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

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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. 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 participates in American College of Chest Physicians, American Heart Association, and American College of Cardiology. 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. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Acute liver failure (ALF) and acute on chronic liver failure (ACLF) are conditions frequently encountered in the ICU and are associated with high mortality. The purpose of these guidelines was to develop evidence-based recommendations addressing common clinical questions surrounding the unique manifestations of liver failure in the critically ill patient.

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

METHODS

Co-chair and vice-chairs were appointed by the Society of Critical Care Medicine (SCCM). Twenty-five other panel members were chosen in accordance with their clinical and/or methodological expertise. Corresponding with individual expertise, the panel was then divided into nine subgroups; the recommendations of five of those subgroups (cardiovascular, hematology, pulmonary, renal, and endocrine) are presented in this document. Each panel member followed all conflict of interest procedures as documented in the American College of Critical Care Medicine/SCCM Standard Operating Procedures Manual. The panel proposed, discussed, and finally developed 30 Population Intervention Comparator Outcome questions which they deemed most important to the patient and the end-users of this guideline. We used Grading Recommendations, Assessment, Development, and Evaluation (GRADE) approach to prioritize outcomes, assess quality of evidence, and determine the strength of outcomes (1). We then used the Evidence-to-Decision framework to facilitate transition from evidence to final recommendations. We classified each recommendation as strong or conditional as per GRADE methodology. We accepted a recommendation if 80% consensus was achieved among at least 75% of panel members. We developed best practice statements as ungraded strong recommendations in adherence with strict conditions.

RESULTS

We report 29 recommendations on the management acute or ACLF 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, a recommendation was not issued because due to insufficient evidence. A summary of recommendations is presented in **Table 1**, and we discuss the abbreviated rationale for the six strong recommendations. The full recommendations and complete rationales can be found in the main article published in critical care medicine.

Question 1

In critically ill patients with ALF or ACLF, should we recommend using hydroxyethyl starch or gelatin for initial resuscitation versus crystalloid solutions?

Recommendation: We recommend against using hydroxyethyl starch for initial fluid resuscitation of patients with ALF or ACLF (strong recommendation, moderate-quality evidence).

Rationale: Although the available evidence is limited by indirectness because few patients with liver failure were included, meta-analyses of available trials in critically ill patients suggest no benefit of hydroxyethyl starch over crystalloids. Starches may exacerbate coagulopathy in liver failure and a there is not a compelling physiologic rationale for their use in patients with liver failure (2, 3).

Question 2

In critically ill patients with ALF or ACLF who remain hypotensive despite fluid resuscitation, should norepinephrine be used as a 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: Patients with liver failure exhibit hyperdynamic circulation and shock states in these patients is typically characterized by distributive physiology. Despite the paucity of studies directly related to liver failure, indirect evidence from trials in other distributive states such as septic shock suggest norepinephrine is superior compared with dopamine is reversing hypotension as well as associated with lower mortality and risk of arrhythmias (4). Epinephrine may cause splanchnic vasoconstriction and increase the risk of mesenteric and hepatic ischemia in the setting of liver failure. Studies comparing vasopressin as a first-line agent to other vasoactive agents are not available.

Question 3

In critically ill patients with ALF or ACLF undergoing invasive or surgical procedures should we use INR, platelet count, or fibrinogen level versus viscoelastic testing (thromboelastography/rotational thromboelastometry [TEG/ROTEM]) to assess bleeding risk?

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

Rationale: Quantification of INR, platelet count, and fibrinogen fails to consistently provide an assessment of overall hemostatic function and risk of bleeding. Routine use of viscoelastic testing is a well-established way to

TABLE 1. Summary of Recommendations

Recommendation	Strength of Recommendation	Quality of Evidence
1) We recommend against using hydroxyethyl starch for initial fluid resuscitation of patients with ALF or ACLF	Strong	Moderate
2) We suggest against using gelatin solutions for initial fluid resuscitation of patients with ALF or ACLF	Conditional	Low
3) 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	Low
4) We suggest targeting a mean arterial pressure of 65 mm Hg in patients with ALF or ACLF, with concomitant assessment of perfusion	Conditional	Moderate
5) We suggest placing an arterial catheter for blood pressure monitoring in patients with ALF or ACLF and shock	Conditional	Low
6) We suggest using invasive hemodynamic monitoring to guide therapy in patients with ALF or ACLF and clinically impaired perfusion	Conditional	Low
7) 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	Moderate
8) 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	Low
9) We suggest using viscoelastic testing (TEG/ROTEM) over measuring INR, platelet, and fibrinogen in critically ill patients with ALF or ACLF	Conditional	Low
10) We suggest using a transfusion threshold of 7 mg/dL, over other thresholds, for critically ill patients with ALF or ACLF	Conditional	Low
11) We suggest using LMWH or vitamin K antagonists, over conservative management, in patients with portal venous thrombosis or pulmonary embolus	Conditional	Very low
12) We suggest using LMWH, over pneumatic compression stockings for VTE prophylaxis in hospitalized patients with ACLF	Conditional	Low
13) We recommend viscoelastic testing (TEG/ROTEM), over measuring INR, platelet, fibrinogen, in critically ill patients with ALF or ACLF undergoing procedures	Strong	Moderate
14) We recommend against using Eltrombopag in ACLF patients with thrombocytopenia prior to surgery/invasive procedures	Strong	Low
15) We suggest using a low tidal volume strategy over high tidal volume strategy in patients with ALF or ACLF and ARDS	Conditional	Low
16) We suggest against using high PEEP, over low PEEP, in patients with ALF or ACLF and ARDS	Conditional	Low
17) We suggest treating portopulmonary hypertension with agents approved for pulmonary arterial hypertension in patients with mean pulmonary artery pressure > 35 mm Hg	Conditional	Very low
18) We recommend supportive care with supplemental oxygen in the treatment of hepatopulmonary syndrome, pending possible liver transplantation	Best practice statement	Best practice statement
19) We recommend placing chest tube with an attempt to pleurodesis for hepatic hydrothorax in patients in whom TIPS is not an option or as a palliative intent	Best practice statement	Best practice statement
20) We suggest using high-flow nasal cannula over noninvasive ventilation in hypoxic critically ill patients with ALF or ACLF	Conditional	Low

(*Continued*)

TABLE 1. (*Continued*). Summary of Recommendations

Recommendation	Strength of Recommendation	Quality of Evidence
21) There is insufficient evidence to recommend either continuing or discontinuing RRT intraoperatively (during liver transplant surgery) in patients who were receiving RRT preoperatively	Not applicable	Not applicable
22) We suggest using RRT early in patients with ALF and AKI	Conditional	Very low
23) We recommend using vasopressors, over not using vasopressors, in critically ill patients with ACLF who develop HRS	Strong	Moderate
24) There is insufficient evidence to recommend either using or not using TIPS in patients with cirrhosis and refractory ascites to prevent HRS	Not applicable	Not applicable
25) We recommend targeting a serum blood glucose of 110–180 mg/dL in patients with ALF or ACLF	Strong	Moderate
26) We suggest using stress-dose glucocorticoids in the treatment of septic shock in patients with ALF or ACLF	Conditional	Low
27) We suggest against using a low protein goal in patients with ALF or ACLF, but rather targeting protein goals comparable to critically ill patients without liver failure (1.2–2.0 g protein/kg dry or ideal body weight per day)	Conditional	Very low
28) We suggest not using branch chain amino acids in critically ill patients hospitalized with ALF or ACLF who are tolerating enteral medications	Conditional	Very low
29) We suggest enteral nutrition over parenteral nutrition in critically ill patients hospitalized with ALF or ACLF without contraindication for enteral feeding	Conditional	Low
30) 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	Best practice statement	Best practice statement
31) 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	Best practice statement	Best practice statement

ACLF = acute on chronic liver failure, ALF = acute liver failure, ARDS = acute respiratory distress syndrome, HRS = hepatorenal syndrome, LMWH = low molecular weight heparin, PEEP = positive end-expiratory pressure RRT = renal replacement therapy, TEG/ROTEM = thromboelastography/rotational thromboelastometry, TIPS = transjugular intrahepatic portosystemic shunt.

determine global coagulation status in circumstances such as liver transplant surgery. It allows for real time global and functional evaluation of altered activity of the pro- and anticoagulant pathways, identifying platelet function, hyperfibrinolysis, and premature clot dissolution. In one open label randomized controlled trial blood product transfusion guided by viscoelastic testing compared with that guided by quantification of INR or platelet count resulted in significantly fewer patients being transfused with no increase in bleeding complications (5).

Question 4

In critically ill patients with ALF or ACLF should we use novel coagulation agents (prothrombin complexes, thrombopoietin receptor agonists, antifibrinolytics) to achieve pre-procedure or pre-surgery hematologic targets to reduce bleeding complications/transfusions?

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

Rationale: Thrombocytopenia is common in ACLF. Although Eltrombopag raised platelet counts and avoided platelet transfusions in significantly more patients as compared with placebo in patients with chronic liver disease undergoing elective invasive procedures, it was also associated with thrombotic events of the portal venous system resulting in early termination of the trial (6). Although data on other novel coagulation agents such as prothrombin complex concentrate are not available for ALF/ACLF patients, their use should be tempered by the inability to determine derangements in hemostasis by traditional indices such as INR, fibrinogen and platelet count.

Question 5

In critically ill patients with ACLF who develop hepatorenal syndrome (HRS) should we use vasopressors?

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

Rationale: HRS is a distinct form of kidney injury in patients with cirrhosis and ascites. It occurs in approximately 20% of hospitalized patients with cirrhosis and AKI and portends a very poor

prognosis. In the absence of liver transplantation, vasoconstrictor agents combined with albumin remain a common intervention. Patients receiving terlipressin are more likely to survive than those receiving placebo, however, there the available evidence is insufficient to recommend it over other vasoconstrictors (norepinephrine or the combination of midodrine and octreotide) (7, 8).

Question 6

In critically ill patients with ALF or ACLF and hyperglycemia, should we target very tight (80–109 mg/dL) or conventional (110–180 mg/dL) glycemic 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: Evidence does not suggest the benefit of very tight glucose control as compared with conventional glucose control. Very tight glucose control is associated with increased risk of hypoglycemia (9). Further, patients with ALF/ACLF are at risk for hypoglycemia and the risks of hypoglycemia in this population may be underestimated (10). Glycemic management in these patients should incorporate the prevention of hypoglycemia to optimize outcomes.

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