Executive Summary: Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Neurology, Peri-Transplant Medicine, Infectious Disease, and Gastroenterology Considerations

KEY WORDS: acute liver failure; acute on chronic liver failure; clinical practice guidelines; Grading Recommendations, Assessment, Development, and Evaluation

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Acute liver failure (ALF) and acute on chronic liver failure (ACLF) are conditions frequently encountered in the ICU and are associated with high mortality. We previously published recommendations for the management of the critically ill patient with liver disease focused on cardiovascular, hematological, pulmonary, renal, and endocrine/nutrition issues (1). In continuation of this document, we developed evidence-based recommendations addressing infectious disease, peri-transplant, gastrointestinal and neurologic issues that present unique challenges in this population of patients.

Clinical care is very often adapted to individual clinical circumstances and patient/family preferences. These guidelines are meant to supplement and not replace an individual clinician's cognitive decision-making. The primary goal of these guidelines is to aid best practice and not represent standard of care.

METHODS

Co-chair and vice-chairs were appointed by the Society of Critical Care Medicine (SCCM). Twenty-five other panel members were chosen in accordance with their clinical and/or methodological expertise. Corresponding with individual expertise, the panel was then divided into nine subgroups; the recommendations of five of those subgroups (cardiovascular, hematology, pulmonary, renal, and endocrine) are presented in this document. Each panel member followed all conflict-of-interest procedures as documented in the American College of Critical Care Medicine/SCCM Standard Operating Procedures Manual. The panel proposed, discussed, and finally developed 32 Population Intervention Comparator Outcome questions which they deemed most important to the patient and the end-users of this guideline. We used Grading Recommendations, Assessment, Development, and Evaluation (GRADE) approach to prioritize outcomes, assess quality of evidence, and determine the strength of outcomes (2). We then used the Evidence-to-Decision framework to facilitate transition from evidence to final recommendations. We classified each recommendation as strong or conditional as per GRADE methodology.

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We accepted a recommendation if 80% consensus was achieved among at least 75% of panel members. We developed best practice statements as ungraded strong recommendations in adherence with strict conditions.

RESULTS

We report 28 recommendations (from 31 Population Intervention Comparison Outcome questions) on the management ALF and ACLF in the ICU related to four groups (neurology, infectious diseases, gastroenterology, and peri-transplant). Overall, five were strong recommendations, 21 were conditional recommendations, two were best-practice statements, and we were unable to issue a recommendation for five questions due to insufficient evidence. A summary of main recommendations is presented in **Table 1**, and we discuss the abbreviated rationale for the five strong recommendations. The full recommendations and complete rationales can be found in the main article published in critical care medicine.

Question: In critically ill ACLF patients with upper gastrointestinal bleeding (UGIB), should we recommend using antibiotic prophylaxis versus no antibiotic prophylaxis?

Recommendation: We recommend using antibiotic prophylaxis in critically ill ACLF patients with any type of UGIB. (Strong Recommendation, moderate quality of evidence).

Rationale: In patients with ACLF, UGIB is a major risk factor for the subsequent development of bacterial infections with 45% to 66% of patients developing infections within the first 7 days of the bleeding episode. Administration of prophylactic antibiotics (typically third generation cephalosporins) in ACLF patients with UGIB substantially reduces the occurrence rate of infections and rebleeding as well as improves survival (3).

Question: In critically ill ACLF patients with spontaneous bacterial peritonitis (SBP), should we recommend using albumin versus no albumin?

Recommendation: We recommend using albumin in critically ill ACLF patients with SBP. (Strong recommendation, moderate quality of evidence).

Rationale: SBP is the most common infection-related complication in cirrhotic patients with ascites. Once SBP develops, the inherent vasodilated and immune-dysfunctional state of cirrhotic patients places them at high risk of developing shock, acute kidney injury, and

TABLE 1.
Summary of Main Recommendations

Recommendation	Strength of Recommendation	Quality of Evidence
We recommend performing esophagogastroduodenoscopy no later than 12 hr of presentation in critically ill ACLF patients with portal hypertensive bleeding (known or suspected)	Best practice statement	Best practice statement
We recommend performing large volume paracentesis with measurement of intra-abdominal pressure in critically ill ACLF patients with tense ascites and intra-abdominal hypertension or hemodynamic, renal or respiratory compromise	Best practice statement	Best practice statement
We recommend using antibiotic prophylaxis in critically ill ACLF patients with any type of upper gastrointestinal bleeding	Strong	Moderate
We recommend using albumin in critically ill ACLF patients with SBP	Strong	Moderate
We recommend using octreotide or somatostatin analog for the treatment of portal hypertensive bleeding in critically ill ACLF patients	Strong	Moderate
We recommend using proton pump inhibitors in critically ill ACLF patients with portal hypertensive bleeding	Strong	Low
We recommend using broad spectrum antibiotic agents for the initial management of SBP in critically ill ACLF patients	Strong	Low

ACLF = acute on chronic liver failure, SBP = spontaneous bacterial peritonitis.

other organ failures. Evidence suggests that use of albumin in SBP substantially reduces the risk of mortality and development of acute kidney injury (4). Further, because effective arterial circulating volume characterizes cirrhosis, albumin should be administered at diagnosis of SBP even without the obvious need of volume resuscitation to prevent progression to ACLF.

Question: In critically ill ACLF patients with SBP, should we recommend using broad spectrum antibiotics versus narrow spectrum antibiotics for the initial management?

Recommendation: We recommend using broad spectrum antibiotic agents for the initial management of SBP in critically ill ACLF patients. (Strong recommendation, low quality of evidence).

Rationale: SBP is a common life-threatening complication in cirrhosis (5). Delayed administration of appropriate antimicrobial therapy is associated with increased mortality. Third generation cephalosporins are generally accepted agents of choice for empirical treatment of community-acquired SBP. However, there is a trend of increased Gram-positive and multidrug resistance pathogen, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase (ESBL) in multiple geographic areas that mandate careful consideration of the initial treatment agent for SBP in settings with high drug resistance patterns (6, 7). Thus, use of third generation cephalosporin as the initial empirical treatment should be limited to low-risk community acquired SBP patients in the setting of low prevalence of drug resistance. Active agents against ESBL-producing pathogen should be considered for the empirical treatment of healthcare associated SBP. In high-risk critically ill patients and nosocomial infections, tailored approach according to the antimicrobial prevalence pattern covering resistant pathogens (ESBL, MRSA, ± VRE) is best suited for the empirical therapy.

Question: In critically ill ACLF patients with portal hypertensive bleeding should we recommend using proton pump inhibitors (PPIs) versus no PPIs?

Recommendation: We recommend using PPIs in critically ill ACLF patients with portal hypertensive bleeding. (Strong recommendation, low quality of evidence).

Rationale: In nonvariceal UGIB, PPIs have consistently been shown to reduce rates of rebleeding, need for surgical or repeat endoscopic intervention (8). Evidence suggests that use of PPIs in patients with portal hypertensive bleeding reduces the risk of rebleeding rate but does not impact mortality (9). Furthermore, extrapolating from the indirect evidence of the nonvariceal cohorts, short-term physiologic benefits as well as the consistent demonstration of reduction in rebleeding across the studies, we issued a strong recommendation.

Question: In critically ill ACLF patients with portal hypertensive bleeding should we recommend using octreotide or somatostatin analogs (SSAs) versus no octreotide and no SSA?

Recommendation: We recommend using octreotide or SSA in the treatment of portal hypertensive bleeding in critically ill ACLF patients. (Strong recommendation, moderate quality of evidence).

Rationale: In patients with ACLF, acute variceal bleeding is associated with mortality rates greater than 10% per episode. Besides endoscopic variceal banding or sclerotherapy, pharmacological agents that may be used for the treatment of acute variceal bleeding are terlipressin and its analogs (not available in North America) or SSAs (i.e., octreotide). The use of SSA compared with placebo is associated with reductions in mortality and may be associated with reductions in rebleeding risk (10).

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Conflicts of interest were reviewed and adjudicated by the co-chairs and co-vice chairs of the guidelines. In the event an individual disclosed a conflict or potential conflict by submitted form or verbally during the process of guidelines, those individuals abstained from voting on related questions. The task-force followed all procedures as documented in the American College of Critical Care Medicine/Society of Critical Care Medicine (SCCM) Standard Operating Procedures Manual. Drs. Singbartl, Nanchal, Killian, Olson, Karvellas, Subramanian, and Truwit disclosed authorship on several related articles with potential intellectual conflicts explored and adjudicated. Dr. Dionne described volunteer service for Canadian Association of Gastroenterology, American College of Gastroenterology, American Gastroenterological Association, and European Society of Intensive Care Medicine. Dr. Hyzy described volunteer service for American Thoracic Society, Quality Improvement and Implementation Committee, and the SCCM Finance Committee as well as service as an expert witness in a previous medical case involving this subject matter. Taylor advised of service as an author on the SCCM/American Society for Parenteral and Enteral Nutrition (ASPEN) nutrition guidelines and service on the ASPEN research committee. Dr. Huang disclosed service on the American College of Emergency Physicians sepsis task force. Dr. Karvellas disclosed service on an acute liver failure study group. Dr. Hyzy and Dr. Olson disclosed being expert witnesses. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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