Editorial

Management of decompensated liver cirrhosis in the surgical intensive care unit

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Liver cirrhosis is the end-stage of chronic progressive liver diseases (1). The most common causes of cirrhosis worldwide include alcohol-related liver disease, non-alcoholic fatty liver disease, hepatitis B, hepatitis C, autoimmune liver diseases (e.g., autoimmune hepatitis), cholestatic liver diseases (e.g., primary biliary cholangitis, primary sclerosing cholangitis), hemochromatosis or Wilsons' disease (1).

Liver cirrhosis is widely prevalent and represents a considerable healthcare burden (1,2). Recent data showed that cirrhosis is responsible for an estimated 1.3 million deaths every year and complications of cirrhosis rank as the 11th most common cause of death worldwide, and the fourth in Europe (2,3).

Liver cirrhosis can be divided into an asymptomatic form (compensated cirrhosis) and a symptomatic form, referred to as decompensated cirrhosis, which often result in hospitalization and impaired quality of life (1,4). Decompensated cirrhosis is a common clinical entity, with approximately 10.6 million prevalent cases annually worldwide (1).

Acute decompensation (AD) of cirrhosis is characterized by the development of ascites, hepatic encephalopathy, jaundice, and/or gastrointestinal (GI) bleeding (4). Decompensated disease can be further worsened by infections, acute kidney injury (AKI) with or without features of hepatorenal syndrome, or rebleeding (4). Once hepatic decompensation has manifested, cirrhosis becomes a severe systemic disease with multi-organ dysfunction and poor prognosis (4).

Hepatic decompensation represents a prognostic turning point, as the median survival-time drops from approximately 12 years for patients with compensated cirrhosis to about two years for patients with decompensated cirrhosis (5).

Common precipitants of hepatic decompensation include (bacterial) infections, GI bleeding, alcohol-induced hepatitis, reactivation of chronic hepatitis B virus infection, acute hepatitis A or hepatitis E infection, drug induced liver injury (DILI) and surgical interventions (6). However, the latter is often not sufficiently considered as a risk factor for decompensation in daily clinical practice.

Although, previous studies have clearly demonstrated an increased perioperative risk in patients with cirrhosis undergoing surgery (7), surgical treatment in patients with liver cirrhosis as a trigger for decompensation remains frequently underestimated.

Among the various types of surgery, hepatobiliary surgery (e.g., liver resection) is associated with the highest risk of liver-related mortality. High mortality was also reported after abdominal surgery (e.g., colorectal resection) and thoracic surgery (e.g., valvular heart surgery), whereas lower mortality rates have been reported after orthopedic

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surgery (7,8).

When patients are transferred to an intensive care unit (ICU) after surgery, postoperative manifestation of acute liver decompensation is associated with a significant increase in mortality and worsening of prognosis (9).

Patients with decompensated cirrhosis are particularly challenging to manage in the surgical ICU due to their comorbidities and the different problems associated with the underlying liver dysfunction (e.g., coagulopathy, encephalopathy).

However, international guideline-based recommendations for the management of decompensated cirrhosis in the surgical ICU remain scarce.

In order to close this gap and to improve the care of these patients, a clinical consensus document has now been published by the American Association for the Surgery of Trauma Critical Care (AAST) (9).

In their comprehensive consensus paper Seshadri and colleagues reviews practical clinical questions regarding the critical care management of patients with decompensated cirrhosis on ICU to facilitate best practices for the bedside provider.

In detail, the consensus document addresses several important practical considerations for intensivists in the care of the critically ill patients with decompensated cirrhosis including: volume status assessment and end points of resuscitation; fluid management and vasopressor use; ascites management and avoidance of post-paracentesis circulatory dysfunction; identification and management of AKI in decompensated cirrhosis (HRS-AKI); GI bleeding; venous thromboembolism prophylaxis in the setting of hepatic coagulopathy; management of hepatic encephalopathy and nutritional support (9).

The authors are to be congratulated as they have succeeded in writing such a comprehensive and practically relevant consensus document.

The present recommendations highlight, that in addition to the treatment of the precipitating event, optimal management strategies for possible complications of decompensated cirrhosis and a prevention of decompensation of other organ systems are essential to improve the prognosis of these patients.

Aside from etiological treatments, disease-modifying agents that can antagonize central pathogenetic mechanisms of decompensated cirrhosis would be promising approaches and urgently needed.

In recent years, the repurposing of "old drugs" that have already been established for other indications in hepatology or for other diseases has provided promising candidates, including human albumin, statins, and non-absorbable oral antibiotics such as rifaximin (10).

The availability of disease modifying agents that could be administered to patients with decompensated cirrhosis to prevent and reduce the risk of progressive of organ dysfunction or severe complications would be auspicious.

One of the most promising options seems to be albumin. The administration of albumin is well established in patients with decompensated cirrhosis and spontaneous bacterial peritonitis, hepatorenal syndrome, or the prevention post-paracentesis circulatory dysfunction (4). Albumin is a pleiotropic molecule that, in addition to volume expansion, has anti-inflammatory properties that are believed to be beneficial in the setting of decompensation (10).

However, current evidence remains inconclusive. While long-term administration in clinically stable patients with cirrhosis shows benefits within the ANSWER trial, a recent study on albumin substitution in hospitalized patients with decompensated cirrhosis (ATTIRE trial) show no significant differences with respect to the composite primary endpoint (infection, renal failure or death) between patients who received daily albumin infusions to increase the albumin level to a target of 30 g per liter and those who received standard care (11).

Therefore, a benefit of albumin substitution outside established indications in the intensive care setting appears questionable. Further clinical studies and randomized trials are warranted to proof the clinical benefits of a short-term use of albumin in the setting of acute decompensated liver cirrhosis.

Regarding statins and antibiotics such as rifaximin, current data remain sparse. Moderate quality evidence suggests that statins reduce portal hypertension and the risk of hepatic decompensation (e.g., variceal bleeding) and lower mortality among patients with compensated cirrhosis (12). Regarding rifaximin, recent data reveal that rifaximin could have beneficial effects on the course of cirrhosis by altering the intestinal microbiota profile and thereby affecting the gut-liver axis, which in turn can interfere with major events of the pathogenic cascade underlying decompensated cirrhosis (13). Further studies are currently underway to further evaluate the role of statins and rifaximin as disease modifiers in cirrhosis (e.g., LIVERHOPE trial, STAT-Liver trial, SACRED trial). Although it should be noted that these studies are not being conducted in critically ill patients, their findings may be helpful and applicable to this group of patients in the long-

term (12).

Other drugs commonly used in patients with cirrhosis are proton pump inhibitors (PPI) and non-selective beta blockers (NSBB), such as carvedilol. The impact of PPI medications on adverse outcomes in cirrhosis remains controversial. PPIs, which are often prescribed for stress ulcer prophylaxis on ICU, alter gut microbiome and might lead to small intestinal bacterial overgrowth and increased bacterial translocation to the portal circulation, which were associated with adverse effects in liver diseases. In patients with cirrhosis, PPI exposure is associated with increased risk of infection (e.g., Clostridioides difficile infection) and hepatic decompensation, which may ultimately mediate an increased liver-related mortality (14). An exception are patients with prior upper GI bleeding, where PPI use was associated with reduced all-cause mortality, suggesting benefit in the presence of an appropriate indication (14).

The therapeutic window of NSBB in treating patients with decompensated cirrhosis remains also controversial. While there are first safety data in patients with decompensated cirrhosis or acute-on-chronic liver failure (ACLF), concerns remain for patients with refractory ascites and risk of AKI.

However, current study data clearly demonstrated that NSBB therapy should be held when the mean arterial pressure (MAP) is <65 mmHg or systolic blood pressure is <90 mmHg (15). Thus, use of NSBB in hemodynamically unstable patients with decompensated cirrhosis in a surgical ICU, currently does not seem to be a therapeutic option.

In addition to a lack of disease-modifying agents, there is also a lack of potential biomarkers that could predict the risk of decompensation or treatment response and could help the intensivists to identify patients at risk. In addition to existing risk scores (e.g., CLIF-C-AD and CLIF-C ACLF score), such biomarkers could help to identify high-risk patients in the ICU at an early stage to improve prognosis.

In addition to optimal management of post-operative complications, a careful pre-operative evaluation of cirrhotic patients remains indispensable to ensure a proper risk benefit assessment for (elective) surgery (8). If the surgical and postoperative risk appears higher than the chance of a good clinical outcome, the surgical treatment should be considered futile and avoided (7).

In conclusion, the management of patients with decompensated cirrhosis remains a major challenge in critical care medicine. Due to an increased vulnerability and risk for multi-system organ failure, these patients need special attention, and their management requires effective interprofessional collaboration.

The overarching goal must be to prevent the occurrence of decompensation in compensated cirrhosis and to avoid further progression of decompensation that has already occurred. Practice-based guidelines, like those from the American Association for the Surgery of Trauma Critical Care Committee, are of great importance and can help to improve the outcome of patients with decompensated cirrhosis in the surgical ICU significantly.

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