Seminar

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Management of the critically ill patient with cirrhosis: A multidisciplinary perspective

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Introduction

The occurrence of complications in patients with cirrhosis such as jaundice, ascites, encephalopathy, infection, renal dysfunction or variceal bleeding requiring hospitalization alters the natural history of the disease with an increase in 5-year mortality as high as 40–50% [1]. A significant proportion of these patients with acute decompensation require management in the intensive care unit (ICU) with organ support and have a high rate of in-hospital mortality. This category of patients with cirrhosis, acute decom-

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Abbreviations: ICU, intensive care unit; ACLF, acute on chronic liver failure, CLIF, chronic liver failure organ failure; AST, American society of transplantation; ASTS, American society of transplant surgeons; EASL, European association for the study of the liver; AKI, acute kidney injury; Scr, serum creatinine; KDIGO, Kidney disease improving global outcomes; UO, urine output; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD-6, Modified Diet in Renal Disease 6; ADQI, acute dialysis quality initiative; ICA, international club of ascites, AKIN, acute kidney injury network; HRS, hepatorenal syndrome; CKD, chronic kidney disease, RRT, renal replacement therapy; ATN, acute tubular necrosis; CRRT, continuous renal replacement therapy; PAC, pulmonary artery catheter; ScvO2, venous oxygen saturation; SVV, stroke volume variation; PPV, pulse pressure variation; StO_2, tissue oxygen saturation; HES, hydroxyethyl starch; SBP, spontaneous bacterial peritonitis; GIB, gastrointestinal bleed; TMP-SMX, trimethoprim/sulfamethoxazole; CRP, c-reactive protein; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; BAL, bronchial lavage; FFP, fresh frozen plazma, INR, internationalized ratio; PT, prothrombin time; PCC, prothrombin complex concentrates; HE, hepatic encephalopathy; EEG, electroencephalogram; WHC, west-haven criteria; CHESS, clinical HE staging scale (CHESS); HESA, HE scoring algorithm; MO-log, modified orientation log; GCS, Glasgow coma scale; PEG, polyethylene glycol (PEG); LOLA, L-ornithine L-aspartate.

pensation and organ failure has been recently classified by a consensus conference as having acute on chronic liver failure (ACLF) [2]. Diagnosis of ACLF is made using the Chronic Liver Failure Organ Failure (CLIF) score (Table 1) and its prognosis is determined using the CLIF-ACLF score (www.clifconsortium.com, ACLF calculator). ACLF occurs in approximately 30% of hospitalized cirrhotic patients who present with a complication following an identified or unidentified precipitating event, is characterized by hepatic and/or extrahepatic organ failures, and is associated with a 28-day mortality rate 15 times higher than patients without ACLF [2,3]. In the U.S. each year, approximately 200,000 patients with cirrhosis are hospitalized of which approximately 10% require ICU care [3]. The cost of providing healthcare to these patients amounts to about $13 billion per year [4].

ACLF is a newly recognized and complex condition in which the host response to injury and the type and number of organ failures all play important roles in determining the prognosis of the patient [2,3]. At present, the most effective management of patients with ACLF is unclear because of paucity of clinical trial data and the lack of evidence-based guidance. The occurrence of ACLF increases the mortality risk, but the prognosis might be improved by optimal ICU management involving multiple disciplines, including hepatology, critical care, nephrology, infectious disease and transplant surgery. It is with this in mind that a Consensus meeting, endorsed by the American Society of Transplantation (AST), American Society of Transplant Surgeons (ASTS) and the European Association for the Study of the Liver (EASL), was organized whereby a group of invited experts in the field of liver transplantation reviewed the current knowledge of diagnostic approaches and treatment strategies that currently exist in the critical care management of patients with ACLF who are awaiting liver transplantation. The goal was to develop a consensus of opinions, based on best available evidence, on optimal practices and to articulate a research agenda to focus on important unanswered questions.

Methods

Prior to the conference, the organizing committee identified topics relevant to the management of patients with ACLF. A diverse international panel representing multiple relevant disciplines (nephrology, hepatology, transplant surgery, critical care/anesthesiology and infectious disease), from a variety of countries and scientific societies based on their expertise in this topic were assembled. Panelists were assigned to five person working groups, with each work group addressing one key topic. Prior to the conference, each group identified a list of key questions, conducted a systematic literature search and generated a bibliography of key studies. We then conducted a two and a half day conference, whereby work groups assembled in breakout sessions, as well as in plenary sessions where their findings were presented, debated and refined. A series of summary statements was then developed during the breakout sessions and presented to the entire group, revising each statement as needed until a final version was agreed upon by all members of the Consensus meeting.

Each work group conducted literature searches related to their topic questions via MEDLINE, PubMed, and the bibliographies of all articles that met the search criteria. The majority of the work group resources were devoted to the reviewing of randomized trials, as these were deemed to be the most likely to provide data to support level 1 recommendations with high quality evidence. The quality of the overall evidence and the strength of recommendations were graded using the Grading of Recommendations Assessment, Development and Evaluation system (Supplementary Table 1) [5]. Recommendations were "not graded" if they were not based on systematic evidence and used to provide guidance where the topic did not allow adequate application of evidence.

Table 1. Chronic Liver Failure (CLIF) Consortium Organ Failure Score. (www.clifconsortium.com).

Organ system	Score = 1	Score = 2	Score = 3
Liver, bilirubin (mg/dl)	<6	6-≤12	>12
Kidney, creatinine (mg/dl)	<2	2-<3.5	≥3.5 or renal replacement therapy
Brain, grade (West-Haven)	0	1-2	3-4
Coagulation, INR	<2	2-<2.5	≥2.5
Circulation, MAP (mmHg)	≥70	<70	Vasopressors
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	>300 >358	≤300 and >200 >214 and ≤357	≤200 ≤214

MAP, mean arterial pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.

Renal dysfunction

Acute kidney injury (AKI) occurs in up to 50% of patients admitted with cirrhosis and represents one of the criteria that define ACLF [6–9]. This increased risk of AKI is due to the combination of an impaired effective arterial blood volume secondary to arterial vasodilation, with increased intra-renal vasoconstriction and impaired renal autoregulation. Factors such as bacterial infections and gastrointestinal bleeding (GIB) that further impair circulatory status and reduce renal perfusion can precipitate AKI [10–12]. The development of AKI not only increases the risk of mortality, but also reduces kidney function in the long-term following liver transplantation [13–17].

Defining and classifying renal dysfunction

Recommendations

1. *We recommend that serum creatinine (Scr) values be interpreted with caution in cirrhotic patients especially those with ascites and fluid due to an overestimation of values (**1A**).*
2. *Diagnose and stage AKI in patients with liver disease guided by Kidney Disease Improving Global Outcomes (KDIGO), Scr and urine output (UO) criteria (**Ungraded**).*
3. *Use a value of Scr obtained in the previous 3 months as baseline Scr. In patients with more than one value within the previous 3 months, the value closest to the hospital admission when the patient was stable can be used as the baseline. In patients without a baseline Scr value, the admission Scr should be used as the reference Scr (**Ungraded**).*
4. *We do not recommend the use of estimated glomerular filtration rate (eGFR) equations for assessing renal function in patients with AKI (**1D**).*

Rationale. In the setting of cirrhosis, Scr tends to overestimate renal function due to decreased creatinine production by the