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

OBJECTIVES: To develop evidence-based recommendations for clinicians caring for adults with acute liver failure (ALF) or acute on chronic liver failure (ACLF) in the ICU.

DESIGN: The guideline panel comprised 27 members with expertise in aspects of care of the critically ill patient with liver failure or methodology. We adhered to the Society of Critical Care Medicine standard operating procedures manual and conflict-of-interest policy. Teleconferences and electronic-based discussion among the panel, as well as within subgroups, served as an integral part of the guideline development.

INTERVENTIONS: In part 2 of this guideline, the panel was divided into four subgroups: neurology, peri-transplant, infectious diseases, and gastrointestinal groups. We developed and selected Population, Intervention, Comparison, and Outcomes (PICO) questions according to importance to patients and practicing clinicians. For each PICO question, we conducted a systematic review and meta-analysis where applicable. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach. We used the evidence to decision framework to facilitate recommendations formulation as strong or conditional. We followed strict criteria to formulate best practice statements.

MEASUREMENTS AND MAIN RESULTS: We report 28 recommendations (from 31 PICO questions) on the management ALF and ACLF in the ICU. 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.

CONCLUSIONS: Multidisciplinary, international experts formulated evidence-based recommendations for the management ALF and ACLF patients in the ICU, acknowledging that most recommendations were based on low quality and indirect evidence.

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

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In a previous document, we 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 the previous document, the current article addresses infectious disease, peri-transplant, gastrointestinal, and neurologic issues that present unique challenges in this population of patients.

Patients with acute liver failure (ALF) or acute on chronic liver failure (ACLF) are at high risk of developing critical illness. Once critical illness

DOI: 10.1097/CCM.0000000000005824

occurs, mortality is exceedingly high and often the definitive treatment is liver transplantation (LT). The unique pathophysiology of liver disease leading to critical illness portends unique manifestations in various organ systems. Strategies used to manage organ complications in general critical illness are not always applicable to the care of the patient with liver failure. As with many other illnesses, early recognition and prompt management of liver failure and its complications may improve outcomes.

In this document, we provide evidence-based recommendations intended to guide the practicing clinicians (critical care and emergency physicians, pharmacists, nurses, advanced practice providers, and dietitians) caring for the critically ill patient with ALF or ACLF. 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.

For the purposes of this guideline, we defined ACLF as a syndrome characterized by acute decompensation of liver cirrhosis, organ dysfunction, and high short-term mortality (2). Presence of organ failure distinguishes ACLF from acute decompensation of cirrhosis (acute development of ascites, variceal bleeding, and hepatic encephalopathy). In contrast, we defined ALF by the occurrence of encephalopathy and hepatic synthetic dysfunction within 26 weeks of the first symptoms of liver disease in a patient without evidence of chronic liver disease (3).

METHODOLOGY

Selection and Organization of Committee Members

Co-chairs and co-vice chairs were appointed by the guidelines committee of the Society of Critical Care Medicine (SCCM). Chairs and vice chairs in collaboration with SCCM chose committee members from two groups of individuals: 1) practicing clinicians with expertise in aspects of care of the critically ill patient with liver failure and 2) experts in methodology. Methodologists were provided by the Guidelines in Intensive Care, Development, and Evaluation group. Members of the guideline committee were intensivists, gastroenterologists, hepatologists, anesthesiologists, infectious disease specialists, transplant physicians, pharmacists, dieticians, and advanced practice providers.

The panel had a total of 27 members and was then divided into the following groups: neurology, peri-transplant, infectious diseases, and gastrointestinal groups. Each group was assigned a group leader, a methodologist, and expert panel members. The group leader was responsible for development of Population, Intervention, Comparison, and Outcomes (PICO) questions for their respective group (with input from the chairs and entire guideline committee), leading group meetings, assignment of tasks to group members, managing activities culminating in recommendations, and finalizing drafts of recommendations prior to guideline committee voting.

Management of Conflict of Interest

The guideline panel completed a standardized SCCM conflicts of interest (COI) declaration form. The chairs of the guideline reviewed and adjudicated all reported COI by panel members. Individuals who disclosed a COI or potential COI (electronically or verbally) during the process of guideline development were asked to abstain from voting on recommendations where conflict existed. The committee followed all procedures as documented in the American College of Critical Care Medicine/SCCM Standard Operating Procedures Manual. Overall, 11 panel members disclosed potential secondary COI (intellectual COI). All panel members were asked to disclose any financial COI; none disclosed any financial COI. We assigned panel members with potential intellectual COI to groups where COI did not exist.

Question Development and Outcome Prioritization

In this document, we only included questions from four groups (neurology, peri-transplant medicine, infectious diseases, and gastrointestinal groups). All questions were developed in the PICO format when applicable. Questions were developed via in-person meetings, emails, and teleconferences with input from the guideline committee. Final decisions regarding question inclusion were determined by arriving at consensus through discussion between the co-chairs, vice chairs, group heads, and methodologists; prioritization was based on potential importance to patients and end users of the guidelines rather than experts' perspectives or interests. While additional questions were

considered, 32 questions are included in these guidelines. We provide the complete list of PICO questions for this document in **Supplementary Table 1** (http://links.lww.com/CCM/H302).

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to prioritize outcomes and took the patient perspective during the prioritization process. First, we asked panel members in each group to list potentially relevant outcomes for each PICO questions. Then, we sent an electronic survey asking each panelist to rate each of the listed outcomes on a scale from 1 (not important) to 9 (critical). Outcomes with a mean rating of 7 or more were considered critical and were included under each question.

Systematic Review

For each of the questions, the medical librarian, with input from panelist and methodologist, performed independent literature searches. Group members in concert with group heads and methodology leads provided pertinent search terms and appropriate key words for each question. A minimum of two major databases (Medline, Cochrane Registry, or EMBASE) were searched for relevant studies from inception to 2018.

Screening and Data Abstraction

After finalizing the searches for each PICO question, a panel member screened the titles and abstracts, reviewed full text of potentially relevant articles. The aim was to identify recently published systematic reviews, relevant randomized controlled trials (RCTs), and lastly, relevant observational studies. Panel members then used a standardized data abstraction sheet to abstract data on population, interventions, and outcomes.

Risk of Bias Assessment

Panel members, with input from methodologists, used the Cochrane risk of bias tool to assess the risk of bias of RCTs (4), and Newcastle Ottawa Scale to assess risk of bias of nonrandomized studies (5).

Summarizing the Evidence

When applicable, the methodologists used meta-analytic techniques to generate pooled estimates for two or more studies. For meta-analysis of RCT data, we used random-effects model and inverse variance method to pool estimates across relevant studies. We reported relative risks (RRs) and 95% CI for binary outcomes, and mean difference and 95% CI for continuous outcomes. For observational (nonrandomized) data, we conducted meta-analysis if all individual studies provided adjusted estimates and not just crude values and included both an intervention and a control arm, we used random-effects model and inverse variance method to pool adjusted odds ratio (OR) across relevant studies, presenting OR and 95% CI for binary outcomes. All analyses were conducted using RevMan software (Review Manager, Version 5.3. Copenhagen, Denmark: The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

Grading of Recommendations

The GRADE approach principles guided the assessment of quality of evidence from high to very low and were used to determine the strength of recommendations. The GRADE approach to assess the quality of evidence is based on the evaluation of six domains: 1) risk of bias, 2) inconsistency, 3) indirectness, 4) imprecision, 5) publication bias, and 6) other criteria (6). The methodologist in each group performed the initial assessment of quality of evidence (as high, moderate, low, or very low), incorporated feedback from panel members, and generated evidence profiles using GRADE pro GDT software (Evidence Prime, Hamilton, ON, Canada) (7).

Formulation of Recommendations

In a series of webinars, methodologists reviewed the relevant data for each PICO question with subgroup members to formulate initial recommendations. Each of the groups used the evidence-to-decision (EtD) framework to facilitate transition from evidence to the final recommendation. The EtD framework ensure that panel members take into consideration the quality of evidence, magnitude of effect, patients' values and preferences, resources, cost, acceptability, and feasibility (8).

Applying the GRADE approach, we classified recommendations as strong or conditional using the language "We recommend…" or "We suggest…," respectively. The strength of a recommendation reflects the confidence regarding whether the desirable consequences

of the recommended intervention would outweigh the undesirable consequences. Thus, a strong recommendation in favor of an intervention reflects that the desirable effects of adherence will clearly outweigh the undesirable effects. The implications of calling a recommendation strong are that most patients would accept that intervention and that most clinicians should use it in most situations. However, a strong recommendation does not imply a standard of care, and circumstances may exist in which a strong recommendation cannot or should not be followed for an individual patient. A conditional recommendation indicates that the desirable effects of adherence will probably outweigh the undesirable effects, but confidence is diminished either because the quality of evidence or the benefits and risks were closely balanced. We anticipate that a conditional recommendation, while still relevant for most patients in most settings, will be more heavily influenced by clinical circumstances and patients' values (**Table 1**). Strong recommendations based on low quality of evidence can be justified rarely, such as in life- threatening scenarios or when there is a critical imbalance in benefit and risk (9).

Best practice statements (BPSs) were developed as ungraded strong recommendations in adherence with strict conditions (10).

Voting Process

After each group formulated draft recommendations, all committee members received links to an electronic survey, each nonconflicted member had to indicate agreement or disagreement, while conflicted members abstained from voting on recommendations in which COI exists. We defined consensus and accepted the recommendation if there was 80% consensus agreement among at least 75% of the committee members. Disagreements were resolved through teleconference calls, emails and revoting with modifications to statements to reach consensus. We used up to three rounds of voting to resolve disagreements.

Neurology Section

Intracranial Pressure Monitoring.

Recommendation. We suggest not using invasive intracranial pressure (ICP) monitoring for critically ill ALF patients with advanced-grade encephalopathy (Conditional recommendation, very low quality of evidence).

Rationale. Cerebral edema is common in ALF, especially in patients with grade III and IV hepatic encephalopathy. We did not identify any RCTs evaluating invasive ICP monitoring in patients with ALF. Three observational studies evaluated epidural, subdural and intra parenchymal ICP monitors and compared them to a control group (frequent neurologic examinations and imaging as needed). Two studies compared mortality in those who received ICP monitoring versus those who did not (11, 12). Bleeding rates were higher with subdural and intra-parenchymal devices in comparison to extradural devices (11–13). The rates of infection were lowest in extradural devices when compared with subdural and intra-parenchymal devices (12). However, ICP monitoring was not associated with any tangible benefits in outcomes (OR for mortality, 1.21; 95% CI, 0.84–1.75; **Supplementary Table 2**, http://links.lww.com/CCM/H302). Risk of bias was high secondary to the observational nature of the studies; thus, a conditional recommendation was issued.

Plasma Exchange for Treatment of Hyperammonemia in ALF.

Recommendation. We suggest, when available, using plasma exchange in critically ill ALF patients who develop hyperammonemia (Conditional recommendation, low quality of evidence).

Remarks. Hyperammonemia is defined as ammonia level greater than 150 umol/L.

Rationale. Hyperammonemia is associated with cerebral edema and intracranial hypertension in ALF patients. Various modalities have been studied in literature for chronic liver failure; however, there are very limited studies in ALF population. Unlike ACLF, ALF patients are not preconditioned to cope with hyperammonemia and are more susceptible to intracranial hypertension. Treatments such as lactulose and rifaximin used in ACLF, have not demonstrated benefit in ALF (14–20). Bernal et al (21) evaluated the relation of the admission arterial ammonia concentration and other clinical variables with the development of HE and ICH. Variables associated with intracranial hypertension and hepatic encephalopathy were investigated; ammonia was an independent risk factor for the development of both intracranial hypertension and hepatic encephalopathy. Intracranial hypertension developed in 55% of ALF patients with an ammonia level greater than 200 umol/L (21). Continuous renal

TABLE 1.
Implications of the Strength of Recommendation

Stakeholder	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action but many would not.
Clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances. Those circumstances may include the patient or family's values and preferences.
Policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

replacement therapy remains the first-line treatment for hyperammonemia and is often used in the absence of acute kidney injury (AKI). Further, ICH in ALF is driven by both hyperammonemia and systemic inflammatory response syndrome. High-volume plasma exchange (HVPE) was found to have a beneficial effect in one RCT (22). In 92 patients receiving HVPE, compared with standard medical therapy alone (90 patients), HVPE improved the LT-free survival rate of patients with ALF and grade II hepatic encephalopathy. This amelioration appears to be mainly related to the improvement of arterial pressure, with decreased vasopressor requirement. The improvement of the hospital survival seemed to be limited to the improved outcome of the 68 nontransplanted patients managed with HVPE; on meta-analysis, overall risk of mortality was no different between groups (RR, 0.79; 95% CI, 0.58–1.08; **Supplementary Table 3*a***, http://links.lww.com/CCM/H302).

Therapies to Decrease ICP in Patients With ALF.

Recommendation. We suggest using hypertonic saline in critically ill ALF patients who are at risk of developing intracranial hypertension (Conditional recommendation, low quality of evidence).

Remarks. Risk factors for intracranial hypertension include hyperammonemia (> 150 umol/L), high-grade hepatic encephalopathy or evidence of multiple organ failure (21).

Rationale. In a single-center RCT, Murphy et al (23) examined the effect of induced hypernatremia on the occurrence rate of intracranial hypertension in patients with ALF. Thirty patients with ALF and grade III or IV encephalopathy were randomized. Patients in group 1 (n = 15) received the normal standard of care, patients in group 2 (n = 15) received standard care and hypertonic saline (30%) via infusion to maintain serum sodium levels of 145–155 mmol/L. ICP was monitored in all patients with a subdural catheter for up to 72 hours after inclusion. Serum sodium levels became significantly different from the levels observed in the control group at 6 hours. ICP decreased significantly relative to baseline over the first 24 hours in the treatment group but not in the control group. The occurrence rate of intracranial hypertension (ICP > 25 mm Hg or greater) was significantly higher in the control group. Mortality from intracranial hypertension was no different between group (RR, 0.67; 95% CI, 0.13–3.44; **Supplementary Table 3*b***, http://links.lww.com/CCM/H302). Rise in serum sodium levels should be gradual to provide a constant gradient between brain and plasma. Thirty percent saline is not routinely available; thus, in clinical practice infusions of 3% saline can be used to raise sodium levels. Serum sodium levels should be maintained between 145 and 155 mmol/L as dictated by the clinical situation.

Targeted Temperature Management in ALF.

Recommendation. We suggest not routinely using induced moderate hypothermia (< 34°C) for critically ill ALF patients who are at risk of developing intracranial hypertension (Conditional recommendation, very low quality of evidence).

Rationale. Moderate hypothermia has been successful in decreasing ICP and has been reported to help to bridge to liver transplant in some uncontrolled studies (24–26). Its use in ALF remains controversial, as two studies have demonstrated both absence of benefit and harm (27, 28). A retrospective cohort study of ALF patients in the U.S. Acute Liver Failure Study Group with grade III or IV hepatic encephalopathy found that therapeutic hypothermia in ALF was not associated with increased bleeding or infections. Although young acetaminophen ALF patients may benefit, therapeutic hypothermia did not consistently affect 21-day survival (28). In a multicenter RCT (n = 46), patients with ALF, high-grade encephalopathy, and ICP monitoring were randomized to targeted temperature management groups of 34°C or 36°C (control) for a period of 72 hours. The primary outcome was a sustained elevation in ICP greater than 25 mm Hg. There were no significant differences between the groups in the primary outcome during the study period (35% vs 27%; p = 0.56) (RR, 1.31; 95% CI, 0.53–3.2). Furthermore, both groups had similar occurrence rate of adverse events and overall mortality (41% vs 46%; p = 0.75; RR, 0.89; 95% CI, 0.44–1.80; **Supplementary Table 3*c***, http://links.lww.com/CCM/H302). This study did not confirm an advantage of induced moderate hypothermia in patients with ALF (29).

Treatment of Hepatic Encephalopathy.

Recommendation. There was insufficient evidence to issue a recommendation on using lactulose, rifaximin, flumazenil, branch-chain amino acids, carnitine, zinc, probiotics, and L-ornithine L-aspartate (LOLA) in critically ill ALF patients with hyperammonemia.

Recommendation. We suggest using nonabsorbable disaccharides in critically ill ACLF patients with overt hepatic encephalopathy (Conditional recommendation, low quality of evidence).

Rationale. Nonabsorbable disaccharides (NADs) (i.e., lactulose, lactitol) are used as first-line agents for the treatment of hepatic encephalopathy. In a meta-analysis of 38 RCTs (n = 1,828), Gluud et al (14) found that NADs, compared with placebo/no intervention, reduce hepatic encephalopathy (24 RCTs [n = 1,487]; RR, 0.58; 95% CI, 0.5–0.69) and serious liver-related adverse events such as liver failure, variceal bleeding, serious infections, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (24 RCTs [n = 1,487]; RR, 0.47; 95% CI, 0.36–0.6). Treatment was also associated with a reduction in mortality in patients with overt encephalopathy (RR, 0.36; 95% CI, 0.14–0.94; **Supplementary Table 4**, http://links.lww.com/CCM/H302), although not in patients with minimal hepatic encephalopathy. The quality of evidence was downgraded because the population studied was cirrhotics with hepatic encephalopathy, and most trials were at high risk of bias for lack of blinding. Thus, a conditional recommendation was issued.

Recommendation. We suggest using enteral polyethylene glycol (PEG) as an alternative to lactulose in critically ill ACLF patients with overt hepatic encephalopathy (Conditional recommendation, low quality of evidence).

Rationale. A single center RCT (n = 50) demonstrated that using 4 L of PEG enterally over 4 hours led to faster hepatic encephalopathy resolution compared with standard therapy with lactulose (30). Thirteen of 25 patients in the standard therapy arm (52%) had an improvement of one or more in hepatic encephalopathy score, compared with 21 of 23 evaluated patients receiving PEG (91%) (RR, 0.18; 95% CI, 0.04–0.72; **Supplementary Table 5**, http://links.lww.com/CCM/H302). The median time for hepatic encephalopathy resolution was 2 days for standard therapy and 1 day for PEG group. PEG safety profile and balanced electrolytes make it an attractive alternative to lactulose in the ICU setting. However, volume of 4 L may be a concern for aspiration, especially in advanced grades of encephalopathy and should be used cautiously.

Recommendation. We suggest using oral rifaximin as adjunctive therapy in critically ill patients ACLF patients with overt hepatic encephalopathy (Conditional recommendation, low quality of evidence).

Rationale. Rifaximin is an oral nonsystemic antibiotic with less than 0.4% absorption. In a RCT (n = 120) comparing rifaximin (550 mg bid) and lactulose with lactulose and placebo in which 80% of patients had severe hepatic encephalopathy, patients who received rifaximin demonstrated an increased proportion of complete encephalopathy reversal and improvement

in 10-day mortality. In a recent meta-analysis evaluating the role of rifaximin in hepatic encephalopathy (19 RCTs, *n* = 1,370), rifaximin was associated with a beneficial effect in secondary prevention of encephalopathy (RR, 1.32; 95% CI, 1.06–1.65) (15). Patients receiving rifaximin were more likely to recover from hepatic encephalopathy (RR, 0.59; 95% CI, 0.46–0.76) and had reduced mortality (RR, 0.50; 95% CI, 0.31–0.82; **Supplementary Table 6**, http://links.lww.com/CCM/H302). The high cost of rifaximin may be a significant barrier to its routine use.

Recommendation. We suggest using LOLA in critically ill ACLF patients with overt hepatic encephalopathy (Conditional recommendation, very low quality of evidence).

Rationale. LOLA is substrate for urea cycle and stimulates enzymatic activity in residual hepatocytes leading to increased urea excretion. LOLA is more frequently used for treatment of hepatic encephalopathy outside the United States. A recent systematic review (six RCTs, *n* = 597) suggested a possible beneficial effect of LOLA on mortality, hepatic encephalopathy, and serious adverse events in comparisons with placebo or no intervention (**Supplementary Table 7**, http://links.lww.com/CCM/H302) (18). However, because the quality of the evidence was very low, the panel was very uncertain about these findings.

Recommendation. We suggest not routinely using IV flumazenil, probiotics, zinc supplementation, glycerol phenylbutyrate (GPB), or acarbose as adjunctive therapies in critically ill ACLF patients with overt hepatic encephalopathy (Conditional recommendation, very low quality of evidence).

Rationale. A recent systematic review (12 controlled trials, *n* = 842) found low-quality evidence suggesting a short-term beneficial effect of IV flumazenil in hepatic encephalopathy in cirrhosis with no difference in all-cause mortality (18). If used, flumazenil should be used in a closely monitored environment as it has a potential of provoking seizures. A meta-analysis that included 21 RCTs (*n* = 1,420) suggested that probiotics may lead to improvements in the development of overt hepatic encephalopathy (10 RCTs [*n* = 585; RR, 0.29; 95% CI, 0.16–0.51]). Conversely, probiotics were not associated with differences in mortality (seven RCTs [*n* = 404; RR, 0.58; 95% CI, 0.23–1.44]) (16). Oral zinc supplementation from a meta-analysis of four RCTs (*n* = 233) showed significant improvement in performance on the number connection test (standardized mean difference, –0.62; 95% CI, –1.12 to –0.11) but not in a reduction in encephalopathy recurrence (RR, 0.64; 95% CI, 0.26–1.59). However, mortality, liver-related morbidity, and quality of life were not reported (31). GPB lowers ammonia by providing an alternate pathway to urea for waste nitrogen excretion in the form of phenylacetylglutamine (PAGN), which is excreted in urine. In a randomized phase II trial of 178 cirrhotic patients (*n* = 59 receiving rifaximin) who had experienced greater than or equal to 2 hepatic encephalopathy events in the previous 6 months, GPB was associated with decreased encephalopathy events, serum ammonia levels, and no difference in adverse events (32). GPB use may be cost prohibitive and is limited by its dependence on renal clearance to eliminate PAGN and must be used with caution in the setting of AKI. Acarbose, an alpha-glycosidase inhibitor and hypoglycemic agent was tested in one RCT in patients with grade I or II hepatic encephalopathy and type II diabetes. Although there was a salutary effect on serum ammonia levels, sample size was small, an indirect and inaccurate marker of hepatic encephalopathy was used and other outcomes such as mortality were not reported (33). Please see **Supplementary Table 8** (http://links.lww.com/CCM/H302) for complete evidence profiles and summary of judgments.

Infectious Diseases

Antibiotic Prophylaxis With Upper Gastrointestinal Bleeding.

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

Rationale. 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 may attenuate the occurrence rate of infections and rebleeding as well as improve survival.

A meta-analysis of 12 RCTs (*n* = 1,241) found that antibiotic prophylaxis of bacterial infections in cirrhotic patients with UGIB in comparison to no antibiotic prophylaxis/placebo was associated with a reduction

in all-cause mortality (RR, 0.79; 95% CI, 0.63–0.98), bacterial infections (RR, 0.35; 95% CI, 0.26–0.47), bacteremia (RR, 0.25; 95% CI, 0.15–0.40), overall rebleeding episodes (RR, 0.53; 95% CI, 0.38–0.74), and SBP (RR, 0.45; 95% CI, 0.27–0.75) (34). Further rebleeding at 7 days was also significantly reduced (RR, 0.24; 95% CI, 0.12–0.50). We downgraded the evidence as included studies were at high risk of bias from lack of blinding and proper sample size calculations (**Supplementary Table 9**, http://links.lww.com/CCM/H302).

Albumin Infusion in SBP.

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, AKI and other organ failures (ACLF). In a meta-analysis of four RCTs (288 patients with SBP), albumin reduced the odds of mortality (OR, 0.34; 95% CI, 0.19–0.60) and renal impairment (OR, 0.21; 95% CI, 0.11–0.42) (35). Only three trials used no albumin as the comparator, while one used an artificial colloid. Patients in all four trials received antibiotics. We downgraded the evidence based on the lack of blinding in trials (**Supplementary Table 10**, http://links.lww.com/CCM/H302). We issued a strong recommendation based on direct evidence of the application of albumin in SBP. Further, secondary to the vasodilated state leading to decreased effective arterial circulating volume that is characteristic of cirrhosis, albumin should be administered at diagnosis of SBP even without the obvious need of volume resuscitation to prevent progression to ACLF. Typical initial dose is 1.5 g/kg of 25% albumin regardless of serum albumin levels.

Systemic Antifungal Prophylaxis for the Liver Transplant Recipient.

Recommendation. We suggest using systemic antifungal prophylaxis in critically ill liver transplant recipients with risk factors for invasive fungal infections (Conditional recommendation, very low quality of evidence).

Recommendations. We suggest not using antifungal prophylaxis in critically ill liver transplant recipients at low risk for invasive fungal infections (Conditional recommendation, very low quality of evidence).

Remarks. Risk factors for invasive fungal infections include renal failure requiring dialysis, rejection treatment, cytomegalovirus viremia or disease, acute hepatic insufficiency, early graft failure, retransplantation, preoperative use of broad-spectrum antibiotics, fungal colonization, and re-exploration after transplantation (36).

Rationale. Invasive fungal infections are an important cause of mortality and morbidity in liver transplant recipients. The most common infections are with Candida, followed by Aspergillus. Systemic antifungal prophylaxis may reduce the occurrence rate of invasive fungal infections and improve outcomes. Conversely, prophylaxis may also be associated with unnecessary drug toxicity, development of resistance and increased costs. In a meta-analysis, Evans et al (37) found that systemic antifungal prophylaxis compared with placebo was associated with a significantly reduced risk of invasive fungal infections (OR, 0.37; 95% CI, 0.19–0.72) and mortality attributable to invasive fungal infections (OR, 0.32; 95% CI, 0.10–0.83). However, overall mortality was not impacted by the use of prophylaxis (OR, 0.87; 95% CI, 0.54–1.39). We downgraded the strength of evidence and issued a conditional recommendation because most included studies were at high risk of bias due to small sample sizes, unclear allocation concealment, and inadequate blinding (**Supplementary Table 11**, http://links.lww.com/CCM/H302).

Although risk of acquiring invasive fungal infections was attenuated, overall mortality was unchanged. Weighing the risks versus benefits, it is likely prudent to use prophylaxis in patients who have risk factors for developing such infections.

Timing of Antibiotics in SBP and Septic Shock.

Recommendation. We suggest using appropriate antibiotics as soon as possible after recognition and within 1 hour of shock onset in critically ill ACLF patients with SBP and septic shock (Conditional recommendation, low quality of evidence).

Rationale. There are no RCTs to guide this recommendation. The surviving sepsis guidelines recommend initiating IV antibiotics as soon as possible after recognition and within one hour for both sepsis and septic shock. In an unselected patient population with sepsis or septic shock, the timing and appropriateness of empiric antibiotic therapy demonstrated significant impact on outcomes such as mortality, AKI, length of stay, and acute lung injury.

Karvellas et al (38) in a retrospective cohort study of SBP-associated septic shock from the Cooperative Antimicrobial Therapy of Septic Shock database found that survivors compared with nonsurvivors were more likely to receive appropriate antibiotic therapy as well as receive therapy earlier. On multivariable adjustment, each hour delay to appropriate antibiotic therapy was significantly associated with mortality (OR, 1.86; 95% CI, 1.10–3.14 per hour increment). Similarly, Arabi et al (39) from the same database found in a retrospective cohort of patients with cirrhosis and septic shock that the likelihood of death was significantly higher if initial therapy was either inappropriate (OR, 9.5; 95% CI, 4.3–20.7) or delayed (OR, 1.1; 95% CI, 1.1–1.2 for each 1 hr delay). Overall hospital mortality exceeded 75% in both studies, which is significantly higher than other comparable septic shock studies.

Both studies are at high risk of bias from their retrospective nature and small sample sizes. The data from the general population are not directly applicable to ACLF patients (**Supplementary Table 12**, http://links.lww.com/CCM/H302). However, there is strong rationale for the use of early appropriate antibiotic therapy in SBP. This recommendation is applicable to other infections in ACLF and ALF patients as well.

Large Volume Paracentesis in SBP.

Recommendation. We suggest not performing large volume paracentesis (LVP) in critically ill ACLF patients with SBP (Conditional recommendation, very low quality of evidence).

Remarks. LVP is defined as removing greater than 4 L of ascitic fluid.

Rationale. In patients with ACLF and ascites, SBP is a common complication and is associated with significant mortality, particularly when co-existent with septic shock (38). As antibacterial activity in the ascitic fluid correlates with total protein, SBP occurs commonly in patients with ascites of large volume and low protein content (40, 41). LVP (defined as removing > 4 L of ascitic fluid) is widely used for the treatment of refractory ascites. LVP may induce circulatory dysfunction, which can be mitigated with albumin as a plasma expanders (8 g/L ascites removed) (42–44). However, there remains equipoise regarding the safety and effectiveness of its use in patients with SBP. Choi et al (45) randomized 42 cirrhotic patients with SBP to treatment with LVP (> 4L) and IV albumin (intervention, n = 21) or diuretics and IV albumin (control, n = 21). There were no statistically significant differences for mortality (OR, 1.42; 95% CI, 0.21–0.55), renal impairment (OR, 3.00; 95% CI, 0.23–31.63) or resolution of SBP (OR, 0.33; 95% CI, 0.03–3.51) (**Supplementary Table 13**, http://links.lww.com/CCM/H302) (45).

Selective Bowel Decontamination in the Liver Transplant Candidate.

Recommendation. We suggest not using selective bowel decontamination (SBD) for critically ill liver transplant recipients (conditional recommendation, low quality of evidence).

Rationale. Bacterial sepsis and wound complications after LT increase mortality, morbidity, or hospital stay and are likely to increase overall transplant costs. All LT patients receive IV antibiotic prophylaxis post-LT. The aim of SBD is to preemptively reduce aerobic Gram-negative bacterial and yeast carriage in the gut without elimination of anaerobic bacteria. A regimen typically consists of unabsorbed oral antibiotics that have selective antimicrobial activity, with or without a brief period of systemic antibiotic therapy. The use of SBD has not been widely adopted in North America due to uncertainty regarding its net benefit to patients and potential it may promote the spread of antibiotic resistance. Recently, Gurusamy et al (46) performed a systematic review of SBD of which identified four trials compared SBD versus placebo or no treatment (47–50). Including all four studies (n = 256 subjects), there were no statistically significant differences in rates of infection between patients who received SBD and controls (RR, 0.94; 95% CI, 0.63–1.41). In the three studies (n = 190 subjects) that reported mortality (47, 49, 50), there was no statistically significant difference in mortality between patients who received SBD and controls (RR, 0.91; 95% CI, 0.31–2.72) (**Supplementary Table 14**, http://links.lww.com/CCM/H302). There were no significant differences in pooled risk of graft rejection or retransplantation in reporting studies. Hence, given concerns regarding potential side effects and risk of antibiotic resistance, we cannot advocate for routine use of SBD in ACLF/ALF patients undergoing LT.

Initial Antibiotic Therapy for SBP.

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 (51). Delayed administration of appropriate antimicrobial therapy is associated with increased mortality (38, 39). Third-generation cephalosporins are generally accepted agents of choice for empirical treatment of community acquired SBP (52). 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 (53, 54). Risk factors associated with Gram-positive and multidrug-resistant SBP are patients with advanced liver disease, severe critical illness, those receiving prophylactic antibiotics and nosocomial or community-acquired SBP (55, 56). A recent systematic review of the literature (nine studies, 520 nosocomial SBP positive ascitic culture) revealed a remarkable high prevalence (30–66%) of multidrug-resistant pathogen, indicating that third-generation cephalosporin may not be viable choices for nosocomial SBP (54). In another systematic review (seven studies, 1,701 participants), third-generation cephalosporin-resistant pathogen were reported in community (33.8%) as well as in nosocomial infections (54.3%), with pooled estimate indicating that nosocomial SBP was associated with a higher risk for resistance compared with community acquired SBP (RR, 1.67; 95% CI, 1.14–2.44; $p = 0.008$) (57). For healthcare-associated SBP, carbapenem-based empirical therapy was associated with lower rate of mortality and treatment failure and more cost effectiveness compared with third-generation cephalosporin-based regimen (6% vs 25%; $p = 0.01$, 18% vs 51%; $p = 0.001$, respectively) (**Supplementary Table 15**, http://links.lww.com/CCM/H302) (58, 59). Thus, we recommend limiting the use of third-generation cephalosporin as the initial empirical treatment to low-risk community-acquired SBP patients in the setting of low prevalence of drug resistance. Active agents against ESBL-producing pathogen (Carbapenems) 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) would be best suited for the empirical therapy. Once culture results are available, antibiotic therapy should be tailored to the narrowest spectrum based on organism sensitivities.

Midodrine and Terlipressin for SBP.

Recommendation. We suggest not using midodrine or terlipressin empirically for critically ill ACLF patients with SBP (Conditional recommendation, very low quality of evidence).

Rationale. SBP is a common infection in ACLF patients. Patients with SBP are at increased risk of developing hepatorenal syndrome. Administration of albumin has been shown to reduce the risk of mortality and renal impairment. Given the underlying vasodilated state, it is possible that administration of vasopressors concomitant with albumin further reduces the risk of renal injury and mortality. Salman et al (60) randomized 200 cirrhotic patients with SBP to one of four groups: albumin, terlipressin, low-dose albumin plus terlipressin, or midodrine. They failed to demonstrate significant differences in mortality or renal impairment in any of the groups. On analysis of the data, we found no differences in the risk of mortality (OR, 1.63; 95% CI, 0.68–3.91), renal failure (OR, 2.63; 95% CI, 0.97–7.17), or resolution of SBP (OR, 0.48; 95% CI, 0.08–52.74) (**Supplementary Table 16*a***, http://links.lww.com/CCM/H302) associated with the use of midodrine in SBP. Two RCTs informed our recommendation regarding Terlipressin. In addition to the above study, Chelarescu et al (61) randomized 55 cirrhotic patients with SBP to cefotaxime or cefotaxime and terlipressin. The cefotaxime and terlipressin group had decreased mortality and increased resolution of SBP at 48 hours and 5 days as well as lower recurrence rates of SBP. On meta-analysis of the data from these two trials, we found no differences in the risk of mortality (OR, 0.66; 95% CI, 0.27–1.58), renal failure (OR, 1.0; 95% CI, 0.32–3.09), or resolution of SBP (OR, 0.86; 95% CI, 0.67–5.15) associated with the use of terlipressin in SBP (**Supplementary Table 16*b***, http://links.lww.com/CCM/H302).

Both studies did not use albumin as standard of care. Furthermore, both studies were at high risk of bias secondary to small sample sizes and lack of concealment, blinding and description of randomization. Further, the study by Chelarescu et al (61) was only published in abstract form.

Gastroenterology Section

Timing of Endoscopy.

Recommendation. We recommend performing esophagogastroduodenoscopy no later than 12 hours of presentation in critically ill ACLF patients with portal hypertensive bleeding (known or suspected) (Best Practice Statement).

Rationale. Acute portal hypertensive UGIB in a frequent complication in ACLF patients and often if the triggering event for ACLF. The American Association of the Study of Liver Diseases recommends that endoscopic evaluation occur no later than 12 hours of presentation (62). There are no prospective data to guide this recommendation. A recent meta-analysis comparing urgent (< 12 hr) versus nonurgent (> 12 hr) endoscopy in acute variceal bleeding found that there were no differences in mortality, rebleeding rates, and other outcomes. However, this meta-analysis comprised five retrospective studies and was at high risk of selection bias (63). Given that early endoscopy would potentially lead to earlier intervention and cessation of bleeding source, reduce blood transfusions, and prevent hemodynamic instability for continued bleeding, the panel strongly voted for early endoscopy. Because of the lack of high-quality data, we issued a BPS in favor of early endoscopy.

Use of Proton Pump Inhibitors in Portal Hypertensive Bleeding.

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

Rationale. PPIs block the final step of acid production by inhibiting hydrogen potassium ATPase in gastric parietal cells (64). In nonvariceal UGIB, they have consistently been shown to reduce rates of rebleeding, need for surgical or repeat endoscopic intervention (65). Potential mechanisms of benefit include stimulation of platelet aggregation and stabilization of fibrin clots by raising the gastric pH (66, 67). Whether these benefits extend to portal hypertensive bleeding is unclear. Furthermore, the use of PPIs, especially in the population with cirrhosis is associated with alterations in the microbiome leading to dysbiosis (68–70), increased risk of SBP and hepatic encephalopathy (71) as well possibly increased mortality (72). Three meta-analyses found that use of PPIs in patients with portal hypertensive bleeding reduces the risk of rebleeding rate but does not impact mortality (73–75). We downgraded the level of evidence because across meta-analyses included studies were mostly retrospective and at high risk of bias from nonstandardized inclusion and treatment criteria (**Supplementary Table 17**, http://links.lww.com/CCM/H302). However, 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 in favor of PPIs.

Octreotide or Somatostatin Analogs in Portal Hypertensive Bleeding.

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

Rationale. In patients with ACLF, acute variceal bleeding is associated with mortality rates greater than 10% per episode (76). Besides endoscopic variceal banding or sclerotherapy, two classes of pharmacological agents for the treatment of acute variceal bleeding have been evaluated (77): terlipressin and its analogs (not available in North America) and SSAs (i.e., octreotide). Based on pooled analysis of systematic reviews of previous prospective controlled studies (78–80), the use of SSAs versus placebo was associated with 30 fewer deaths per 1,000 patients (RR, 0.85; 95% CI, 0.72–1.00), although the effect on rebleeding outcome was less clear (RR, 0.85; 95% CI, 0.52–1.37) (**Supplementary Table 18**, http://links.lww.com/CCM/H302).

Transjugular Intrahepatic Portosystemic Shunt for Recurrent Variceal Bleeding.

Recommendation. We suggest using transjugular intrahepatic portosystemic shunt (TIPS) for recurrent variceal bleeding after medical and endoscopic intervention over continued endoscopic therapy in critically ill ACLF patients (conditional recommendation, low quality of evidence).

Remark. TIPS requires appropriate screening for contraindications. This intervention requires access to an experienced operator at a center with expertise.

Rationale. In patients with ACLF, the decision to prevent rebleeding after a significant variceal bleed is a challenge. Traditionally, TIPS has been employed in the salvage/rescue setting after failure endoscopy. Most

recently, Garcia-Pagan et al (81) demonstrated in a randomized trial of 63 cirrhotic/ACLF patients at high risk of treatment failure that patients who underwent TIPS within 72 hours post-bleed after randomization that rebleeding rates (3% vs 50%) and mortality (14% vs 39%; $p < 0.001$ for both) were significant lower in the early TIPS group compared with pharmacotherapy/band ligation. In a recent meta-analysis, Halabi et al (82) demonstrated that in nine RCTs involving 608 cirrhotic patients, early TIPS was associated with decreased 1-year mortality (RR, 0.68; 95% CI, 0.49–0.96; $p = 0.03$) and 1-year occurrence rate of rebleeding (RR, 0.28; 95% CI, 0.20–0.40; $p < 0.001$). No significant difference in the occurrence rate of hepatic encephalopathy at 1 year was observed (RR, 1.36; 95% CI, 0.72–2.56; $p = 0.34$). While our systematic review of 11 studies did not demonstrate increased rates of hepatic encephalopathy (RR, 1.36; 95% CI, 0.72–2.56) (**Supplementary Table 19**, http://links.lww.com/CCM/H302), in patients with a model for end-stage liver disease (MELD) greater than 20 or significant hepatic encephalopathy, consider the use of TIPS on a case-by-case basis.

LVP in Intra-Abdominal Hypertension.

Recommendation. We recommend performing LVP 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).

Rationale. Ascites is a common complication in patients with ACLF. When ascites becomes tense, renal respiratory and cardiovascular function maybe compromised from rises in intra-abdominal pressure (83–86). Secondary to the vasodilated state of liver disease and limited compensatory mechanisms, critical abdominal organ hypoperfusion may occur in ACLF patients with tense ascites. In a study of 22 critically ill patients with decompensated cirrhosis and intra-abdominal hypertension, Mayr et al (87) demonstrated reduced clearance of indo-cyanine green (ICG) dye which dramatically improved upon LVP. Concomitantly hepatic artery resistance and blood flow velocities improved, intra-abdominal pressure fell, and abdominal perfusion pressure rose. Mayr et al (87) attributed the ICG clearance changes to improved hepatosplanchnic blood flow. Observational studies have also demonstrated improvement in lung function and Pao_2/Fio_2 ratio upon LVP concomitant with decreases in intra-abdominal pressure (86).

There are no randomized trials to guide recommendations. In heterogeneous critically ill patients, relief of intra-abdominal hypertension is associated with improvements in organ function and outcomes (88, 89). In ACLF patients with tense ascites and raised intra-abdominal pressure, drainage of ascites lowers intra-abdominal pressure. There is a strong physiologic rationale to attempt a trial of LVP in ACLF patients, especially if concomitant intra-abdominal hypertension is present. Therefore, we issued a BPS in favor of LVP.

Peri-Transplant Section

Corticosteroid Administration to Deceased Donors.

Recommendation. We suggest using systemic corticosteroids for deceased liver graft donors (Conditional recommendation, very low quality of evidence).

Rationale. In a systematic review of brain-dead organ donors (of any organ) (90), the pooled results of RCTs (91, 92) demonstrated that liver grafts from 183 deceased donors receiving corticosteroids showed a reduction in post-transplantation graft dysfunction (4.2% absolute risk reduction; 91 fewer to 72 more per 1,000; **Supplementary Table 20**, http://links.lww.com/CCM/H302) compared with grafts from the control group. Please refer to the SCCM "Guidelines for the Management of the Potential Organ Donor in the ICU" (93).

Fluid Management of Deceased Donor.

Recommendation. We suggest either using goal-directed fluid management for the deceased organ donor or standard fluid management strategies (Conditional recommendation, very low quality of evidence).

Remarks. Goal-directed fluid management refers to management directed by invasive hemodynamic monitoring (measurement of filling pressures, cardiac output, and central venous oximetry). In contrast, standard fluid management refers to management based on clinical assessment of peripheral perfusion (e.g., capillary refill time).

Rationale. Goal-directed fluid management of deceased donors, compared with standard management, is associated with negligible desirable effects (1 per 1,000 absolute reduction in mortality, range 24 fewer to 33 more deaths) (**Supplementary Table 21**, http://links.lww.com/CCM/H302), and a small likelihood of undesirable effects due to delays or complications

related to invasive monitoring and fluid overload (94). No data directly addressed the impact of goal-directed fluid management or other components of goal-directed donor management specifically on the outcomes of liver recipients. The SCCM "Guidelines for the Management of the Potential Organ Donor in the ICU" recommends maintaining euvolemia in the donor (mean arterial pressure at least 60 mm Hg, urine output of 1 mL/kg/hr, left ventricle ejection fraction > 45%) using an isotonic crystalloid and low doses of vasopressor (e.g., ≤ 10 μg/kg/min); pulmonary artery or central venous catheter or noninvasive monitoring should be considered to guide fluid management (93).

Recipient Acuity and Donor Assessment.

Recommendation. There was insufficient evidence to issue a recommendation on using the donor risk index (DRI) in selection of liver allograft.

Remark. Clinicians should use their judgment regarding severity of illness of the potential transplant recipient with donor graft factors (i.e., cold ischemia time, steatosis, donor age, etc).

Rationale. Based upon low-quality evidence from three observational studies that were unable to be pooled, the DRI of the graft did not appear to affect patient survival. Two of the three studies found graft factors were associated with graft survival. One study (n = 1,090) found that a high DRI graft (> 1.8) may adversely affect graft survival, particularly in recipients with low and intermediate MELD scores; however, in recipients with high MELD scores (> 30), graft survival appeared to be similar for low and high DRI grafts (95). A second, smaller study (n = 115) used three categories of graft risk (standard graft, 1–2 risk factors, 3–4 risk factors). Graft risk factors were associated with graft, but not patient, survival (96). The remaining observational trial (n = 70) compared two categories of grafts (more than one extended donor criteria [EDC] vs grafts with none or one EDC) and found no difference in early (5-d post-transplant) graft function (97).

Extracorporeal Liver Support for Acute or Acute-on-Chronic Liver Failure.

Recommendation. We suggest using either extracorporeal liver support or standard medical therapy in critically ill ALF or ACLF patients (Conditional recommendation, very low quality of evidence).

Remarks. Providers may choose to use artificial liver support based on local availability, familiarity with its use, and available resources.

Rationale. Extracorporeal liver support is used as a bridge to transplant or spontaneous recovery in ALF and as a bridge to transplant in ACLF. Based upon pooled data from 24 RCTs (n = 1,778), which included patients with either ALF or ACLF, the desirable effects of liver support (artificial and bioartificial combined) range from 3.1% absolute reduction in mortality for acute liver disease (range for acute liver disease: 85 fewer to 36 more deaths per 1,000) to 11.5% absolute reduction for acute-on-chronic liver disease (range for acute-on-chronic liver disease: 180 fewer to 42 more deaths per 1,000); neither mortality reduction is statistically significant (**Supplementary Table 22**, http://links.lww.com/CCM/H302). The selection of bioartificial support systems is further limited by feasibility (98). Artificial liver support has small desirable effects, moderate undesirable effects and is associated with high costs and limited access.

Peri-Transplant Fluid Restriction Accompanied by Vasopressor Support in the Liver Transplant Recipient.

Recommendation. There was insufficient evidence to issue a recommendation on peri-transplant fluid restriction accompanied by vasopressor use in liver transplant recipients.

Rationale. We were unable to identify high-quality evidence addressing whether low central venous pressure (CVP) and vasopressor infusion impacts patient or graft survival in LT. A 2011 Cochrane review addressed the impact of low CVP and vasopressor use; however, mortality and graft survival were not reported (99). Mean blood transfusion volume was reduced by low CVP (1.2 L lower; range: 1.63 lower to 0.77 lower) compared with controls. There were no significant differences in peri-transplant renal function or postoperative complications in the low CVP group. Norepinephrine use, compared with control, resulted in no significant difference in allogeneic blood transfusion requirements, platelets volume transfused, or plasma volume transfused. An increasingly common intraoperative practice is to restrict fluid during the preanhepatic and anhepatic stages in the liver transplant recipient in order to lessen transfusion requirements. Mean arterial pressure may be supported by vasopressors as needed.

TABLE 2.
Summary of 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 LVP 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
We suggest, when available, using plasma exchange in critically ill ALF patients who develop hyperammonemia	Conditional	Low
We suggest using hypertonic saline in critically ill ALF patients who are at risk of developing intracranial hypertension	Conditional	Low
We suggest using nonabsorbable disaccharide in critically ill ACLF patients with overt hepatic encephalopathy	Conditional	Low
We suggest using enteral polyethylene glycol as an alternative to lactulose in critically ill ACLF with overt hepatic encephalopathy	Conditional	Low
We suggest using oral rifaximin as adjunctive therapy in critically ill ACLF patients with overt hepatic encephalopathy	Conditional	Low
We suggest using appropriate antibiotics as soon as possible after recognition and within 1 hr of shock onset in critically ill ACLF patients with SBP and septic shock	Conditional	Low
We suggest not using selective bowel decontamination for the critically ill liver transplant recipient	Conditional	Low
We suggest using transjugular intrahepatic portosystemic shunt in critically ill ACLF patients with recurrent variceal bleeding after medical and endoscopic intervention over continued endoscopic therapy	Conditional	Low
We suggest using balanced (or normochloremic) crystalloid solution over normal (hyperchloremic) saline for peri-transplant fluid replacement in liver transplant recipients	Conditional	Low
We suggest using albumin over crystalloid for intraoperative volume replacement during liver transplantation	Conditional	Low
We suggest not using invasive intracranial pressure monitoring for critically ill ALF patients with advanced-grade encephalopathy	Conditional	Very low
We suggest not routinely using induced moderate hypothermia (< 34°C) for critically ill ALF patients who are at risk of developing intracranial hypertension	Conditional	Very low
We suggest using LOLA in critically ill ACLF patients with overt hepatic encephalopathy	Conditional	Very low

(Continued)

TABLE 2. (*Continued*).
Summary of Recommendations

Recommendation	Strength of Recommendation	Quality of Evidence
We suggest not routinely using IV flumazenil, zinc supplementation, glycerol phenylbutyrate, probiotics, or acarbose as adjunctive therapies in critically ill patients ACLF patients with overt hepatic encephalopathy	Conditional	Very low
We suggest using systemic antifungal prophylaxis in critically ill liver transplant recipients with risk factors for invasive fungal infections	Conditional	Very low
We suggest not using antifungal prophylaxis in critically ill liver transplant recipients at low risk for invasive fungal infections	Conditional	Very low
We suggest not performing LVP in critically ill ACLF patients with SBP	Conditional	Very low
We suggest not using midodrine or terlipressin for critically ill ACLF patients with SBP	Conditional	Very low
We suggest using systemic corticosteroids for deceased liver graft donors	Conditional	Very low
We suggest either using goal-directed fluid management for the deceased organ donor or standard fluid management strategies	Conditional	Very low
We suggest using either extracorporeal liver support or standard medical therapy in critically ill ALF or ACLF patients	Conditional	Very low
There was insufficient evidence to issue a recommendation on using lactulose, rifaximin, flumazenil, branch-chain amino acids, carnitine, zinc, probiotics, and LOLA in critically ill ALF patients with hyperammonemia	Not applicable	Not applicable
There was insufficient evidence to issue a recommendation on using the donor risk index in selection of liver allograft	Not applicable	Not applicable
There was insufficient evidence to issue a recommendation on peri-transplant fluid restriction accompanied by vasopressor use in liver transplant recipients	Not applicable	Not applicable
There was insufficient evidence to issue a recommendation for the choice of intraoperative monitoring in liver transplantation recipients	Not applicable	Not applicable
There was insufficient evidence to issue recommendation on early extubation of liver transplant recipients	Not applicable	Not applicable

ACLF = acute on chronic liver failure, ALF = acute liver failure, LOLA = L-ornithine L-aspartate, LVP = large volume paracentesis, SBP = spontaneous bacterial peritonitis.

Fluid Management: Choice of Peri-Transplant Crystalloid.

Recommendation. We suggest using balanced (or normochloremic) crystalloid solution over normal (hyperchloremic) saline for peri-transplant fluid replacement in liver transplant recipients (Conditional recommendation, low quality of evidence).

Rationale. We found no direct evidence comparing different types of crystalloids and risk of survival or graft failure after LT. In a 2014 meta-analysis, indirect evidence (in nonliver transplant populations) showed that balanced crystalloid, compared with normal saline, improved survival in sepsis patients (low-level evidence) (100). A 2017 Cochrane review of surgical patients evaluated 18 RCTs of 1,096 patients receiving either buffered (normochloremic or balanced) or nonbuffered (normal saline) crystalloid and found no mortality difference; however, the total number of deaths was low. There was no difference in need for renal replacement therapy between groups (101). A recently published RCT of 7,900 critically ill patients from five ICUs showed an absolute reduction in adjusted mortality of 20 patients per 1,000 (range: from 12 more to 45 fewer per 1,000) in the normochloremic (balanced) crystalloids group. Major adverse kidney events were also reduced in the normochloremic group (**Supplementary Table 23**, http://links.lww.com/CCM/H302) (102).

Fluid Management: Crystalloid Versus Colloids.

Recommendation. We suggest using albumin over crystalloid for intraoperative volume replacement during LT (Conditional recommendation, low quality of evidence).

Remark. Starches should not be used due to the risk of coagulopathy and renal failure.

Rationale. For patients undergoing LT, no studies were identified comparing the effects of colloids versus crystalloids on mortality or graft survival. Using indirect evidence (patients with traumatic injuries, patients undergoing surgery and critically ill patients), a meta-analysis showed decrease mortality with albumin (absolute mortality 47 fewer patients per 1,000; range: 95 fewer to seven more deaths per 1,000) (**Supplementary Table 24**, http://links.lww.com/CCM/H302) (100). In another meta-analysis, colloid administration with starch (tetrastarch, pentastarch, dextran, and gelatin) increased the risk of renal replacement therapy without a difference in morality (103).

Intraoperative Hemodynamic Monitoring.

Recommendation. There was insufficient evidence to issue a recommendation for the choice of intraoperative monitoring in LT recipients.

Rationale. Many studies have compared traditional hemodynamic monitors to newer monitoring techniques primarily in terms of measurement accuracy and other performance characteristics; however, no studies of newer monitors (including transesophageal echocardiography) were designed to show improvements in patient or graft survival.

Early Extubation of Liver Transplant Recipients.

Recommendation. There was insufficient evidence to issue recommendation on early extubation of liver transplant recipient.

Remark. Clinicians should use clinical judgment based on center expertise and recipient status.

Rationale. New evidence is emerging regarding decreased respiratory complications with early extubation post-LT. Among liver transplant recipients, patients who received anesthetic technique using shorter acting agents (vs traditional anesthetic technique) were extubated sooner (553 vs 1,081 min; $p < 0.001$) but spent similar duration in the ICU (104). The study was not designed to assess patient's or graft survival. Institutional staffing and ICU service environments appear to affect post-transplant disposition and length of post-transplant ventilation.

DISCUSSION

We report 29 recommendations on the management ALF or ACLF in the ICU, related to four groups (neurology, infectious disease, gastroenterology, and peri-transplant). A summary list of recommendations is provided in **Table 2**. We assembled multidisciplinary experts to address pertinent questions that are commonly encountered by clinicians taking care of patients with ALF and ACLF. We used a rigorous methodological approach lead by international experts in methodology to summarize the evidence and subsequently used the expertise of content experts to issue recommendations. Our approach led to the generation of a contemporary document that can be used as a reference for clinicians. There are some important limitations of this guideline, which include the lack of patient participation in the guideline development process, although panel members focused on the patient perspective when issuing the recommendations; it is possible that this perspective does not entirely reflect the values and preferences of patients. Last, we were unable to comment on other pertinent PICO questions that were not prioritized by the guideline committee. However, we identified several areas where evidence for this population is lacking and should be targeted for future research.

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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 taskforce 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. Dr. Taylor advised of service as an author on the SCCM/American Society of 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. Hollenberg disclosed that he is a member of American College of Chest Physicians, American Heart Association, and American College of Cardiology. Dr. Olson disclosed that she is a member of American Association for the Study of Liver Disease. Dr. Steadman disclosed that he is a co-author on "Management of the Critically Ill Patient with Cirrhosis: A Multidisciplinary Perspective." J Hepatology 2015 pending publication, and that he is currently writing guidelines for Anesthesiology Transplant fellowship for the International Liver Transplant Society. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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