Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary, and Renal Considerations

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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. Nanchal, Subramanian, Karvellas, Singbartl, Truwit, Killian, and Olson disclosed authorship on several related manuscripts with potential intellectual conflicts explored and adjudicated. Dr. Karvellas disclosed service on an acute liver failure study group. Dr. Hollenberg participates in American College of Chest Physicians, American Heart Association, and American College of Cardiology. 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. Huang disclosed that he is on the American College of Emergency Physicians sepsis task force. 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. Olson participates in American Association for the Study of Liver Diseases, and she has served as an expert witness regarding treatment of hepatitis C virus infection. 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 ACEP sepsis task force. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Objectives: To develop evidence-based recommendations for clinicians caring for adults with acute or acute on chronic liver failure in the ICU.

Design: The guideline panel comprised 29 members with expertise in aspects of care of the critically ill patient with liver failure and/or methodology. The Society of Critical Care Medicine standard operating procedures manual and conflict-of-interest policy were followed throughout. Teleconferences and electronic-based discussion among the panel, as well as within subgroups, served as an integral part of the guideline development.

Setting: The panel was divided into nine subgroups: cardiovascular, hematology, pulmonary, renal, endocrine and nutrition, gastrointestinal, infection, perioperative, and neurology.

Interventions: We developed and selected population, intervention, comparison, and outcomes questions according to importance to patients and practicing clinicians. For each population, intervention, comparison, and outcomes question, we conducted a systematic review aiming to identify the best available evidence, statistically summarized the evidence whenever applicable, and assessed the quality of evidence 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: In this article, we report 29 recommendations (from 30 population, intervention, comparison, and outcomes questions) on the management acute or acute on chronic liver failure in the ICU, related to five groups (cardiovascular, hematology, pulmonary, renal, and endocrine). Overall, six were strong recommendations, 19 were conditional recommendations, four were best-practice statements, and in two instances, the panel did not issue a recommendation due to insufficient evidence.

Conclusions: Multidisciplinary international experts were able to formulate evidence-based recommendations for the management acute or acute on chronic liver failure in the ICU, acknowledging that most recommendations were based on low-quality indirect evidence. (*Crit Care Med* 2020; 48:e173–e191)

Key Words: acute liver failure; acute on chronic liver failure; clinical practice guidelines; evidence-based medicine; Grading of Recommendations Assessment, Development, and Evaluation criteria

Patients with acute liver failure (ALF) or acute on chronic liver failure (ACLF) are at high risk of developing critical illness. Once critical illness occurs, mortality is exceedingly high and often the definitive treatment is liver transplantation. 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 and other healthcare professionals including pharmacists, nurses, advanced practice providers, and dietitians) caring for the critically ill patient with liver failure. 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, ACLF is a syndrome characterized by acute decompensation of cirrhosis, organ dysfunction, and high short-term mortality (1). In contrast, ALF is defined 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 (2).

METHODOLOGY

Selection and Organization of Committee Members

Co-chairs and co-vice-chairs were appointed by 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 29 members and was then divided into groups including cardiovascular, endocrine, hematologic, pulmonary, and renal considerations. 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 (e.g., evidence to decision [EtD] frameworks) and finalizing drafts of recommendations prior to guideline committee voting.

MANAGEMENT OF CONFLICT OF INTEREST

The guideline panel and the Chairs 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 were COI does not exist.

QUESTION DEVELOPMENT AND OUTCOME PRIORITIZATION

In this document, we only included questions from five groups (cardiovascular, hematology, pulmonary, renal, and endocrine and nutrition). 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. Although additional questions were considered 30 questions are included in these guidelines. We provide the complete list of PICO questions for this document in **Appendix Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/F235).

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 one (not important) to nine (critical). Outcomes with a mean rating of seven 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. When more than one relevant systematic review was identified, we prioritized the most recent and higher quality review based on the assessment of the panelist and methodologist assigned to that question. 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 (3) and Newcastle Ottawa Scale to assess risk of bias of nonrandomized studies (4).

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 (MD) 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).

GRADE ASSESSMENT

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 (5). 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,

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

and generated evidence profiles using GRADE pro Guideline Development Tool (GDT) software (6).

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 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 (7).

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 (8).

TABLE 2. Criteria for Best Practice Statement

Criteria for Best Practice Statement
1) Is the statement actionable?
2) Is the message necessary?
3) Is the net benefit (or harm) unequivocal?
4) Is the evidence difficult to collect and summarize?
5) Is the rationale explicit?
6) Is this better to be formally Grading of Recommendations Assessment, Development and Evaluation (GRADE)ed?

Best practice statements (BPSs) were developed as ungraded strong recommendations in adherence with strict conditions (**Table 2**) (9).

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 re-voting with modifications to statements to reach consensus. We used up to three rounds of voting to resolve disagreements.

CARDIOVASCULAR SECTION

Choice of Initial Resuscitation Fluid

Recommendation: We recommend against using hydroxyethyl starch for initial fluid resuscitation of patients with

ALF or ACLF (strong recommendation, moderate-quality evidence).

Recommendation: We suggest against using gelatin solutions for initial fluid resuscitation of patients with ALF or ACLF (conditional recommendation, low-quality evidence).

Rationale: Liver failure is a hyperdynamic state resulting in increased cardiac output and decreased or near-normal blood pressure. The primary mechanism behind this hyperdynamic circulation is peripheral and splanchnic vasodilation (10). As such, most patient are candidates for fluid resuscitation.

There are no large randomized trials comparing different resuscitation fluids in patients with liver failure. Meta-analyses of trials in critically ill patients suggest no benefit of hydroxyethyl starch (11) or gelatin solutions (12) over crystalloids, with some suggestion of risk when higher-quality trials are analyzed separately (11). These trials are limited by indirectness, as few patients with liver failure are included (**Appendix Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/F236), but there is no compelling rationale for use of these agents in patients with liver failure. Furthermore, starches may exacerbate coagulopathy in liver failure.

Albumin As Resuscitation Fluid

Recommendation: We suggest using albumin for resuscitation of patients with ALF or ACLF over other fluids, especially when serum albumin is low (< 3 mg/dL) (conditional recommendation, low-quality evidence).

Rationale: Human serum albumin is synthesized in the liver and is the main plasma protein responsible for oncotic pressure. The rationale for its administration has traditionally rested on increasing intravascular volume, but albumin also has antioxidant, immunoregulatory, and endothelial regulatory functions (13, 14). In patients with liver failure, in addition to low circulating levels consequent to decreased production, albumin function may be impaired (14). As such, the rationale for albumin administration in patients with liver failure may be stronger than in other conditions.

Administration of albumin in conjunction with high-volume paracentesis in patients with ascites has been shown by meta-analysis to prevent paracentesis-induced circulatory dysfunction (OR, 0.39; 95% CI, 0.27–0.55) and to decrease mortality (OR, 0.64; 95% CI, 0.41–0.98) (15). This suggests that the benefit of albumin results at least in part from improved hemodynamics, but contributions from other effects remain possible.

A robust network meta-analysis did not show benefits of albumin compared with crystalloids in patients with sepsis (OR, 0.81; 95% CI, 0.64–1.03) (**Appendix Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/F237) (16). The Albumin Replacement in Patients with Severe Sepsis or Septic Shock (ALBIOS) trial did not show decreased mortality with albumin replacement targeted to a serum level greater than 3 mg/dL for the first 28 days in 1,818 patients with severe sepsis and septic shock (OR, 1.00; 95% CI, 0.87–1.04), but mortality was decreased (RR, 0.87; 95% CI, 0.77–0.99) in patients with septic shock at enrollment (17).

The septic shock data are indirect for liver failure, costs may be prohibitive in resource poor settings and the paracentesis data may not be directly applicable to resuscitation for shock; nonetheless, the pathophysiologic rationale in liver failure suggest that albumin administration could be considered in this population.

Blood Pressure Targets

Recommendation: We suggest targeting a mean arterial pressure (MAP) of 65 mm Hg in patients with ALF or ACLF, with concomitant assessment of perfusion (conditional recommendation, moderate-quality evidence).

Remarks: Some patients will have adequate perfusion at a lower MAP, and others will have improvement of perfusion at a higher MAP.

Rationale: The precise MAP goal target in patients with liver failure remains uncertain, particularly because liver failure is a hyperdynamic vasodilatory state in which flow may be maintained at lower pressures (18). Animal models of hemorrhagic shock suggest that below a MAP of 60 mm Hg, autoregulation is compromised in the coronary, renal, and cerebrovascular vascular beds (19, 20).

In sepsis, guidelines recommend that MAP should be maintained above 60 (21) or 65 mm Hg (22). Randomized trials in patients with septic shock testing increases in MAP from 65 to 85 mm Hg have in general found similar effects on metabolic variables or renal function (23–25) although a prespecified subgroup with preexisting hypertension in the Sepsis and Mean Arterial Pressure (SEPSISPAM) trial of patients had less risk of needing renal replacement therapy (RRT) with high MAP (**Appendix Table 4**, Supplemental Digital Content 4, http://links.lww.com/CCM/F238) (25). The Surviving Sepsis Guidelines strong recommendation with moderate-quality evidence was based on data pertaining to raising MAP above 65. Data that failure to maintain MAP at 60–65 mm Hg worsens outcome are sparse. One retrospective study reported that area/time under MAP of 60 correlated with 30-day mortality in patients with septic shock (26).

In view of this indirect evidence, a target MAP of 65 mm Hg in patients with liver failure seems reasonable. It should be recognized that individual patients may have blood pressures somewhat lower than these thresholds without hypoperfusion. The blood pressure target should be individualized and supplemented by assessment of the adequacy of perfusion.

Monitoring Blood Pressure

Recommendation: We suggest placing an arterial catheter for blood pressure monitoring in patients with ALF or ACLF and shock (conditional recommendation, low-quality evidence).

Rationale: In shock states, estimation of blood pressure using a cuff, especially an automated measurement system, may be inaccurate. Use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure (21, 27) and allows beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information (28).

Insertion of radial arterial catheters is generally safe in both general critical care patients (29) and in patient with liver failure

(30), especially when guided by ultrasound (31). Radial catheters may underestimate arterial pressure in some instances (32) but the infection risk is higher with femoral artery catheters (33).

Invasive Hemodynamic Monitoring

Recommendation: We suggest using invasive hemodynamic monitoring to guide therapy in patients with ALF or ACLF and clinically impaired perfusion (conditional recommendation, low-quality evidence).

Rationale: Clinical assessment of the adequacy of intravascular volume and cardiac output can be particularly challenging in patients with liver failure.

In patients with persistent hypoperfusion despite empiric adjustment of standard therapies, uncertain fluid status, symptomatic low blood pressure, worsening renal function despite therapy or in those who require parenteral vasoactive agents, invasive hemodynamic monitoring can help determine the relative contributions of filling pressures, cardiac function, and vascular tone to that decompensation. This can help guide both the type of therapy and its dosing.

Proving that use of a monitoring technique improves a therapeutic outcome is challenging since the outcome depends on the efficacy of the therapy, particularly for hemodynamic therapies in patients with liver failure, in whom hepatic function rather than cardiovascular function drives outcomes.

Many of the complications of invasive hemodynamic monitoring pertain to central venous cannulation and do not differ between pulmonary artery and central venous catheter insertion in clinical trials (34–39). Pulmonary artery catheterization (PAC) is associated with the potential for tachyarrhythmias, although this is not associated with increased mortality (36, 37).

Complications of invasive monitoring (including arterial cannulation for measurement of blood pressure) after liver transplantation are low; PAC was not associated with any complications in this report (30).

However, it is important to recognize that invasive hemodynamic monitoring is best reserved for situations in which a specific clinical or therapeutic question needs to be addressed. Depending of the clinical scenario, clinicians may use judgment to determine the type of invasive hemodynamic monitor that is appropriate for the individual patient

The role of noninvasive hemodynamic monitoring through modalities such as echocardiography is expanding in the care of the critically ill patient; however, as of this writing, there is a lack of data on the use of such monitoring in ALF/ACLF. At the discretion of the treating clinician and after careful evaluation of advantages and pitfalls, noninvasive technology maybe used for hemodynamic monitoring and clinical decision-making in ALF/ACLF

Choice of First-Line Vasopressor Agent

Recommendation: We recommend using norepinephrine as a first-line vasopressor in patients with ALF or ACLF, who remain hypotensive despite fluid resuscitation, or those with profound hypotension and tissue hypoperfusion even if fluid resuscitation is ongoing (strong recommendation, moderate-quality evidence).

Rationale: Shock states in liver failure are typically characterized by distributive physiology. Therefore, despite a paucity of studies directly related to liver failure, indirect evidence from studies in septic shock (13) suggests that norepinephrine should be the first-line vasopressor in shock associated with liver failure. Studies comparing norepinephrine to dopamine in septic shock suggest that norepinephrine is more effective than dopamine in reversing hypotension. A systematic review and meta-analysis of 11 randomized clinical trials (n = 1,710) comparing norepinephrine with dopamine indicated that norepinephrine was associated with lower mortality (RR, 0.89; 95% CI, 0.81–0.98) and lower risk of arrhythmias (RR, 0.48; 95 % CI, 0.48–0.58) (**Appendix Table 5**, Supplemental Digital Content 5, http://links.lww.com/CCM/F239) (40).

Studies comparing epinephrine with norepinephrine do not demonstrate a difference in mortality, including a meta-analysis of four RCTs (n = 540) showing uncertain effect on mortality (RR, 0.96; 95% CI, 0.77–1.21) (Appendix Table 5, Supplemental Digital Content 5, http://links.lww.com/CCM/F239) (41). However, human and animal studies suggest that epinephrine may cause more splanchnic vasoconstriction, and therefore may increase the risk of mesenteric and hepatic ischemia in the setting of liver failure. Furthermore, epinephrine may increase aerobic lactate production in muscle tissue. Given the already impaired lactate clearance in liver failure, this may limit the utility of lactate clearance to guide therapy.

There are no studies comparing vasopressin with other vasoactive agents as first-line agents in septic shock.

Considering the above evidence, we recommend the use of norepinephrine as the first-line vasopressor of choice in patients with liver failure.

Use of Vasopressin

Recommendation: We suggest adding low-dose vasopressin to norepinephrine in patients with ALF or ACLF who remain hypotensive despite fluid resuscitation to increase blood pressure (conditional recommendation, low-quality evidence).

Rationale: Vasopressors are essential to restoring a perfusing blood pressure in hypotensive states refractory to fluid resuscitation. A meta-analysis of 17 RCTs including 2,904 patients with distributive shock showed that addition of vasopressin (n = 8) or vasopressin analog (n = 9) to catecholamines increased blood pressure or reduced catecholamine requirements. In this meta-analysis, 28-day mortality was reduced significantly (vasopressin 36.6% vs catecholamines alone 40.7%) (RR, 0.89; 95% CI, 0.82–0.97), but when only low risk of bias trials was considered, significance was lost. Of these 17 trials, three included 292 patients with liver disease and distributive shock; a pooled analysis of these patients also showed a significant reduction in mortality with vasopressin (51.0% vs 69.4%; RR, 0.76; 95% CI, 0.62–0.94), but the results were imprecise and further limited by serious risk of bias (**Appendix Table 6**, Supplemental Digital Content 6, http://links.lww.com/CCM/F240) (41).

The possible mortality benefit with the addition of vasopressin must be weighed against increased risk of digital ischemia. The quality of evidence for this outcome was

downgraded due to indirectness of both the population and the definition for digital ischemia across studies. In the only study including cirrhotic patients (n = 84), digital ischemia rates were increased with vasopressin (28.6% vs 9.5%; RR, 3.00; 95% CI, 1.05–8.55) (41).

The Surviving Sepsis guidelines suggest adding vasopressin to norepinephrine to raise MAP to target or to decrease norepinephrine dosage (22). In our analyses, both potential mortality benefit and digital ischemia risk appear more pronounced in patients with liver disease. Since the distributive shock data are indirect and the liver-specific data sparse, our recommendation is conditional.

HEMATOLOGY SECTION

Assessing Bleeding and Thrombosis Risk

Recommendation: We suggest using viscoelastic testing (thromboelastography/rotational thromboelastometry [ROTEM]) over measuring international normalized ratio (INR), platelet, and fibrinogen in critically ill patients with ALF or ACLF (conditional recommendation, low-quality evidence).

Rationale: Traditional evaluation of coagulation involves quantifying cellular, molecular, and coagulation factor deficiencies; however, quantification of these individual components fails to consistently provide an assessment of overall hemostatic function and risk of bleeding in cirrhosis (42). INR is based on the prothrombin time, which is dependent on pro-coagulant factors I, II, V, VII, and X. INR does not account for deficiencies of the anti-coagulation system, which may result in a hypercoagulable state not captured by a cirrhotic patient's elevated INR. Although bleeding remains of concern (especially during invasive procedures), cirrhotics are thought to be at greater risk of thrombotic complications (43, 44).

Viscoelastic testing, including thromboelastography and ROTEM, allows for real time global and functional evaluation of altered activity of the pro- and anti-coagulant pathways, identifying platelet function, hyper-fibrinolysis, and premature clot dissolution (45).

In a single-center, open-label RCT of 60 patients with liver cirrhosis scheduled to undergo an invasive procedure, blood product transfusion guided by thromboelastography (fresh frozen plasma [FFP] trigger: reaction time > 40 min; platelet trigger: maximum amplitude < 30 mm) versus that guided by standard of care (transfusion guided by INR and platelet count), resulted in significantly fewer patients being transfused (16.7% vs 100%; $p < 0.0001$), with no observed increase in bleeding complications (0% vs 3.3%; p = not significant [NS]) or 90-day mortality (26.6% vs 23.3%; p = NS) (**Appendix Table 7**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241) (46). Only a single patient (1/60), who had received FFP prior to the procedure, experienced a post-procedural bleed, following a low-bleeding risk paracentesis, suggesting that patients with cirrhosis and coagulopathy do not have increased procedure-related bleeding risk (independent of procedure risk categorization) unless a local complication occurs. A larger, multicentered study stratifying patients based on procedure risk categorization or examining spontaneous (i.e., not procedure-related) outcomes would be valuable in assessing the use of viscoelastic testing in guiding transfusion in cirrhotics with coagulopathy.

Hemoglobin Targets

Recommendation: We suggest using a transfusion threshold of 7 mg/dL, over other thresholds, for critically ill patients with ALF or ACLF (conditional recommendation, low-quality evidence).

Rationale: A single-center RCT examined hemoglobin transfusion thresholds in 889 patients with acute gastrointestinal bleed, stratifying for the presence or absence of cirrhosis (47).

Restrictive transfusion target (7 mg/dL), compared with liberal strategy (9 mg/dL), conferred significantly fewer transfusion reactions (hazard ratio [HR], 0.35; 95% CI, 0.19–0.65) and adverse events (HR, 0.73; 95% CI, 0.56–0.95). Stratifying for those with cirrhosis, restrictive transfusion was not significantly different to a liberal transfusion for death by 6 weeks (HR, 0.57; 95% CI, 0.30–1.08; $p = 0.08$), with the study suggesting a mortality benefit in Child-Pugh Class A and B cirrhosis (HR, 0.30; 95% CI, 0.11–0.85) (**Appendix Table 8**, Supplemental Digital Content 8, http://links.lww.com/CCM/F241). Further, RBC transfusion has been shown to be an independent predictor of mortality post liver transplantation (48). Given that endogenous erythropoietin levels are already known to be elevated in patients with cirrhosis and relate to the degree of portal hypertension (49) and that exogenous erythropoietin induces thrombopoiesis and platelet activity (50), it has been hypothesized that transfusion may play a role in worsening thrombosis. To date, no study examining a solely cirrhotic population is available. A conditional recommendation is made due to the low quality of evidence.

Venous Thromboembolism Treatment

Recommendation: We suggest using low molecular weight heparin (LMWH) or vitamin K antagonists, over no anticoagulation, in patients with portal venous thrombosis or pulmonary embolus (conditional recommendation, very low-quality evidence).

Rationale: Patients with cirrhosis have increased risk of thromboembolic disease, with rates of portal vein thrombosis (PVT) estimated at 8% per year in those awaiting liver transplantation (51, 52). Improved outcomes have been reported in those anti-coagulated at 1 year, especially those with more extensive mesenteric thrombosis (44, 53, 54). Four observational studies, comparing anticoagulation versus no treatment in 121 cirrhotics with nonmalignant portal venous thrombosis, reported significantly greater rates of complete or partial recanalization with anti-coagulation (RR, 3.82; 95% CI, 1.86–7.85) (53, 55, 56). One of these studies reported no difference in risk of major bleeding (RR, 0.20; 95% CI, 0.02–1.62) or heparin-induced thrombocytopenia (RR, 1.94; 95% CI, 0.08–45.54) with anticoagulation treatment (**Appendix Table 9**,

Supplemental Digital Content 9, http://links.lww.com/CCM/F241) (55). Despite the increased clinical effect observed with decreased anti-thrombin III levels in cirrhotics (57), LMWH use is favored. Although the quality of the evidence is very low, cirrhotics with PVT have increased risk of variceal bleeding and may be ineligible for liver transplant, while those treated with anticoagulation may demonstrate recanalization.

Venous Thromboembolism Prophylaxis

Recommendation: We suggest using LMWH over pneumatic compression stockings for venous thromboembolism prophylaxis in hospitalized patients with ACLF (conditional recommendation, low-quality evidence).

Remark: There is insufficient evidence to allow a recommendation for patients with ALF.

Rationale: Patients with cirrhosis/ACLF are at an increased risk of developing venous thrombosis. An open-label, single-center RCT examined the use of prophylactic LMWH versus no treatment in 70 cirrhotics (44). At 2 years follow-up, patients who received LMWH had significantly lower risk of PVT (RR, 0.05; 95% CI, 0.00–0.83), with three of 34 (8.8%) LMWH-treated patients and 10 of 36 controls (27.7%) developed PVT ($p = 0.048$). There was no appreciable increase in mortality (RR, 0.65; 95% CI, 0.31–1.37) or bleeding (RR, 2.12; 95% CI, 0.20–22.30) (**Appendix Table 10**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241). A further observational study of 203 chronic liver disease patients receiving pharmacologic versus mechanical prophylaxis reported no difference in mortality (RR, 0.29; 95% CI, 0.07–1.17) or bleeding (RR, 0.35; 95% CI, 0.05–2.69) (58). Three observational studies incorporating 408 patients favored lower rate of venous thromboembolism with pharmacologic prophylaxis (RR, 0.47; 95% CI, 0.09–2.32), although 95% CI includes both the potential for benefit and harm (58–60). Patients receiving pharmacologic prophylaxis experience lower rates of complications; however, some patients may prefer to avoid subcutaneous injections. Additionally, although the preponderance of data is for LMWH, unfractionated heparin maybe considered for prophylaxis.

Assessing Bleeding Risk for Invasive Procedures

Recommendation: We recommend viscoelastic testing (thromboelastography/ROTEM), over measuring INR, platelet, fibrinogen, in critically ill patients with ALF or ACLF undergoing procedures (strong recommendation, moderate-quality evidence).

Rationale: Bleeding rates after minimally invasive procedures in patients with cirrhosis/ACLF are low for paracentesis (0–3.3%) and thoracentesis (2%) (61). Bleeding does not appear to correlate with platelet count or INR. Reported frequency of major bleeding complications after liver biopsy was between 0.22% and 0.58% with 0.1% mortality. Bleeding rates were higher in patients with advanced hepatic fibrosis and platelet count less than or equal to 60×10^9/L (62, 63). Trans-jugular liver biopsy is relatively safe even in patients with thrombocytopenia or prolonged INR (64). Risk of bleeding after liver surgery probably correlates with surgical and hemostatic techniques rather than coagulation parameters (65). Although the optimal fibrinogen level is uncertain (normal 2–4.5 g/L), in bleeding/surgical patients, fibrinogen levels of greater than 1 g/L are advocated (66, 67). The routine use of viscoelastic testing during liver transplantation appears a well-established way to determine global coagulation status (68). As described in the section of assessing bleeding risk and thrombosis, in a single-center, open-label RCT of 60 cirrhotics scheduled to undergo an invasive procedure, blood product transfusion guided by thromboelastography versus that guided by standard of care, the use of thromboelastography resulted in significantly fewer patients being transfused (RR, 0.18; 95% CI, 0.08–0.39), with no observed increase in bleeding complications (RR, 0.33; 95% CI, 0.01–7.87), or 90-day mortality (RR, 1.14; 95% CI, 0.47–2.75) (**Appendix Table 11**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241) (46). A larger, multicentered study stratifying patients based on procedure risk categorization would be valuable in assessing the use of viscoelastic testing in guiding transfusion in cirrhotics/ACLF with coagulopathy undergoing invasive nonsurgical and surgical procedures.

Use of Novel Coagulation Agents

Recommendation: We recommend against using Eltrombopag in ACLF patients with thrombocytopenia prior to surgery/invasive procedures (strong recommendation, low-quality evidence).

Remarks: There is insufficient evidence to issue a recommendation for or against prothrombin complex concentrates (PCCs).

Rationale: Thrombocytopenia is common in ACLF. In trials, the oral thrombopoietin receptor agonist eltrombopag increased platelet count in thrombocytopenic hepatitis C virus (HCV) patients, improving tolerance of anti-HCV therapy (69). Eltrombopag is an oral thrombopoietin-receptor agonist. The Eltrombopag Evaluated for Its Ability to Overcome Thrombocytopenia and Enable Procedures (ELEVATE) study evaluated the efficacy of eltrombopag for increasing platelet counts and reducing the need for platelet transfusions in patients with thrombocytopenia and chronic liver disease undergoing elective invasive procedures (70). The investigators randomized 292 patients with chronic liver disease of diverse causes and platelet counts of less than 50×10^9/L to receive eltrombopag, at a dose of 75 mg daily, or placebo for 14 days before a planned elective invasive procedure. Platelet transfusion was avoided in 104 of 145 patients who received eltrombopag (72%) and in 28 of 147 who received placebo (19%) ($p < 0.001$) (**Appendix Table 12**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241).

Thrombotic events of the portal venous system were observed in six patients who received eltrombopag, when compared with one who received placebo, resulting in the early termination of the study. Nplate (romiplostim) has also been associated with reports suggesting increased thrombotic risk, particularly in patients with platelet counts over 200×10^9/L (71, 72). Although the quality of evidence was low, due to concerns about harm

(thrombosis) and cost, the panel issued a strong recommendation against using eltrombopag prior to procedures.

PCCs are available as 3-factor (FII, IX, X) and 4-factor products (same factors plus FVII). Some contain endogenous anticoagulants (protein C, protein S, antithrombin III) with or without heparin to lessen the thrombotic risk (73). Thrombotic complications in ACLF patients may be reduced by limiting repeat dosing of PCCs. Factor II and X have long half-lives (60 and 30 hr, respectively) and may accumulate during repeated administration. Although there is no direct randomized evidence for the use of PCC in ACLF or ALF patients, in massive trauma patients (indirect evidence) thromboelastometry-guided PCC administration, when compared with FFP transfusion, resulted in a higher likelihood of avoidance of RBC and platelet transfusion (74). Due to the lack of direct evidence, we cannot make a recommendation on the use of PCC or antifibrinolytics in ACLF/ALF.

PULMONARY SECTION

Tidal Volumes for Mechanically Ventilated Patients

Recommendation: We suggest using a low tidal volume strategy over high tidal volume strategy in patients with ALF or ACLF and acute respiratory distress syndrome (ARDS) (conditional recommendation, low-quality evidence).

Rationale: Positive pressure ventilation is a life-saving intervention for patients with ARDS. Conversely, positive pressure ventilation has been associated with ventilator-induced lung injury by means of alveolar stress and strain from overdistention and increased transpulmonary pressure (75–80). Cytokines are released as result of both volutrauma and barotrauma which is associated with increased nonpulmonary organ dysfunction and mortality (81–85).

Walkey et al (86) conducted a meta-analysis of low versus nonvolume limited tidal volume strategies for ARDS. This analysis of nine studies with 1,629 subjects demonstrated a reduction in mortality with low tidal volume strategies (RR, 0.80; 95% CI, 0.66–0.98). Two studies had the co-intervention of high positive end-expiratory pressure (PEEP) and when excluded, 1,481 subjects were analyzed and the reduction in mortality was no longer significant (RR, 0.87; 95% CI, 0.70–1.08). Of note, the greater the difference between low and nonvolume limited tidal volumes the greater the mortality benefit.

Ventilator-free days (VFDs) and barotrauma were no different across the nine studies (VFDs: mean 0.03 d; 95% CI, –5.88 to 5.95 d) and (barotrauma: RR, 0.96; 95% CI, 0.67–1.37) (**Appendix Table 13**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241). The authors, as with other studies, concluded that a low tidal volume approach may be beneficial. We assessed the quality of evidence for mortality, VFDs, and barotrauma as moderate, very low, and low, respectively.

The general nature of critically ill patients in these studies limits our confidence when applying the findings to liver failure patients. We do not have specific outcomes such as hospital mortality, VFDs, barotrauma, or transplant-free survival. However, we believe that improved mortality from low tidal volume strategy was compelling and overshadowed any undesirable effects or lack of benefit in VFDs. Concerns over increased sedation with low tidal volume in patients with liver disease was expressed; however, two studies did not demonstrate increased need for sedatives in low tidal volume groups.

Use of Positive End-Expiratory Pressure

Recommendation: We suggest against using high PEEP, over low PEEP, in patients with ALF or ACLF and ARDS (conditional recommendation, low-quality evidence).

Remarks: Clinicians may cautiously choose high PEEP in moderate to severe ARDS after balancing potential benefit to risk of increasing intracranial pressure (ICP) and reducing venous return.

Rationale: PEEP is almost universally applied to patients with ARDS to recruit atelectatic lung for participation in gas exchange and prevent collapse of alveoli that are recruited during tidal volume ventilation (87–91). The application of PEEP is distributed to all alveoli and may lead to overdistention of alveoli that are open throughout the respiratory cycle, leading to overdistention at end of inspiration, increased deadspace ventilation, increased pulmonary vascular resistance, and reduced venous return (80, 92).

Walkey et al (93) conducted a meta-analysis of high versus low PEEP in general ICU patients. The use of high PEEP in unselected patients with ARDS did not show benefit in mortality (RR, 0.91; 95% CI, 0.80–1.03), new organ failure (RR, 0.89; 95% CI, 0.67–1.19), or ventilated free days (MD, 1.68 d; 95% CI, –1.5 to 4.9 d). The high PEEP group did have better Pao_2/Fio_2 ratios (MD, 61.24; 95% CI, 45.92–76.57) and did not have greater frequency of barotrauma (RR, 1.09; 95% CI, 0.84–1.40) (**Appendix Table 14**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241). Briel et al (94) conducted an individual patient data meta-analysis and found that subjects with moderate to severe ARDS (Pao_2/Fio_2 < 200 mm Hg) had lower mortality rates (RR, 0.90; 95% CI, 0.81–1.0; p = 0.049) when randomized to high PEEP arm (94).

The general nature of critically ill patients in these studies limits our confidence when applying the findings to liver failure patients. As such, we do not have outcomes specific to liver failure patients on mortality, VFDs, barotrauma, transplant-free survival, nor impact on ICP. We rated the quality of evidence as low for mortality and moderate for oxygenation.

The Large observational study to Understand the Global impact of Severe Acute respiratory Failure (LUNG SAFE) study was a convenience sample of 2,377 patients with severe respiratory failure from 459 ICUs in 50 countries (95). The decision to apply high or low PEEP was at the discretion of the clinical teams. There were 103 patients with chronic liver disease, and mortality rates were high at 72.8%. High PEEP did not result in reduced mortality rates; the separation of high versus low PEEP was at 8 or 12 cm H_2O (J. G. Laffey and E. Rezoagli, personal communication, 2019).

Patients in whom high PEEP was applied had significantly lower Pao_2/Fio_2 ratios at baseline. We believe that high PEEP does not offer benefit over low PEEP for unselected patients with liver failure but may benefit patients with moderate to severe ARDS. PEEP titration should account for the potential of increased PEEP levels negatively impacting ICP and venous return.

Use of Pulmonary Arterial Hypertension Therapy in Portopulmonary Hypertension

Recommendation: We suggest treating portopulmonary hypertension (POPH) with agents approved for pulmonary arterial hypertension (PAH) in patients with mean pulmonary artery pressure greater than 35 mm Hg (conditional recommendation, very low-quality evidence).

Rationale: POPH is a well-known serious pulmonary vascular complication of portal hypertension. POPH is defined as the presence of PAH that evolves because of portal hypertension and is included in Group 1 of the clinical classification of pulmonary hypertension (96). POPH has been documented in ~4.5–8.5% of liver transplant candidates (97, 98), and patients with POPH represent 7–10% of those with PAH (99). POPH has worse survival outcomes than many other forms of PAH. Despite falling under the Group 1 classification of PAH, POPH patients have been excluded from most previously published RCTs of targeted therapy in PAH. Only one RCT including exclusively POPH patients has been completed showing that macitentan improved hemodynamics and was safe in this population (100). Another RCT assessing the role of riociguat in the management of PAH included 13 patients with POPH (101). Thus, much of the application of PAH-targeted therapy in POPH patients is extrapolated from the broader PAH literature. Uncontrolled, small observational studies have suggested that PAH-targeted therapies used for other types of PAH could be beneficial for patients with POPH (102–117). Prostacyclin analogs, such as parenteral epoprostenol or treprostinil, have shown improvements in POPH hemodynamics (102, 104, 109–111, 116). Sildenafil, a phosphodiesterase inhibitor subtype 5, has shown improvement in functional capacity and hemodynamics when used in POPH patients (105, 107, 113). The use of endothelin receptor antagonists such as bosentan or ambrisentan in POPH patients has also shown improvement of hemodynamics and functional class without significant liver toxicity (103, 106, 108, 115). By improving hemodynamic and clinical parameters, PAH therapy can lead to a response that meets liver transplantation eligibility criteria; however, careful patient selection is required. Specific guidelines for the management and treatment of patients with POPH have been recently published (118).

Hypoxemia in Patients With Hepatopulmonary Syndrome

Recommendation: We recommend supportive care with supplemental oxygen in the treatment of hepatopulmonary syndrome (HPS), pending possible liver transplantation (BPS).

Rationale: HPS is characterized by dilatation of pulmonary precapillary and capillary vessels resulting in hypoxemia early on due to ventilation perfusion mismatch and later also due to shunt. Loss of hypoxic pulmonary vasoconstriction in ~30% of cirrhotics leads to loss of pulmonary vascular tone with gravitational changes with the development of platypnea and orthodeoxia (119). Pharmacologic treatment of HPS has been ineffective long term and is largely limited to case reports and small case series from the involving agents, such as methylene blue (120) or pentoxifylline (121). One small RCT of 20 HPS patients suggested oral garlic supplementation to be beneficial, with a 24% increase in Pao_2 over baseline and reversal of HPS in 14 of 21 patients (122). At present, liver transplantation is the only proven beneficial therapy long term (123). Hence, patients with HPS should be treated with supplemental oxygen as needed, or as a bridge to liver transplantation. Severe hypoxemia occurs in 6–21% of patients with HPS early on (< 24 hr) following liver transplant and carries a 45% mortality (124).

Trendelenburg positioning, followed by inhaled epoprostenol, inhaled nitric oxide and IV methylene blue have been suggested as supportive modalities in these patients (125).

Tube Thoracostomy in Hepatic Hydrothorax

Recommendation: We recommend placing chest tube with an attempt to pleurodesis for hepatic hydrothorax in patients in whom transjugular intrahepatic portosystemic shunt (TIPS) is not an option or as a palliative intent (BPS).

Rationale: Four percent to 6% of patients with liver cirrhosis develop hepatic hydrothorax. General medical management is aimed toward reducing formation of pleural effusion with salt restriction and diuretics. In patients with recurrent effusions, the best studied and effective treatment is TIPS with a complete response in 55.8% and partial in 17.6% (126). However, TIPS is complicated by hepatic encephalopathy (HE) which may exclude its use. Traditionally, chest tubes for hepatic hydrothorax were considered a relative contraindication due to fear of infection and leakage of excessive fluids and electrolytes. The infection rates in tube thoracotomy have ranged from 0% to 29% (127–131). A metaanalysis reported infection rate of 2.3% (95% CI, 0–4.7%) in patients with nonmalignant effusions (127). Volume and electrolyte losses have been reported but only in case reports. Most studies do not report this as a common complication (128–131). In a systemic review, rates of spontaneous pleurodesis was reported to be 163 of 325 (51.3%) in tube thoracotomy for nonmalignant effusions (127). In another systemic review, patients with hepatic hydrothorax undergoing pleurodesis, complete response was reported in 148 of 206 patients (72%; 95% CI, 65–79%) (132). Tube thoracotomy has been used as a bridge to liver transplant in a small series of patients (133).

With 50% of these patients achieving spontaneous pleurodesis, tube thoracotomy may be considered in hepatic hydrothorax if there is contraindication for TIPS, as a palliative intent or as a bridge to liver transplant. Although indwelling pleural catheter is present, it may be reasonable to attempt pleurodesis when not achieved spontaneously if the patient can tolerate the procedure.

Risk of infection is high and should be discussed with the patient.

Use of High-Flow Nasal Cannula and/or Noninvasive Ventilation

Recommendation: We suggest using high-flow nasal cannula (HFNC) over noninvasive ventilation in hypoxic critically ill patients with ALF or ACLF (conditional recommendation, low-quality evidence).

Remarks: In patients with hypercarbia, it may be more appropriate to use noninvasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation over HFNC.

Rationale: NIPPV is often applied to avoid intubation in critically ill patients and is more effective than conventional oxygen therapy (134). Applying this modality is uncomfortable to the patient, often results in facial skin breakdown, interferes with speech and eating, and is resource intensive. In comparison with NIPPV, HFNC offers the promise of greater patient comfort and less resource utilization (135).

Ni et al (134) performed a meta-analysis on six RCTs of HFNC compared with NIPPV, six of which provided data on intubation and five of which provided data on mortality (134). There were no differences in intubation rates between HFNC and NIPPV (OR, 0.73; 95% CI, 0.47–1.13). There was no difference in mortality rates (OR, 0.63; 95% CI, 0.34–1.18) (**Appendix Table 15**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241).

These studies were not blinded, allowing for bias. The general nature of critically ill patients in these studies limits our confidence when applying the findings to liver failure patients. As such, we do not have evidence specific to liver failure patients regarding the outcome of mortality or need for intubation. The evidence was evaluated as low quality.

We believe that HFNC eliminates many of the undesirable consequences of NIPPV, particularly patient-specific issues. We would also expect less impact on ICP or venous return as PEEP with HFNC flows of 35–50 L/min is between 3 and 5 cm H_2O which is lower than that seen with continuous positive airway pressure (135). Mean airway pressures range with flows between 30 and 50 L/min HFNC range from 1.5 + 0.6 and 3.01 + 1.2 cm H_2O, which is lower than that seen with NIPPV (136, 137).

This recommendation applies to patients without hypercarbia. If hypercarbia is present, the panel recommends NIPPV or invasive mechanical ventilation over HFNC. Concern of over reliance on HFNC leading to delays in intubation were expressed (138, 139).

RENAL SECTION

Intraoperative Renal Replacement Therapy During Liver Transplant Surgery

Recommendation: There is insufficient evidence to issue a recommendation.

Remarks: Patients with ongoing emergent indications for RRT such as hyperkalemia or severe acid-base abnormalities should not have RRT discontinued.

Rationale: Management of patients with liver cirrhosis and acute kidney injury (AKI) during liver transplant surgery remains a clinical challenge, in particular because of profound changes in fluid status as well as acid-base and electrolyte homeostasis. Proponents of intraoperative RRT highlight the better control of temperature, electrolyte, and volume management during critical phases of liver transplant surgery, for example, reperfusion. Nonetheless, intraoperative RRT carries risks and requires additional resources: exposing and connecting the patient to an extracorporeal circuit, need for anticoagulation, and need for additional consultants and trained personnel to oversee and adjust RRT during surgery.

So far, clinical data are only available in the form of retrospective studies (140–142). Analyses of pooled data from 664 patients revealed that the use of intraoperative RRT was associated with 13 fewer deaths (OR, 0.91; 95% CI, 0.40–2.07) and 53 fewer graft dysfunctions (OR, 0.54; 95% CI, 0.27–1.08) per 1,000 patients (**Appendix Table 16**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241). The quality of evidence for these outcomes is very low. There is very little data on the frequency and severity of side effects, additional resources required, and cost-effectiveness.

The panel concluded that the current evidence is insufficient to determine the balance between desirable and undesirable effects of continuing versus discontinuing intraoperative continuous renal replacement therapy (CRRT); therefore, a recommendation could not be issued. Directed by clinical judgment and circumstances, clinicians may choose to either continue or discontinue CRRT intraoperatively in patients who were receiving CRRT preoperatively.

Timing of RRT in Patients With Acute Kidney Injury

Recommendation: We suggest using RRT early in patients with ALF and AKI. "Conditional recommendation, very low-quality evidence."

Remarks: There is insufficient evidence to issue a recommendation for the ACLF population. Early initiation of RRT is defined as initiation of RRT before 1) hyperkalemia (> 6 mmol/L with electrocardiographic abnormalities), 2) fluid overload/pulmonary edema resistant to diuretic administration, 3) severe metabolic acidosis (pH < 7.15), 4) blood urea concentration greater than 35.7 mmol/L, or 5) Kidney Disease Improving Global Outcomes stage 3 AKI.

Rationale: Identifying the right time to start RRT continues to be a challenge in all critically ill patients. In ALF, the use of continuous RRT early prior to the development of traditional indications (hyperkalemia, uremia, oliguria) has been associated with improved outcomes, potentially related to mitigation of the development of cerebral edema (143). In the absence of severe life-threatening complications (e.g. hyperkalemia, metabolic acidosis), the optimal timing and thresholds to commence RRT remain unknown. Most available data stem from observational studies or a few single-center trials, at times confounded by case heterogeneity, indication, or severity of illness (144). Without the ability to predict the need for RRT in critically ill patients overall, careful evaluation of a patient's clinical situation and prognosis continue to be the main determinants as to whether and when to commence RRT.

Data from one retrospective observational study showed 216 fewer deaths per 1,000 patients with ALF and subsequent AKI (OR, 0.31; 95% CI, 0.09–1.03), if RRT was started early (**Appendix Table 17**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241) (145). The authors used an arbitrary blood urea nitrogen (BUN) cutoff of 80 mg/dL to identify patients who had received early versus late RRT. The early RRT group had pre-RRT BUN and creatinine values of 46.2 ± 20.2 (mean ± SD) and 2.9 ± 1.7 mg/dL, respectively. In the late RRT group, patients had pre-RRT BUN and creatinine levels of 118.8 ± 33.1 and 4.7 ± 1.7 mg/dL, respectively.

We therefore give a conditional recommendation in favor of early start of RRT in patients with ALF and subsequent AKI. Further clinical trials are urgently needed to better address this question in more detail.

Vasopressors in Hepatorenal Syndrome

Recommendation: We recommend using vasopressors, over not using vasopressors, in critically ill patients with ACLF who develop hepatorenal syndrome (HRS) (strong recommendation, moderate-quality evidence).

Remarks: Vasopressors could be any of the following terlipressin, norepinephrine, or midodrine and octreotide.

Rationale: HRS is a distinct form of kidney injury in patients with liver cirrhosis and ascites (147). HRS occurs in the absence of underlying structural kidney disease, nephrotoxic agents, or sepsis. HRS is considered a form of pre-renal dysfunction, characterized by severe intra-renal vasoconstriction and simultaneous global (systemic and splanchnic) vasodilation. Type I HRS represent the acute, more severe form of HRS and corresponds to stage 2 AKI, whereas type II HRS shows a more slowly and less severe degree of renal dysfunction (146). HRS occurs in ~20% of all patients with cirrhosis hospitalized with AKI and carries a very poor prognosis. Liver transplantation is currently considered the best therapy for HRS. Otherwise, administration of vasoconstrictors together-with albumin remains a frequently employed intervention.

A recent Cochrane review identified nine RCTs, comparing terlipressin to placebo or no treatment in 534 patients with HRS (147). Seven trials included only patients with type I HRS. Two trials included 96 participants with either type I or type II HRS. There were 92 fewer deaths per 1,000 HRS patients receiving terlipressin compared with those receiving placebo/notreatment (RR, 0.85; 95% CI, 0.73–0.98) (**Appendix Table 18**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241).

A separate Cochrane review assessed 10 RCTs with 474 participants (148), comparing terlipressin to norepinephrine (seven trials), octreotide (one trial), midodrine and octreotide (one trial), or dopamine (one trial) in patients with HRS. All participants received albumin as a co-intervention. There was insufficient evidence to support or refute the use of terlipressin over other vasoactive agents.

We, therefore, make a strong recommendation for the use of vasopressors versus placebo or no intervention in critically ill patients with ACLF who develop HRS.

Transjugular Intrahepatic Portosystemic Shunt for Prevention of HRS

Recommendation: There is insufficient evidence to issue a recommendation.

Rationale: Creation of TIPS is an established treatment option for major complications of portal hypertension, for example, refractory ascites and variceal bleeding. TIPS has also been discussed as a potential intervention to improve the management of refractory ascites and HRS.

Six RCTs (149–154), summarized in a recent meta-analysis (155), have compared TIPS placement versus paracentesis in patients with chronic liver disease and refractory ascites in a total of 390 patients. Occurrence of HRS following TIPS was assessed in 136 patients. Patients with TIPS developed HRS significantly less often than patients without TIPS (9% vs 24%; RR, 0.38; 95% CI, 0.16–0.94; $p = 0.02$). Following the meta-analysis and upon inclusion of additional data from the RCTs, we found TIPS placement also may result in improved transplant-free survival (28 fewer per 1000, RR, 0.91; 95% CI, 0.70–1.17) and decrease liver disease-related mortality (49 fewer per 1000, RR, 0.91; 95% CI, 0.75–1.10).

However, TIPS resulted in higher risk of hepatic encephalopathy (RR, 1.64; 95% CI, 1.15–2.33) (**Appendix Table 19**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241). The evidence is also limited by indirectness, as the RCTs did not focus on critically ill patients and did not have prevention of HRS as a primary outcome.

The panel concluded that the current evidence is insufficient to support a recommendation. Directed by clinical judgment and circumstances, clinicians may elect to either use or not use TIPS in patients with cirrhosis and refractory ascites to prevent HRS.

ENDOCRINE AND NUTRITION SECTION

Target Glucose Control

Recommendation: We recommend targeting a serum blood glucose of 110–180 mg/dL in patients with ALF or ACLF (strong recommendation, moderate-quality evidence).

Rationale: Endocrine abnormalities are common in patients with liver disease and often necessitate pharmaco-therapeutic intervention to prevent adverse events, including death (156, 157). Management should incorporate the prevention of both hyperglycemia and hypoglycemia to promote the shortest safe hospital stay and provide an effective transition out of the hospital that prevents acute complications and readmission (158).

Currently, the American Diabetes Association recommends initiating treatment for persistent hyperglycemia at greater than or equal to 180 mg/dL for most critically ill patients and targeting moderate glucose range of 140–180 mg/dL (158). Additionally, the Surviving Sepsis Campaign Guidelines recommend a protocolized approach to the management of hyperglycemia in ICU patients with sepsis with a target glucose level less than or equal to 180 mg/dL (22).

A meta-analysis of thirty-six trials including 17,996 critically ill patients suggests no short-term mortality or infection

benefit of very tight (80–109 mg/dL) glycemic control compared with tight (110–139 mg/dL), moderate (140–180 mg/dL), or liberal (> 180 mg/dL) glycemic control (159). Very tight and tight glycemic control were associated with the highest risk of hypoglycemia (159). A second meta-analysis also found no mortality benefit in the very tight group but was associated with increased hypoglycemia (**Appendix Table 20**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241) (160). No group maximized the benefit for both lower mortality and decreased hypoglycemia, although moderate glycemic control (140–180 mg/dL) achieved the best outcome for all-cause mortality. These data are downgraded for indirectness.

The consequences of hypoglycemia in patients with liver disease may be underestimated. A retrospective analysis of 312 patients with acute decompensated cirrhosis found that hypoglycemia is associated with increased mortality (161). As such, management should incorporate the prevention of hypoglycemia to optimize outcomes (158).

Role of Stress-Dose Glucocorticoids

Recommendation: We suggest using stress-dose glucocorticoids in the treatment of septic shock in patients with ALF or ACLF (conditional recommendation, low-quality evidence).

Remarks: Stress dose glucocorticoids should be used if adequate fluid resuscitation and vasopressor agents are unable to restore hemodynamic stability.

Rationale: Relative adrenal insufficiency is common in acutely ill patients with cirrhosis, especially those with septic shock (162, 163). However, there are limited data evaluating the use of stress-dose steroids in patients with ALF/ACLF and septic shock. A single-center RCT of 75 patients with cirrhosis and septic shock demonstrated no mortality (RR, 0.92; 95% CI, 0.66–1.30) or shock reversal (RR, 1.58; 95% CI, 0.98–2.55) benefit from administering glucocorticoids, but was associated with higher rate of major adverse events (RR, 1.65; 95% CI, 1.02–2.64) such as shock relapse and gastrointestinal bleed (**Appendix Table 21**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241) (164). The study was stopped for futility at an interim analysis and therefore judged to be at high risk for bias.

Conversely, a meta-analysis of 36 RCTs including 9,389 patients suggested a small absolute reduction in mortality with the use of corticosteroids in patients with septic shock (165). It should be noted, however, that these studies did not specifically include patients with liver disease. Most of the studies used hydrocortisone, and doses were less than 400 mg of hydrocortisone or equivalent per day. Patients who received corticosteroids had higher rates of shock reversal (RR, 1.26; 95% CI, 1.12–1.42) and lower SOFA scores (MD, –1.39 points; 95% CI, –1.88 to 0.89; 6.22 vs 7.61 points) at day 7 (165). Patients who received corticosteroids were more likely to have hypernatremia (RR, 1.64; 95% CI, 1.32–2.03) and hyperglycemia (RR, 1.16; 95% CI, 1.08–1.24) (165). This recommendation is consistent with those from guidelines for both the management of critical illness-related corticosteroid insufficiency and septic shock where steroids are recommended to treat patients with septic shock if adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability (22, 166).

Dietary Protein Load

Recommendation: We suggest against using a low protein goal in patients with ALF or ACLF, but rather targeting protein goals comparable with critically ill patients without liver failure (1.2–2.0 g protein/kg dry or ideal body weight per day [IBW/d]) (conditional recommendation, very low-quality evidence).

Rationale: It seems intuitive in the patient with worsening HE, to delay feeding and reduce the protein load to "spare" the liver the work of the metabolic processes of digestion, absorption, and utilization of nutrients during times of stress. However, reductions in hepatic glycogen synthesis and storage leads to increased gluconeogenesis with rapid depletion of carbohydrate stores, increasing utilization of amino acids and ammonia production (167–170). Protein restriction only worsens this response. These metabolic derangements combined with poor oral intake (due to ascites, hepatic encephalopathy, etc.) lead to protein-calorie malnutrition, which negatively influences morbidity and mortality (171, 172).

Indirect evidence from one small RCT in noncritically ill cirrhotic patients demonstrated no benefit with protein restriction on degree of HE or mortality. One-hundred twenty patients were randomized to the intervention group and received a nutrition therapy program (30–35 Kcal/kg and 1.0–1.5 g protein/kg IBW/d with sodium restriction of 2 g/d and nutrition education with monthly follow-up phone calls by the dietitian) or the control group receiving no nutrition therapy program (2 g sodium restricted diet without specific calorie and protein recommendations or nutrition education) (173). In the final analysis, the intervention group received significantly more protein (1.2 + 0.19 vs 0.65 + 0.22 g/kg IBW/d; $p < 0.001$) and yet were less likely to advance to overt HE (6/38 vs 13/35; RR, 0.43; 95% CI, 0.18–1.0; $p = 0.04$) than the control group (173). Although not a primary outcome, five patients in the intervention group and nine in the control group died (RR, 0.56; 95% CI, 0.20–1.56) (**Appendix Table 22**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241) (173).

Branched-Chain Amino Acids in ALF/ACLF

Recommendation: We suggest not using branched-chain amino acids (BCAAs) in critically ill patients hospitalized with ALF or ACLF who are tolerating enteral medications (conditional recommendation, very low-quality evidence).

Rationale: In a 2017 Cochrane Review, out of 16 RCTs encompassing 827 noncritically ill patients, four trials (195 patients) provided indirect evidence regarding the addition of branch chain amino acids (BCAA) in patients receiving lactulose or neomycin and found, no further benefit on HE (RR, 0.66; 95% CI, 0.34–1.30) (174). In those patients, refractory to medication use, enteral BCAA supplementation alone was found to have a beneficial effect on HE in 15 trials of noncritically ill patients with cirrhosis (RR, 0.67; 95% CI, 0.52–0.88) (174). It is unclear if critically ill patients would achieve the same benefit; therefore, until enough direct evidence is available, we issued

a conditional recommendation against the use of BCAA in patients with ALF or ACLF.

Route and Timing of Feeding

Recommendation: We suggest enteral nutrition (EN) over parenteral nutrition (PN) in critically ill patients hospitalized with ALF or ACLF without contraindication for enteral feeding (conditional recommendation, low-quality evidence).

Rationale: Preferential use of EN has not been studied in patients with ALF or ACLF. However, previous guidelines and a recent meta-analysis representing a heterogeneous group of critically ill patients recommend EN over PN (175–177). EN bestows nutritional and other important non-nutritional benefits to critically ill patients including preservation of lean body mass, maintenance of structural and functional gut integrity, preservation of intestinal microbial diversity, and potentially improved gut-mediated immunity (178–180). It is hypothesized that patients receiving PN may have increased risk of infectious complications due to the nondelivery of some of these non-nutritional benefits, in addition, PN may cause hepatotoxicity with prolonged exposure.

A meta-analysis of 23 RCTs (6,478 critically ill patients) found no significant decrease in mortality with EN (OR, 0.98; 95% CI, 0.81–1.18) compared with PN; 14 of the 23 RCTs (6,075 critically ill patients) also evaluated bloodstream infections and found beneficial effects with EN (OR, 0.59; 95% CI, 0.43–0.82) (**Appendix Table 23**, Supplemental Digital Content 7, http://links.lww.com/CCM/F241) (177). These findings are consistent with a previous meta-analysis (181) (18 RCTs, 3,347 critically ill patients) which demonstrated a reduction in infectious complication, but not mortality, associated with EN.

Screening for Drug Induced Causes of Liver Failure

Recommendation: We recommend screening patients with ALF or ACLF for drug-induced causes of liver failure. Drug that are proven or highly suspected to be the cause of ALF or ACLF should be discontinued (BPS).

Rationale: Drug-induced liver injury accounts for more than half of ALF in the United States and other developed countries (182). Acetaminophen (74% females, median age: 36 yr) accounts for 46% of cases and other idiosyncratic drug reaction (67% females, median age: 43 yr) account for another 11%, although 14% of cases are indeterminate (182). Drugs of all types, including prescription, over-the-counter, herbal/supplements, and recreational drugs, have been associated with liver injury (183–185). To appropriately evaluate the risk for drug-induced liver injury, a thorough history, screening, and systematic approach is recommended (182, 186).

Serum drug concentrations, especially acetaminophen, may aid in confirming drug-induced causes in cases of patient denial or encephalopathy (185, 186). Multiple references can be used to determine the likelihood of a medications risk of causing liver injury based on typical clinical presentation and frequency (186–188). Although drug-induced liver injury is sometimes a diagnosis of exclusion, the use of a validated tool, such as the Roussel Uclaf Causality Assessment Method, can increase certainty and should be used when possible. Drug therapy proven or highly suspected of being related to ALF/ACLF should be immediately discontinued (187, 188). When available, an antidote should be administered, accompanied by supportive care.

Dose Adjustment of Medications

Recommendation: In patients with ALF or ACLF, we recommend adjusting the doses of medications that undergo hepatic metabolism based on the patient's residual hepatic function and using the best available literature. When available, a clinical pharmacist should be consulted (BPS).

Rationale: The liver plays a critical role in the metabolism of many drugs including biotransformation to and elimination of active metabolites. Both ALF and ACLF result in alterations in hepatic extraction ratio, biliary excretion, volume of distribution, and protein binding (189). The net effect is a reduction in the intrinsic ability of the impaired liver to metabolize medications, increasing the risk for drug accumulation and toxicity. Additionally, HRS can lead to impaired excretion of drugs, thus further reducing drug clearance. Metabolism and clearance may further be affected by supportive modalities such as RRT, extracorporeal membrane oxygenation, and molecular adsorbent recirculating system. These variables must be considered in aggregate when dose-adjusting medications in patients with liver failure. Although these principles are well understood, their application to individual patients becomes less clear as these alterations yield significant interpatient variability. The optimal approach for determining appropriate drug dosing is to use therapeutic drug monitoring when possible.

Alternatively, pairing pharmacologic principles with pharmacokinetic and pharmacodynamic studies offer the next best approach to empiric dose adjustments (190).

DISCUSSION

In this article, we report 29 recommendations on the management ALF or ACLF in the ICU, related to five groups (cardiovascular, hematology, pulmonary, renal, and endocrine).

The strengths of our guideline include our assembly of 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 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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