Acute-on-Chronic Liver Failure: A New and Important Entity in the ICU

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Traditionally two types of liver failure were recognized: acute liver failure (ALF), characterized by a rapid deterioration of the liver function in the absence of a preexisting liver disease, and the progression with a slow deterioration over time of preexisting end-stage liver disease leading to an acute hepatic insult [1]. Recently, a new clinical form of liver failure has been described: Acute-on-chronic liver failure (ACLF). This new entity is characterized by acute complications of compensated or even decompensated cirrhosis with a high rate of organ failure and a high short-term mortality rate. ACLF is now an increasingly recognized entity in both the hepatology and critical care literature and poses several challenges to clinicians. In fact, the liver's position at the apex of multiple synthetic, detoxifying, metabolic, immunological, and hormonal processes predisposes patients with ACLF to a number of complications. The present review aims at summarizing the most updated knowledge about this particularly severe syndrome.

8.1 Definition of ACLF

Until 2013, there was no shared, established, evidence-based definition of ACLF, and the only published definitions were based on expert opinion. Moreover, the used definitions of ACLF differed between Eastern and Western countries. In Asia, the following liver-centered definition has been suggested: an acute hepatic insult manifesting as jaundice (serum bilirubin level > 5 mg/dL) and coagulopathy (international normalized ratio [INR] >1.5) complicated within 4 weeks by ascites

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and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease [2]. In Europe and the USA, a different definition of ACLF was used identifying ACLF as an acute deterioration of liver function in patients with cirrhosis which usually is associated with a precipitating event and results in the failure of one or more organs and high short-term mortality rates [3]. Finally, the sequential organ failure assessment (SOFA) score was also used to diagnose organ failures in patients with cirrhosis admitted to the intensive care unit [4].

Since diagnostic criteria of ACLF were based in both definitions on personal expert opinions rather than on objective data, in 2009, a group of European investigators decided to create the Chronic Liver Failure (CLIF) Consortium with the objective of stimulating research on complications of cirrhosis. The Consortium was endorsed by the European Association for the Study of the Liver (EASL) resulting in the EASL-CLIF Consortium. One of the first decisions by the Steering Committee of the Consortium was to perform a multicenter, prospective, observational study in patients with an acute decompensation of cirrhosis. This study was named *CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study* and aimed at assessing the prevalence, diagnostic criteria, precipitating events, natural course, and prognosis of ACLF. The CANONIC study prospectively enrolled 1343 patients with cirrhosis hospitalized in 29 liver units from 8 European countries between February and September 2011. Enrolled patients were hospitalized for at least 1 day and had an acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infections, or any combination of these [5]. For the diagnosis of organ failures, investigators used a modified SOFA scale, called the CLIF-SOFA scale, which had been designed specifically by the Writing Committee of the CANONIC study before the onset of this study. The CLIF-SOFA scale assesses the function of six organ systems (liver, kidneys, brain, coagulation, circulation, and lungs) but also takes into consideration some specificities of cirrhosis. Each organ system receives a subscore ranging from zero (normal) to four (most abnormal). A total CLIF-SOFA score ranging from 0 to 24 can thus be calculated. Notably, all variables included in the CLIF-SOFA are easy to obtain in every hospital.

In the CANONIC study, three types of risk factors obtained from the CLIF-SOFA score at enrollment were found to be related to high 28-day mortality rate: (1) the presence of two organ failures or more, (2) the presence of one organ failure when the organ that failed was the kidney, and (3) the coexistence of a single "non-kidney" organ failure with kidney dysfunction (i.e., serum creatinine level ranging from 1.5 to 1.9 mg/dL) and/or mild to moderate hepatic encephalopathy [5].

Based on the findings from the CANONIC study, four stages of ACLF can be nowadays recognized:

A. *No ACLF*. This group comprises three subgroups: (1) patients with no organ failure, (2) patients with a single "non-kidney" organ failure (i.e., single failure of the liver, coagulation, circulation, or respiration) who had a serum creatinine level > 1.5 mg/dL and no hepatic encephalopathy, and (3) patients with single cerebral failure who had a serum creatinine level > 1.5 mg/dL.

B. *ACLF grade 1*. This group includes three subgroups: (1) patients with single kidney failure; (2) patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL and/or mild to moderate hepatic encephalopathy; and (3) patients with single cerebral failure who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL.
C. *ACLF grade 2*. This group includes patients with two organ failures.
D. *ACLF grade 3*. This group includes patients with three organ failures or more.

These results show that ACLF is a new clinical entity that is distinct from decompensated cirrhosis.

8.2 Prevalence, Risk Factors, and Prognosis of ACLF (According to the CANONIC Study)

The prevalence of ACLF in the CANONIC Study was 30% (20% at admission and 10% during hospitalization), and the overall 28-day and 90-day mortality rates were 33% and 51%, respectively. Mortality rates in patients without ACLF were low (28-day, 1.9%; 90-day, 10%). The prevalence and 28-day and 90-day mortality rates associated with the different grades of ACLF were 15.8%, 22%, and 41%, respectively, in ACLF-1; 10.9%, 32%, and 55% in ACLF-2; and 4.4%, 73%, and 78% in ACLF-3 [5].

Patients with ACLF were significantly younger than those without ACLF, and the main etiologies were alcoholism (60%), hepatitis C (13%), and alcoholism plus hepatitis C (10%). In only 5% of patients, the main etiology was cirrhosis associated with hepatitis B virus (HBV) infection. The commonest organ failure in patients with ACLF was renal failure (56%) with liver coagulation and cerebral, circulatory, and respiratory failures (44%, 28%, 24%, 17%, and 9%, respectively) also very frequent. The prevalence of circulatory and respiratory failure was significant only in patients with ACLF-3. Most importantly, patients with ACLF showed systemic inflammation (high count of C-reactive protein and leukocyte concentration) which was independent on the presence or absence of recognized bacterial infections. Patients with no history of decompensated cirrhosis developed a more severe form of ACLF than patients with previous episodes of decompensation (28-day mortality of 42% vs. 29%).

The most common precipitating events were bacterial infections and active alcoholism. In patients with ACLF the prevalence of alcoholic cirrhosis (60%) was higher than the prevalence of active alcoholism, indicating that alcoholic hepatitis accounts for only part of cases of ACLF associated with alcoholic cirrhosis. There was a small proportion of other precipitating events. As a trigger, gastrointestinal hemorrhage was less frequent in patients with ACLF than in patients without ACLF, suggesting that hemorrhage, if not associated to other complications (i.e., active drinking and/or bacterial infections), is not related to ACLF development. Finally, a significant proportion of patients developing ACLF did so in the absence of any identifiable trigger. Mortality was independent of the presence and type of

precipitating events, indicating that although triggers are important in the development of ACLF, mortality depends on other factors, such as the clinical course and number of organ failure [5, 6].

Regarding the prognostic relevance of ACLF, some findings have been reported as significant in determining patient outcomes [5]:

A. Among patients who are admitted for an acute decompensation and subsequently die, multiorgan failure (i.e., ACLF grade 3) is present in all patients before death.
B. The interval between the diagnosis of ACLF and death is 12.0 ± 7.5 days for ACLS grade 1, 11.0 ± 8.0 days for ACLS grade 2, and 8.0 ± 6.1 days for ACLS grade 3. Therefore, the greater the number of organ failures at diagnosis the shorter the time to death.
C. ACLF is not a temporally fixed syndrome. For example, 50% of patients with ACLF grade 1 at diagnosis improve and survive whereas one-third progress to ACLF grade 3 and die. A majority of patients with ACLF grade 3 at diagnosis acquire new organ failures and die. However, 16% of patients with ACLF grade 3 at diagnosis progress to a no ACLF status.
D. The finding that patients without any organ failure on admission have a 28-day mortality rate of approximately 5% and not 0% is explained by the fact that some of these patients develop in-hospital ACLF, which progresses to ACLF grade 3 and death. Conversely, patients who do not have ACLF on admission and remain free of this syndrome during the following 28 days have a very low short-term mortality rate (1.9%).

Another very important finding from the CANONIC study needs to be outlined: the fact that the presence or absence or the type of precipitating event is not related to the severity of ACLF and the short-term mortality rate [5]. Therefore, precipitating events are important in the occurrence of the syndrome but once it develops the prognosis depends on the number of organ failures. This observation indicates that the severity of ACLF probably depends more on the individual response to the precipitating event [6]. Finally, in almost half of patients enrolled in the CANONIC study with ACLF, the syndrome develops in the absence of a prior history of decompensation or has developed within a few weeks after the first episode of decompensation. This finding outlines that ACLF is not a terminal event in a long-lasting history of decompensated cirrhosis.

8.3 ACLS is Caused by a Derangement of the Inflammatory Pathway

The CANONIC study results clearly show that white cell count and plasma C-reactive protein (CRP) levels are higher in patients with ACLF than in those without indicating higher degree of systemic inflammation in the former patients [5]. Furthermore, the higher white cell count or CRP levels the higher the number of failing organs. All in all, these findings suggest that organ failures may result from an excessive

inflammatory response, for which the term *immunopathology* was proposed [7]. Although the precise mechanisms involved in ACLF have yet to be clarified, the immune system seems to play a predominant role in the setting of cirrhosis. The homeostatic role of the liver in the systemic immune response is already well known, [8, 9] and the definition of "cirrhosis-associated immune dysfunction" which includes the main syndromic abnormalities of immune function, immunodeficiency and systemic inflammation, well depicts the key role of the immune system in this setting [10]. The immune dysfunction in cirrhosis is a dynamic condition which leads to oscillation from predominantly pro-inflammatory to predominantly immunodeficient situations, is multifactorial, and reflects a complex interaction between many systems predisposing these patients to infections [10]. It is thought that this susceptibility is not due to an only sole responsible factor but rather to the concomitant presence of various facilitating mechanisms such as portal hypertension with portosystemic shunting (thus impairing detoxification and reticuloendothelial system phagocytic activity), increased gut permeability and bacterial overgrowth (all of them increases the risk of bacteremia and the occurrence of endotoxemia), albumin and lipoprotein dysfunction, or aberrant toll-like receptor expression in hepatic Kupffer cells [1]. Moreover, comparing septic patients to ACLF patients, Wasmuth et al. formulated the concept of "sepsis- like immune paralysis" based on a profoundly decreased production of TNF-α and low monocyte HLA-DR expression in both groups. They also postulated that this cellular immune impairment could contribute to increased mortality [11]. Endotoxins have also been proposed to play a role in mediating the full activation of neutrophils, which paradoxically would render them unable to act against the insult. The role that cytokines play in ACLF remains a key point in the pathogenesis of the inflammatory response. Elevated serum levels of many cytokines including TNF-α, sTNF-αR1, sTNF-αR2, interleukin (IL)-2, IL-2R, IL-4, IL-6, IL-8, IL-10, and interferon-α has been described. In particular IL-6 and TNF-α had been proposed to have a dual action, producing hepatocyte death and also enhancing hepatocyte proliferation through a complex interplay with Kupffer cells and hepatocytes [1]. This entire cascade eventually leads to hepatocyte death and liver dysfunction. It has also been outlined that hepatocytes apoptosis rather than necrosis can be the predominant mode of cell death in ACLF, as high levels of some apoptosis markers occurs in ACLF patients [12].

8.4 Clinical Features of ACLF

8.4.1 Infections

Although the CANONIC study showed that the trigger of ACLF is not related to an infection in the 70% of cases, the presence of innate immune dysfunction in this class of patients can be inferred from susceptibility to infections: 30–50% of cirrhotic patients presented bacterial infections upon their admission or during hospitalization. The most common bacterial infections were spontaneous bacterial peritonitis (25%), urinary tract infections (20%), pneumonia (15%), and spontaneous bacteremia (12%). In a study of 184 cirrhotic patients from King's College

Hospital, 67 (36%) developed bloodstream infection (BSI) a median of 8 days after admission; BSI was independently associated with higher ICU mortality [13]. This may support the hypothesis that following the initial cytokine storm responsible for acute decompensation and multiorgan dysfunction, these patients enter a later phase of monocyte immunoparalysis (compensatory anti-inflammatory response), which further alters their susceptibility to sepsis and predisposes them to a higher rate of second infection and increased mortality [14, 15]. Finally, it is important to outline that data from a large multicenter study suggested that cirrhotic patients with septic shock, including those on mechanical ventilation or receiving renal replacement therapy, have benefited from the progress in septic shock and organ failures management obtained in recent years in the general population indicating that it is justified to admit ACLF patients to ICU [16].

8.4.2 Kidney Injury

Acute kidney injury (AKI) in critically ill cirrhotic patients is common and often multifactorial.

Renal complications of ACLF can be due to low flow state, infections, nephrotoxic drugs, and chronic diseases such as hypertension and diabetes which can predispose patients to chronic renal failure. However, the characteristic renal complication of end-stage liver diseases is the hepatorenal syndrome (HRS) which is characterized by splanchnic arterial vasodilatation leading to renal vasoconstriction in the setting of a low flow state due to decreased systemic vascular resistance [17, 18]. Although the incidence of HRS is unknown, especially in relation to other causes of renal failure, it is estimated to be 40% over a 5-year period in patients with cirrhosis and ascites [19]. There are two different forms of HRS, type 1 and type 2. Although HRS is associated with a very poor prognosis, overall the natural progression of the disease differs significantly based on the type, with type 1 experiencing a median survival of 2 weeks and type 2 exhibiting median survivals of 3–6 months. Diagnosis of HRS involves the demonstration of low glomerular filtration rate in the absence of shock, infection, fluid losses, and nephrotoxic agents, with no improvement after discontinuation of diuretics and administration of 1.5 L fluid and proteinuria of less than 500 mg/dL, with no ultrasonographic evidence of obstruction or intrinsic parenchymal disease [17, 18]. Recently, a consensus conference proposed that cirrhosis-associated AKI should be defined by an increase in serum creatinine by more than 50% from the stable baseline value in less than 6 months or by 0.3 mg/dl (27 mmol/l) in less than 48 h [20].

8.4.3 Cardiovascular Derangements

Hemodynamic changes observed in patients with end-stage liver disease are characterized by humoral and nervous dysregulation secondary to autonomic nervous system activation and include increased cardiac output, peripheral vasodilatation,

decreased systemic vascular resistance (SVR), and decreased oxygen extraction. Circulatory failure in cirrhotic patients with ACLF is distributive in nature and characterized by a greater decrease in arterial pressure associated with signs of impaired tissue perfusion. Marked splanchnic vasodilatation results in a state of effective hypovolemia with water and sodium retention [19, 21]. Although mechanisms for this autonomic nervous system activation are still poorly understood, it has been associated with higher mortality. In addition to hemodynamic changes, a decline in cardiac function termed cirrhotic cardiomyopathy has also been described [21]. This is characterized by a combination of diastolic and systolic dysfunction. Cirrhotic cardiomyopathy can be associated with a prolonged QT interval and can lead to an increased risk of ventricular arrhythmias/sudden cardiac death.

8.4.4 Neurological Derangements

The most common manifestation is a confusional syndrome superimposed on varying degrees of cognitive impairment that can even evolve to coma [22]. Precipitating factors, such as infection or electrolyte abnormalities, may enhance the disturbances attributable to liver failure or exert a direct effect on the brain. Important contributing factors are the systemic inflammatory response, circulatory dysfunction, and failure of other organs [6]. The activation of inflammatory mediators, such as cytokines, may enhance the effects of neurotoxins such as ammonia. Neuroinflammation increases blood-brain barrier permeability and, by generation of nitric oxide and prostanoids, causes astrocyte swelling. Other cerebrovascular abnormalities include disturbances of neurotransmission, injury to astrocytes, energy impairment, brain edema, loss of autoregulation, and brain atrophy. In cirrhosis, cerebral edema is an uncommon finding; however, cases of increased intracranial pressure have been identified [22, 23]. Patients with ACLF are also more vulnerable to central pontine myelinolysis which has been reported even with relatively modest elevations in sodium in this population. However, the most common cause of changes in mental status is hepatic encephalopathy, a disease process thought to be caused by astrocyte swelling and cerebral edema due to the synergistic effects of excess ammonia and inflammation, although the precise underlying molecular mechanisms are unclear. Hepatic encephalopathy is rarely solely due to worsening liver function, rather a precipitating cause almost always is responsible and determining this precipitant is key to management [19].

8.4.5 Respiratory Derangements

Pulmonary vascular issues affecting patients with ACLF can be divided into two distinct abnormalities: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH). Hepatopulmonary syndrome is characterized by intrapulmonary vasodilation leading to a ventilation/perfusion mismatch with resultant hypoxemia that can be found in up to 40% of patients with end-stage liver disease.

Diagnosis is based on its identification identify either through pulse oximetry or on arterial blood gas and the demonstration of an intrapulmonary shunt (which can usually be demonstrated with contrast echocardiography) if there is a normal chest x-ray and pulmonary function tests [24]. Portopulmonary hypertension is the presence of pulmonary arterial hypertension due to increased pulmonary vascular resistance and pulmonary vasoconstriction leading to right heart failure in the setting of advanced liver disease. The disease is largely believed to be underdiagnosed as a cause of dyspnea and decreased exercise capacity. Doppler echocardiography is a highly sensitive tool for detecting portopulmonary hypertension, using a right heart catheterization for confirmation and definitive diagnosis. The diagnosis is made if mean pulmonary arterial pressure is >25 mm Hg or left ventricular end-diastolic pressure <15 mm Hg in the setting of liver disease or portal hypertension. In general, the presence of portopulmonary hypertension is a poor prognostic sign [24, 25]. Moreover, pulmonary function can also be compromised by direct mechanical effects of hydrothorax and abdominal ascites on diaphragmatic movement. Hydrothorax is defined as a significant pleural effusion, usually >500 mL in a patient with end-stage liver disease, exclusive of primary cardiac or pulmonary disease. A pleural effusion is observed in approximately 5% of patients with ACLF. Various mechanisms have been proposed such as decreased osmotic pressure, leakage of plasma from azygous venous system, and lymph leakage from the thoracic duct, although the prevailing thought is direct transport into pleural space through diaphragmatic defects [19]. Finally, the presence of an exaggerated inflammatory response, coupled with a relative immunocompromised state likely can predispose patients to acute lung injury. The risk of aspiration pneumonia is also high because of altered consciousness, swallowing dysfunction, gastric stasis, increased intra-abdominal pressure due to ascites, and ileus resulting from infection and electrolyte abnormalities [22].

8.4.6 Coagulation Derangements

Coagulopathy in patients with critical liver dysfunction is complex and can quickly decompensate to bleeding as well as to thrombosis [26]. Both are associated with worse outcome. Standard tests of coagulation can be altered as a consequence of impaired synthesis of coagulation factors and increased consumption. However, routine plasmatic coagulation tests such as PT and INR are not able to discriminate between hypo- and hypercoagulability and are not able to predict the risk of bleeding in patients with liver dysfunction. Therefore, prophylactic transfusion of FFP and platelets due to an increased INR should be avoided in this patient population, and hemostatic interventions should only be performed in case of clinically relevant bleeding. In contrast, thrombin generation assays in the presence and absence of thrombomodulin indicate that patients with severe liver dysfunction are rather hypercoagulable with the inherent risk of thrombosis [26]. Altogether, modified thrombin generation assays can be useful for determination of coagulation function in patients with liver dysfunction, but have the major drawback of not being

available as routine laboratory tests. Spontaneous bleeding is rare in ACLS patients. However, bleeding associated with trauma or acute variceal hemorrhage may be more dramatic as a consequence of both attendant coagulopathy and enhanced fibrinolysis. A relative decrease in hepatic-derived anticoagulant factors serves to offset the decrease in procoagulant factors in the patient with cirrhosis who has compensated disease. Alternative techniques for assessing coagulation such as thromboelastography may be helpful in identifying this balance and for guiding blood product replacement [22].

8.4.7 Adrenal Insufficiency

Adrenal insufficiency is reported in 51–68% of patients with cirrhosis, particularly in more severe patients. The impaired adrenal response may reflect either or both primary and secondary adrenal insufficiency with inadequate pituitary response and low adrenocorticotropic hormone levels. Other proposed hypotheses to explain this phenomenon are: decreased cholesterol levels, overstimulation of the hypothalamus-pituitary-adrenal axis by cytokines and endotoxemia. Adrenal dysfunction is frequently reported in patients with chronic liver diseases (compensated or decompensated), and it is associated with increased mortality compared to patients without it [22, 27].

8.5 Management

8.5.1 General Considerations

At present, there is no treatment specific for ACLF. Current treatment consists of supportive measures and therefore it should rely on enhanced care in intensive care units (ICUs) where the management of patients with multiorgan failure is protocolised and patients can be closely monitored. The aim of the general management should be focused on early recognition of any condition or precipitating factor which can cause ACLF or on avoiding exposure to those factors known to trigger multiple organ failure. Although not proven, it is thought that the greatest impact on patient's outcome will be achieved by preventing or slowing a further progression of ACLF. Patients with ACLF present some unique features that may differentiate them from the non-cirrhotic patients and thus, a multidisciplinary approach is essential [1, 19, 22, 27].

8.5.2 Liver Transplantation

Available evidence about liver transplantation (LT) for patients with ACLF is scarce even though this represents the only definitive therapeutic option for the vast majority of patients with ACLF [28, 29]. Nonetheless, a number of factors, including

advanced age, active alcoholism, uncontrolled infections, concomitant diseases, and the presence of associated organ failures, make patients with ACLF often unsuitable to undergo LT [1]. As ACLF is associated with high short-term mortality up to 50–90% and may evolve rapidly into a fatal clinical situation, the timeframe for evaluating patients and assessing them for LT is short. Moreover, evidences regarding the long-term outcome of patients transplanted for ACLF are very limited. Some studies showed similar survival rates of patients with ACLF to patients with chronic liver disease who underwent transplantation for other indications [30, 31]. When interpreting these data sets, differences between western and eastern transplant centers must be taken into consideration. Moreover, published studies are retrospective and have a limited sample size. Most importantly, only one study used intention-to-treat analysis and showed that some potential candidates are not even listed for transplantation and out of those listed mortality is of 50% [30]. Overall, only one-third of potential candidates reach liver transplantation according to this report. There is therefore a clear need for effective therapeutic methods that can "bridge" patients with ACLF to liver transplantation. A study reported outcomes in 183 critically ill patients with ACLF denied listing for LT. It was noted a substantially higher mortality in these patients compared with those who were listed for LT. Several variables were independently associated with mortality in this study. Some of these predictors, such as APACHE II scores, sepsis, and respiratory failure requiring mechanical ventilation are already known to predict mortality in other groups of patients with liver disease. Conversely, the presence of gastrointestinal bleeding is an independent predictor of decreased mortality [32]. Indeed, further studies are still necessary to determine timing of liver transplantation, optimal selection, and whether ACLF patients should be prioritized on a high urgency list.

8.5.3 Infections

Because overt signs of infection may be absent, a high index of suspicion is necessary for diagnosis. When the suspicion for infection is high, early initiation of antibiotics is mandatory. A study by the Cooperative Antimicrobial Therapy for Septic Shock research showed, in a group of 635 critically ill cirrhotic patients with septic shock, a hospital mortality of 76%. The median time to appropriate antimicrobial therapy was 7.3 (3.2–18.3) hours with each hour delay associated with significantly increased mortality (adj-odds ratio per hour 1.1) [33]. Sepsis in ACLF can be managed according to Surviving Sepsis Campaign guidelines [34]. Strict adherence to hand hygiene and "bundles" of care (e.g., ventilator and central line) are required to prevent hospital-acquired infections. For prolonged ICU stays, weekly swabs for resistant organisms should be obtained. Testing for Clostridium difficile infection should also be routinely performed and repeated in critically ill patients with diarrhea. For patients who have active C. difficile infections and are critically ill, a prompt specific treatment should be started. ACLF patients has previously been thought to be especially susceptible to specific sepsis-related complications to include hypoglycemia, adrenal insufficiency, defective arginine-vasopressin

secretion, and compartment syndrome [35]. Although early goal-directed therapy (EGDT) with specific hemodynamic targets is a well-defined approach for general ICU patients, no study has assessed it or the optimal endpoints for resuscitation in cirrhotic patients [27]. Finally, while relative adrenal insufficiency has been identified in patients with septic end-stage liver disease, there are no further guidelines other than standard recommendations supporting the administration of hydrocortisone in cases of shock refractory to fluid and vasopressors [34].

8.5.4 Kidney Injury

AKI in critically ill cirrhotic patients is common and often multifactorial. In the setting of cirrhosis, serum creatinine (SCr) tends to overestimate renal function due to decreased creatine production by the liver, protein calorie malnutrition, muscle wasting, reduced physical activity, and enlarged volume of distribution in the setting of fluid overload. In addition, in the setting of AKI, Scr can lag by several hours to days despite a decrease in glomerular filtration rate especially in the setting of fluid overload [36]. Therefore, it is recommended that Scr values be interpreted with caution in ACLF patients due to overestimation of values. As for HRS, the cornerstone of management remains albumin (1 g/kg initially followed by 20–40 g/day) and vasopressor therapy to mitigate splanchnic and systemic vasodilatation. Terlipressin, a vasopressin analogue, has been shown to reverse Type 1 HRS in 50% of patients without a difference in mortality [37, 38]. Recommended doses currently are 1–2 mg/q4–6 h i.v. bolus for a minimum of 72 h. Other small studies have shown norepinephrine to be equally as effective as terlipressin in Type I HRS [27]. Renal replacement therapies are not a treatment for HRS/cirrhosis induced AKI but is often initiated as a bridge to either liver transplant or definitive decision. Nephrotoxic medications such as nonsteroidal anti-inflammatory drugs, intravascular volume depletion, and avoidance of large-volume paracentesis without albumin replacement should be avoided [14, 19].

8.5.5 Cardiovascular Issues

Management of cirrhotic cardiomyopathy is directed toward left ventricular failure with beta-blockade, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and diuretics as tolerated, although the evidence to support this therapy is not specific to heart failure due to end-stage liver disease [19]. Although there are no clinical studies validating management strategies, afterload reduction is anecdotally not well tolerated if the patient is peripherally vasodilated. Usually, the disease process is subclinical and only becomes apparent during times of physiologic stress. Potential ICU events that can exacerbate cirrhotic cardiomyopathy include shunting of portal flow to systemic circulation after transjugular intrahepatic portosystemic shunt (TIPS) and bacterial infections/endotoxemia leading to a high output hypotensive state. Patients may be hypotensive despite presence of a hyperdynamic state

and being unresponsive to volume challenge. Ventricular compliance is decreased and can be assessed by manipulation of intravascular volume. That is, the change in central venous pressure (CVP) after fluid challenge is more instructive than a single measurement of the CVP and, when properly applied, passive leg raise may be used to assess volume responsiveness [19, 22, 36]. Increased intra-abdominal pressure due to ascites may result in increased CVP without improving cardiac preload. Minimally invasive methods of assessing hemodynamic parameters such as stroke volume variation and pulse pressure variation have gained popularity in the ICU, however in patients who are spontaneously breathing, these methods have limited utility. Moreover, such monitors have failed to demonstrate acceptable accuracy in cirrhotic patients undergoing liver transplantation, which further questions their role in the ICU [39]. Echocardiography provides a much more robust assessment of ventricular function and response to volume infusion. Echocardiography is noninvasive and may be relatively inexpensive. Because pulmonary hypertension is associated with cirrhosis, pulmonary artery catheterization is required to measure pulmonary artery and pulmonary artery occlusion pressures [22, 36]. With regard to the hemodynamic goals, the optimal mean arterial pressure blood lactate or venous oxygen saturation are unknown. In septic shock, in the absence of liver disease, there appears to be no advantage to inducing hypertension. However, HRS responds to increasing perfusion pressure by administration of terlipressin. Circulating intravascular volume should be restored recognizing the difficulties in assessing volume. Vasopressors such as norepinephrine are titrated to achieve a mean arterial pressure of 65–70 mm Hg. Vasopressin (or terlipressin) is norepinephrine-sparing in sepsis and appears to have a similar effect in patients with cirrhosis [19, 36].

8.5.6 Neurological Issues

The mainstay of treatment of hepatic encephalopathy is use of lactulose and nonabsorbable antibiotics. Lactulose is a nonabsorbable disaccharide that is metabolized by colonic bacterial flora into lactic acid, creating an acidic environment in the gut which aids the conversion of ammonia (NH_3) to ionic ammonium (NH4+), which is then passed via fecal excretion. There remains academic debate concerning the routine use of lactulose for the treatment of acute hepatic encephalopathy, as several trials have failed to demonstrate a significant effect on mortality over placebo or antibiotics [19, 22, 36]. The optimal dose of lactulose is not well established; however, titration to two to three semiformed stools per day is recommended [22]. Avoidance of profuse diarrhea and its associated electrolyte abnormalities is essential. When advanced encephalopathy or mechanical ventilation precludes oral administration, administration should be via enteric tube or retention enema. Rifaximin is a poorly absorbed rifamycin-based antibiotic with broad activity against ammonia-producing aerobic and anaerobic enteric flora. Due to low systemic absorption, rifaximin is well tolerated, with a similar occurrence of adverse effects compared to placebo [19]. The combination of lactulose plus rifaximin was shown to be more effective than lactulose alone in the prevention and treatment of

overt hepatic encephalopathy [40]. Avoidance of sedative agents is a mainstay of treatment. In patients who demonstrate signs of cerebral edema or increased ICP, the administration of mannitol is mandatory, and invasive ICP monitoring may be considered [19]. Endotracheal intubation for airway control is mandatory in patients with a Glasgow coma scale score of 8 and/or in the presence of active upper gastrointestinal bleeding [22].

8.5.7 Respiratory Issues

The only definitive treatment for HPS is liver transplantation, which will result in complete resolution in 80% of the cases. Other forms of medical therapy such as somatostatin, indomethacin, methylene blue, and plasma exchange have been used but remain invalidated [19]. Transjugular intrahepatic portosystemic shunt as treatment for HPS can allow for reversal of intrapulmonary vasodilatation and redistribution of pulmonary blood flow via increase in cardiac output. However, its efficacy is only described at the case report level and is therefore not the first-line therapy. With regard to PPH, the diagnosis has specific transplant implications, as orthotopic liver transplant is classified as high risk if mean pulmonary artery pressure is between 35 mm Hg and 50 mm Hg and contraindicated if mean pulmonary artery pressure is >50 mm Hg due to high mortality from acute right heart failure [41, 42]. Medical treatment is generally indicated as a bridge to transplant and is based on the continuous infusion of a prostacyclin such as epoprostenol for mean pulmonary artery pressures >25 mm Hg. Although effective, continuous epoprostenol infusions may be burdensome due to complex dosing and cost [19, 22]. There are reports describing the use of sildenafil. Pulmonary function can also be compromised by direct mechanical effects of hydrothorax and abdominal ascites on diaphragmatic movement. Workup includes chest x-ray, pleural fluid analysis, and echocardiography. Management largely involves thoracentesis, sodium restriction, and diuretics. Symptomatic and refractory hydrothorax can be managed with TIPS cost [19, 22].

8.5.8 Coagulation

Routine correction of coagulation abnormalities in the absence of active bleeding is not indicated as it may be associated with significant complications including transfusion-associated lung injury, transfusion-associated circulatory overload, and transfusion reactions. When correction of bleeding abnormalities is required in the presence of active bleeding, prothrombin time, complete blood count, and activated partial thromboplastin time can be used but with the knowledge that they do not provide an adequate assessment of hemostasis in cirrhosis to guide therapy and thromboelastography should be considered [36]. Correction of coagulation abnormalities prior to placement of central venous or arterial catheters, paracentesis, thoracentesis, or bronchoscopy and endoscopy without biopsy is not required. Vitamin K, given at 2 mg intravenously daily for 3–5 days, should be administered to eliminate

vitamin K deficiency as a source of coagulopathy [22, 36]. Massive acute hemorrhage should be managed with transfusion of red blood cells and fresh frozen plasma given in a 1:1 or 2:1 ratio with transfusion of platelets and fibrinogen concentrates to address consumption. Fibrinolysis is common and is readily assessed by thromboelastography. Treatment of fibrinolysis with tranexamic acid is indicated when bleeding persists, despite correction of thrombocytopenia and clotting factors in the absence of disseminated coagulopathy [22, 36].

8.5.9 Referral to a Liver Transplant Center

The determination of transplant candidacy is complex. All patients admitted to the ICU with complications of cirrhosis deserve a consultation with a transplant center in order to assess candidacy for liver transplantation. "Perceived" contraindication to transplant should never preclude this consultation.

8.5.10 Liver Support Devices

When medical treatments fails, artificial liver support can be considered as a bridge therapy to liver transplantation or while the precipitating event is reversed. Liver support devices are intended to support liver function until such time as native liver function recovers or liver transplantation is feasible. Two types of devices can be distinguished: acellular devices such as albumin dialysis and plasma exchange [mainly molecular adsorbents recirculating system (MARS), and Prometheus devices], and cell-based devices, which incorporate cells from human, animal sources, or immortalized cells. The overall efficacy of liver support devices have, at this time, failed to reach a level sufficient strength of evidence. Recently, two European multicenter randomized control trials have evaluated the impact of MARS and Prometheus. The RELIEF trial concluded that despite biochemical improvement, there was no significant difference in 28-day survival between patients treated with MARS vs. standard medical therapy [43]. Similarly, the HELIOS trial compared Prometheus to standard medical therapy. This study showed no significant survival differences at day 28 or at day 90 [44]. Both of these studies were biased due to confounding by indication. Cirrhotic patients who were and were not liver transplant candidates were included in enrollment representing groups with very different prognoses. Future trials evaluating indications (liver transplant candidates only), timing of treatment and cost effectiveness are still needed to clarify the role for these therapies.

Conclusions

ACLF is a devastating syndrome. It is based not only on the presence of organ failure and high mortality rate but also on younger age, alcoholic etiology of cirrhosis, higher prevalence of some triggers (particularly bacterial infections and active alcoholism), and a higher level of systemic inflammation which make

ACLF a clinically, pathophysiologically, and prognostically distinct entity. ACLF is a new entity also because it cannot be entirely explained by severe sepsis or severe alcoholic hepatitis as a large proportion of cases remains of unknown origin. Rather, ACLF should be considered as a whole that includes subcategories such as severe sepsis, severe alcoholic hepatitis, and other categories that require a more precise definition. Hopefully, new research in end-stage liver disease will allow the determination of modifiable factors that predispose to ACLF in order to personalize their management based on clinical and genetic factors.

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