ACLF follows a precipitating event and is defined as an acute and rapid worsening of liver function accompanied by subsequent multiple end-organ failure in a patient with previously compensated or reasonably compensated liver disease. The mortality of ACLF is known to be high in inpatients (>50%), although no long-term data are available. In ACLF patients, a concept similar to the PIRO concept in sepsis (predisposition, infection/inflammation, response, organ failure) might be useful in describing the pathophysiology and clinical categories of this disorder. The pathophysiology of ACLF relates to an altered response to injury, resulting in an imbalanced inflammatory reaction and immune dysfunction leading to an increased susceptibility to infection. Management of the precipitating injury, multiple organ support and prevention and treatment of complications are the mainstay when dealing with ACLF patients. The liver transplant community will need to be more engaged to define which ACLF patients are better candidates for transplantation, and to define new allocation policies. Finally, a better definition of this clinical scenario is needed, possibly with the use of new biomarkers that allow development of new drugs and devices.

Conflicts of interest

None declared.

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