

# UCSF

## UC San Francisco Previously Published Works

### Title

Management of Decompensated Cirrhosis in the Surgical ICU: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document

### Permalink

<https://escholarship.org/uc/item/1m45f6tt>

### Journal

Trauma Surgery & Acute Care Open, 7(1)

### ISSN

2397-5776

### Authors

Seshadri, Anupamaa  
Appelbaum, Rachel  
Carmichael, Samuel P  
et al.

### Publication Date

2022-08-01

### DOI






10.1136/tsaco-2022-000936

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial License, available at <https://creativecommons.org/licenses/by-nc/4.0/>

Peer reviewed

# Management of Decompensated Cirrhosis in the Surgical ICU: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document

Anupamaa Seshadri ,<sup>1</sup> Rachel Appelbaum,<sup>2</sup> Samuel P Carmichael II ,<sup>2</sup> Joseph Cuschieri ,<sup>3</sup> Jason Hoth,<sup>2</sup> Krista L Kaups ,<sup>4</sup> Lisa Kodadek,<sup>5,6</sup> Matthew E Kutcher,<sup>7</sup> Abhijit Pathak,<sup>8</sup> Joseph Rappold,<sup>9</sup> Sean R Rudnick,<sup>10</sup> Christopher P Michetti <sup>11</sup>

For numbered affiliations see end of article.

## Correspondence to

Dr Anupamaa Seshadri;  
aseshadr@BIDMC.Harvard.edu

Received 4 April 2022  
Accepted 20 July 2022

## ABSTRACT

Management of decompensated cirrhosis (DC) can be challenging for the surgical intensivist. Management of DC is often complicated by ascites, coagulopathy, hepatic encephalopathy, gastrointestinal bleeding, hepatorenal syndrome, and difficulty assessing volume status. This Clinical Consensus Document created by the American Association for the Surgery of Trauma Critical Care Committee reviews practical clinical questions about the critical care management of patients with DC to facilitate best practices by the bedside provider.

## INTRODUCTION

The American Association for the Surgery of Trauma (AAST) Critical Care Committee develops Clinical Consensus Documents to provide practical guidance to the surgical intensivist on challenging topics. These documents are based on expert consensus following review of the literature. The Critical Care Committee chose the management of decompensated cirrhosis (DC) in the intensive care unit (ICU) as a topic appropriate for review. Specifically, these are patients with underlying cirrhosis who have decompensation precipitated by other disease or injury; these recommendations do not apply to patients with acute liver failure or hemorrhage-related shock liver.

DC is a common clinical entity, with an estimated 10.6 million prevalent cases globally in 2017, and with the number of cases having more than tripled since 1990.<sup>1</sup> Patients with DC are particularly challenging to manage in the surgical ICU due to their comorbidities related to underlying liver dysfunction. This clinical consensus document is not intended as a comprehensive overview of the topic. It addresses several important practical considerations for intensivists in the care of the critically ill patient with DC, including: end points of resuscitation, ascites management and avoidance of postparacentesis circulatory dysfunction (PPCD), gastrointestinal (GI) bleeding, venous thromboembolism (VTE) prophylaxis, management of hepatic encephalopathy (HE) and nutritional support (recommendations summarized in [table 1](#)).

## METHODS

The topic of DC management was chosen for review by the AAST Critical Care Committee as a clinically relevant topic for intensivists. A working group was formed from the committee which identified its list of the more commonly encountered yet challenging issues in patients with decompensated cirrhosis in the ICU. The members were assigned specific questions to research using society guidelines as well as peer-reviewed original research in the literature. Authors performed literature search and reference selection at their own discretion. Existing review articles and clinical practice guidelines were used to focus searches toward relevant topics and primary source material. The content was then reviewed by the working group for consensus development, including a transplant hepatologist (SRR), prior to a review by the entire committee. If there were discrepancies in consensus, SRR adjudicated using clinical practice expertise. Final revisions were performed by the first and last authors.

These recommendations consist of consensus statements and do not incorporate Grading of Recommendations, Assessment, Development and Evaluations methodology or other formal processes. The topics reviewed are not comprehensive and only reflect those that the committee deemed challenging, relevant, or interesting for intensivists. The literature search methodology was not standardized, and iterative selection of studies was not performed as in a systematic review. The process focused on recent evidence from the last decade, supported from existing reviews and clinical practice guidelines.

## VOLUME STATUS

**What is the approach to volume status assessment and end points of resuscitation in patients with DC in the ICU?**

### Recommendation

Pulmonary artery catheter measurements, mean arterial pressure, pulse pressure variation, point of care transthoracic echocardiography (TTE), and arterial pulse contour technology can all be used in volume assessment of patients with DC, with the understanding of their limitations in this patient

© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

## To cite:

Seshadri A, Appelbaum R, Carmichael II SP, et al. *Trauma Surg Acute Care Open* 2022;**7**:e000936.

**Table 1** Decompensated cirrhosis consensus summary

Problem	Recommendations
Volume status and end points of resuscitation	MAP, TTE, and PAC measurements more reliable than pulse pressure variation or arterial pulse contour SvO <sub>2</sub> and serum lactate can be inaccurate
Fluid resuscitation and vasopressors	Balanced salt solutions recommended over normal saline Norepinephrine=pressor of choice Albumin useful in SBP, HRS, and PPCD
Ascites management	Preoperative Grade 2 ascites: Na <sup>+</sup> restriction and diuretics Grade 3: large volume paracentesis Consider preoperative TIPS Postoperative Consider postoperative TIPS No recommendation for fluids or drains
Hepatorenal syndrome	Volume expansion with albumin, treatment of infections, stopping diuretics MAP >65 mm Hg with norepinephrine versus terlipressin
GI bleeding	Ceftriaxone plus vasoactive agent (vasopressin, somatostatin, or octreotide) Endoscopy within 12 hours TIPS for recurrent or persistent variceal bleed
Coagulopathy	VTE prophylaxis should follow standard of care; can follow viscoelastic testing Empiric platelet transfusions not indicated for peri-procedural correction of thrombocytopenia
Hepatic encephalopathy	Ammonia can exclude but should not be followed as end point Treatment with non-absorbable disaccharides and rifaximin
Nutrition	Early enteral nutrition preferred; protein restriction not beneficial Hypoglycemia should be aggressively managed
Prognosis	Clinical scores include MELD, ACLF criteria, CLIF-SOFA Biomarkers being investigated include cystatin C, copeptin, procalcitonin, and CRP

ACLF, Acute-on-Chronic Liver Failure; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; CRP, C reactive protein; GI, gastrointestinal; HRS, hepatorenal syndrome; MAP, mean arterial pressure; MELD, Model of End-Stage Liver Disease; Na<sup>+</sup>, sodium; PAC, pulmonary artery catheter; PPCD, postparacentesis circulatory dysfunction; SBP, spontaneous bacterial peritonitis; SvO<sub>2</sub>, central venous oxygenation level; TIPS, transjugular intrahepatic portosystemic shunt; TTE, transthoracic echocardiography; VTE, venous thromboembolism.

population. Typical end points of resuscitation can be used in DC; however, mixed venous oxygen saturation (SvO<sub>2</sub>) and serum lactate should be interpreted cautiously.

### Discussion

The assessment of volume status in patients with DC is complicated secondary to marked systemic inflammation and hemodynamic disturbances including increased cardiac output (CO) and peripheral vasodilation.<sup>2</sup> Portal hypertension leads to compensatory splanchnic and systemic vasodilation mediated by nitric oxide and other vasoactive agents. Decreased arterial blood flow to the kidneys stimulates the renin-angiotensin-aldosterone system which leads to volume expansion with sodium and water retention. However, central blood volume remains low and the hyperdynamic state continues.<sup>3,4</sup> These patients require

thoughtful volume assessment as excess fluid may increase mortality.<sup>2,5</sup>

Central venous pressure is a poor assessment of volume status in DC due to the presence of ascites, left ventricular diastolic dysfunction, and hypoalbuminemia. Pulmonary artery catheter placement can ameliorate some of these challenges using measures of cardiac filling including mean pulmonary artery pressure, CO, and pulmonary capillary wedge pressure.<sup>6</sup> However, non-invasive monitoring has gained popularity and includes evaluation of mean arterial pressure (MAP), pulse pressure variation (PPV), point-of-care TTE (POC TTE), and arterial pulse contour technology.<sup>6</sup>

MAP can be monitored using an intra-arterial catheter or non-invasive blood pressure monitoring to gauge appropriate tissue perfusion, with a MAP goal of ≥60–65 mm Hg.<sup>7</sup> Intra-arterial catheters can also be used to quantify pulse pressure variation, with the caveat that ascites, intra-abdominal hypertension, and low systemic vascular resistance (SVR) may alter aortic compliance which affects PPV utilization.<sup>2</sup> Passive leg raise can provide a surrogate for fluid bolus; if there is an increase in MAP, this implies that the patient is fluid responsive.

POC TTE is a bedside evaluation of cardiac and intravascular volume status using five echocardiography views. Qualitative parameters include gross appearance, wall motion, and estimation of ejection fraction (EF). Quantitative parameters are calculations including but not limited to CO, left ventricular end diastolic area, stroke volume variation, change in velocity time integral, and dynamic inferior vena cava diameter assessment.<sup>8–11</sup> This monitoring strategy is limited by provider training, pulmonary hypertension, cardiomyopathy, large volume ascites, and, in the mechanically ventilated patient, ventilator dyssynchrony. While single measurements can be helpful to assess a patient at a particular moment, trends are likely more useful.

Arterial pulse contour technology can give quantitative parameters similar to more invasive monitoring; however, it is limited by the need for a functioning arterial line and the patient being in sinus rhythm under controlled mechanical ventilation with conservative tidal volume settings (6–8 mL/kg). This technology is highly dependent on vascular integrity, so the hyperdynamic and low SVR state of patients with DC may impact its accuracy.<sup>2,12</sup>

End points of resuscitation include surrogates of micro-circulatory flow and tissue oxygenation, such as vital signs, urine output, serum lactate, and SvO<sub>2</sub>, but should be used with caution in patients with DC. Low SvO<sub>2</sub> indicates that the tissues are extracting a higher percentage of oxygen and the cardiac output is not high enough to meet tissue needs.<sup>13</sup> At the microvascular level, SvO<sub>2</sub> may be elevated in cirrhotic patients even if the patient is volume depleted secondary to high flow and low oxygen extraction.<sup>2</sup> Lactate measurements should be used cautiously in liver disease as elevated lactic acid may be secondary to impaired clearance, and so there is no specific target recommended in these patients although trending may be useful.<sup>2,14</sup>

### FLUID RESUSCITATION AND VASOPRESSORS

#### What fluids and vasopressors should be used in patients with DC in the ICU?

##### Recommendation

Balanced salt solutions should be used over normal saline. Norepinephrine is the vasopressor of choice. Albumin is useful in patients with spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and PPCD.

## Discussion

Fluid management and vasopressor use in patients with DC require an understanding of several pathophysiological parameters and neurohumoral mediators. Recent evidence supports the use of balanced salt solutions such as lactated Ringer's or PlasmaLyte over normal saline, driven by the lower incidence of hyperchloremic acidosis and concomitant renal injury.<sup>15 16</sup> For patients who require vasopressors to maintain MAP >60 mm Hg, norepinephrine is the first-line choice. Epinephrine should be avoided to reduce the risk of ischemia.<sup>17</sup>

Literature supports the use of albumin in some patients with DC. Specifically, albumin has been shown to reduce mortality in patients with SBP (although not in other forms of infection/sepsis) and hepatorenal syndrome, and to prevent PPCD.<sup>18</sup> In the setting of SBP, the patient should be given 1.5 g/kg of albumin on the day of diagnosis (day 1) followed by 1 g/kg on day 3.<sup>18</sup> PPCD is a syndrome after large volume paracentesis (LVP) resulting in splanchnic vasodilation, with resultant rapid reaccumulation of ascites, hyponatremia, and renal injury. As discussed in the next section, peri-paracentesis albumin administration can help prevent PPCD.

There is mixed data on long-term albumin use as therapy in DC to prevent complications and improve survival. The human Albumin for the treatment of ascites in patients with hepatic cirrhosis (ANSWER) trial demonstrated improvement in 18-month survival as well as improvement in management of ascites and decrease in cirrhosis complications including SBP, non-SBP bacterial infections, episodes of renal dysfunction, and severe HE.<sup>19</sup> However, the Effect of Midodrine and Albumin in the Prevention of Complications in Cirrhotic Patients Awaiting Liver Transplantation (MACHT) study, which compared standard therapy with standard therapy plus albumin and midodrine, showed no difference in 1-year mortality or complications of cirrhosis.<sup>20</sup> These conflicting findings may be related to dose differences of albumin in the trials with higher doses being given in ANSWER, and further studies are needed to determine the appropriate patients with DC who should receive long-term albumin therapy.

## ASCITES MANAGEMENT

### How should ascites be managed in the preoperative period?

#### Recommendation

Preoperative ascites control should include sodium restriction and diuretics for grade 2 ascites and LVP with albumin administration for grade 3 ascites. Transjugular intrahepatic portosystemic shunt (TIPS) should be considered preoperatively in patients undergoing elective hernia repair with ascites refractory to medical management.

#### Discussion

Ascites in the cirrhotic patient undergoing abdominal surgery can lead to wound complications including dehiscence, infection, and respiratory insufficiency secondary to abdominal distension. For this reason, the American Gastroenterological Association Clinical Practice Update on Surgical Risk Assessment and Perioperative Management in Cirrhosis recommends avoiding elective abdominal wall hernia surgery in the cirrhotic patient with ascites (in the absence of incarceration or strangulation) until the ascites is completely controlled.<sup>21</sup> Ideally, any patient undergoing surgery should have preoperative ascites management; however, in the emergent setting this may not be feasible.

The American Association for the Study of Liver Diseases (AASLD) recommends sodium restriction (2 g or 90 mmol/day)

and diuretics (spironolactone with or without furosemide) for grade 2 (moderate) ascites and LVP as the first-line treatment for grade 3 (large or gross) ascites, as LVP prior to surgery will minimize the development of PPCD.<sup>22</sup> If LVP is performed removing >5 L, albumin infusion at a dose of 6–8 g/L ascites drained should be administered.<sup>22</sup> After paracentesis, sodium restriction and diuretics should be initiated once renal function has been assessed.<sup>22</sup>

TIPS is usually reserved for patients with refractory ascites, but may be an option for patients with large volume ascites.<sup>22</sup> The utilization of TIPS either preoperatively or postoperatively in small series and case reports in complicated hernias demonstrated improved outcomes.<sup>23 24</sup> However, a small case-control study did not demonstrate benefit for routine use of preoperative TIPS in abdominal surgery.<sup>25</sup> In a retrospective review of patients with DC undergoing abdominal surgery, the use of TIPS correlated to a significantly lower postoperative Model of End Stage Liver Disease Sodium (MELD-Na) score and perioperative TIPS was associated with a decreased incidence of postoperative ascites, infection, and acute kidney injury (AKI), but no mortality benefit.<sup>26</sup> Overall, there is a paucity of data for the prophylactic or routine use of TIPS preoperatively in patients with portal hypertension and its use should be individualized on a case-by-case basis, particularly in those patients with refractory ascites.<sup>27 28</sup> The AASLD guidelines recommend that TIPS should be considered before elective hernia repair or after an emergent operation in patients with uncontrolled ascites.<sup>22</sup>

### How should ascites be managed in the intraoperative or postoperative period?

#### Recommendation

Albumin administration can be considered as part of intraoperative fluid management to help avoid PPCD related to intraoperative ascites evacuation, based on its benefit in PPCD prevention in non-operative situations such as LVP. TIPS should be considered postoperatively in patients with ascites that is refractory to medical management.

No recommendation is made for or against the routine use of intra-abdominal drains. If used, drains should be removed as soon as feasible.

#### Discussion

The presence of significant ascites and its abrupt drainage at the time of surgery can lead to PPCD, which is a rapid decompression of the splanchnic vasculature resulting in splanchnic vasodilatation, decrease in SVR with a decrease in intravascular volume, and activation of the renin-angiotensin-aldosterone system. This in turn results in a more rapid re-accumulation of ascites, hyponatremia, renal insufficiency, and encephalopathy. Albumin administration is the main treatment.<sup>29</sup> Intraoperative fluid management can be challenging and there is limited available evidence regarding whether albumin or crystalloid is preferred.<sup>30</sup>

The accumulation of ascites in the postoperative period increases the risk of intra-abdominal infection, fluid leak from surgical sites, and wound dehiscence.<sup>31</sup> The approach to the management of ascites in the postoperative cirrhotic patient is similar to preoperative strategies. However, hemodynamic status may preclude the use of salt restriction and diuretics. Paracentesis may be used in the setting of significant ascites not amenable to medical management or in the setting of fluid leak from surgical sites. In patients with refractory ascites, TIPS can be considered. However, since outcome data are limited, a multidisciplinary

decision should be individualized to the clinical setting and type of surgical procedure.<sup>23 26 32</sup> Of note, patients who already have an indication for primary or secondary SBP prophylaxis should have that continued in the postoperative setting; if patients cannot take oral medications, a third-generation cephalosporin can be given intravenously.

Placement of intra-abdominal drains at the time of surgery can allow drainage of ascites in order to reduce the risk of wound complications such as fluid leak and dehiscence. Some studies have shown no difference in ascites-related complications or major complications and the need for postoperative paracentesis.<sup>23 31</sup> Others have demonstrated decreased ascites leakage and reduced hospital stay.<sup>33</sup> Liu *et al* randomized 104 patients undergoing elective hepatic resection to drains versus no drains and demonstrated an increased morbidity due to wound complications from routine drainage.<sup>34</sup> Notably, this was in elective patients and therefore may not translate to patients with DC. There is limited available evidence on surgical outcomes to recommend for or against the use of routine intra-abdominal drains. The decision should be individualized based on the clinical setting and the type of procedure. If used, drains should be removed as soon as possible. If not used, frequent LVP with albumin supplementation should be performed in the immediate postoperative setting while diuretics are being titrated.

## HEPATORENAL SYNDROME

### How is hepatorenal syndrome-acute kidney injury diagnosed and treated in the ICU?

#### Recommendation

HRS-AKI is defined as an increase in serum creatinine  $\geq 0.3$  mg/dL within 48 hours or  $\geq 50\%$  increase in serum creatinine within the preceding 7 days in patients with cirrhosis and ascites in the absence of structural kidney disease. Management includes volume expansion with albumin, treatment of infections, stopping diuretics, and use of terlipressin or norepinephrine for MAP  $> 65$  mm Hg.

#### Discussion

In patients with pre-existing liver disease, in-hospital renal impairment is relatively common with a reported incidence of 27%–53%.<sup>22</sup> Hepatorenal syndrome was previously described as either HRS-1, with a doubling of serum creatinine to  $\geq 2.5$  mg/dL within 2 weeks, or HRS-2, with a more gradual increase in creatinine. Since 2015, nomenclature is now based on the designation of HRS-AKI and HRS-non-AKI. This discussion will be limited to HRS-AKI.<sup>22 35</sup>

HRS-AKI represents a specific prerenal circulatory dysfunction unresponsive to fluid administration, attributed to portal hypertension and splanchnic arterial vasodilation, with marked renal vasoconstriction and subsequent pronounced decrease in renal blood flow and glomerular filtration rate (GFR). Systemic inflammation also contributes significantly. Translocation of gut bacteria is believed to produce release of pathogen-associated molecular patterns and damage-associated molecular patterns resulting in immune system activation and the release of pro-inflammatory cytokines.<sup>36</sup>

Risk factors for the development of AKI in DC include infections (ie, spontaneous bacterial peritonitis) and fluid loss (ie, LVP without administration of albumin). Despite advances in diagnosis and treatment, hospital mortality of HRS-AKI may be as high as 32%.<sup>37</sup> Prompt recognition of worsening renal function is critical. Initial therapy is volume expansion with 20%–25% intravenous albumin at 1 g/kg/day for 48 hours (then continued

at lower doses), aggressive treatment of infections, and stopping diuretics. Vasoconstrictors are an important component of early treatment, and improvements in MAP indicate a higher probability of improvement.<sup>35 36 38</sup> Terlipressin, a synthetic selective vasopressin analog, acts as a splanchnic vasoconstrictor and, when administered with albumin, has shown benefit in reversing HRS-AKI (although with significant adverse effects primarily related to vasoconstriction including abdominal pain, cardiovascular events, and respiratory failure) and is widely used in Europe and Asia.<sup>39</sup> As terlipressin is not currently available in North America, norepinephrine is recommended and has demonstrated effectiveness; it is preferred over vasopressin as vasopressin's renal V2 effects can worsen volume overload and hyponatremia. Norepinephrine should be titrated to both MAP and urine output and should be continued until creatinine returns to baseline. Midodrine, albumin, and octreotide combination therapy is more commonly used in a non-ICU setting and will not be discussed here.

Although some small studies have reported promising results, the role of TIPS in patients with HRS-AKI is not well-defined. A meta-analysis of 128 patients demonstrated improvement in renal function in almost all patients, but unclear survival benefits (72% short-term and 47% 1-year survival).<sup>40</sup> Renal replacement therapy addresses volume overload and electrolyte abnormalities, but does not improve survival and is recommended only as a temporizing measure until hepatic transplantation in the appropriate patient.

## GASTROINTESTINAL BLEEDING

### How should gastrointestinal bleeding be managed in patients with DC in the ICU?

#### Recommendation

Patients with DC with gastrointestinal bleeding (GIB) should receive ceftriaxone and a vasoactive agent (vasopressin, somatostatin, or octreotide). Ventilated patients with upper GIB (UGIB) should receive a proton pump inhibitor (PPI). Viscoelastic testing (VET) can guide use of VTE prophylaxis. Transfusion should be performed with goal hemoglobin (Hb) of 7–8 g/dL (70–80 g/L). Endoscopy should be performed within 12 hours and TIPS should be considered for recurrent or persistent variceal bleeding.

#### Discussion

Variceal hemorrhage is one of several disease-defining clinical features of DC.<sup>41</sup> In the critically ill trauma or surgical patient presenting to the hospital for a separate indication, DC due to GIB results in a compounding of morbidity and mortality. The most common etiology of GIB in DC is portal hypertension, and spontaneously resolves in only 50% of cases.<sup>42 43</sup> Failure of combination pharmacological therapy and endoscopy may occur in up to 20%, requiring advanced methods of hemostasis.

Ceftriaxone (1 g intravenous daily) reduces infectious complications, re-bleeding, and mortality in patients with UGIB, regardless of whether it is variceal or non-variceal.<sup>42–45</sup> The duration of treatment is 7 days but discontinuation can be considered once hemorrhage has resolved and vasoactive drugs have been discontinued.<sup>44</sup>

Mechanically ventilated patients receiving PPI rather than H<sub>2</sub> receptor blockade for prophylaxis experience fewer episodes of clinically important UGIB.<sup>46</sup> Although this effect has not been specifically evaluated for prevention of variceal UGIB, both the American College of Gastroenterology and the European Association for the Study of the Liver recommend PPI for patients with



cirrhosis requiring mechanical ventilation and suggest a possible benefit of PPI in reducing ulceration size following endoscopic band ligation.<sup>41–47</sup> If not already initiated as prophylaxis, PPI therapy should be started to reduce recurrence for non-variceal GIB.<sup>42</sup> While chemical VTE prophylaxis has not been shown to provoke GIB, patients with DC with recent GIB may be poor candidates for this, particularly in the setting of thrombocytopenia ( $<50 \times 10^9/L$ ).<sup>41</sup> However, the coagulation profile of patients with DC as a predictor of bleeding risk is poorly understood and potentially better evaluated by VET over traditional assays.<sup>42</sup> In blood product administration, there is no known benefit to achieving a higher Hb through transfusion in patients with DC as compared with balanced resuscitation with a restrictive red-cell transfusion strategy (Hb of 7–8 g/dL).<sup>42–48</sup>

The combination of vasoactive agents with endoscopic treatment is more effective for hemostasis than using either alone.<sup>42</sup> Vasoactive agents (ie, vasopressin, somatostatin or octreotide) should be initiated as soon as variceal hemorrhage is suspected with a bolus (only somatostatin, octreotide) followed by continuous infusion (all agents) for duration 3–5 days, except vasopressin which should only be given for 24 hours.<sup>42–44–45–49</sup> Consider infusion of erythromycin (250 mg given over 20–30 min) or metoclopramide as a promotility agent prior to endoscopy to clear gastric contents and assist with visualization.<sup>45</sup>

Patients with UGIB in the setting of DC should be considered for endoscopy within 12 hours.<sup>42–49–50</sup> Balloon tamponade as a bridge to TIPS should be considered as rescue therapy for patients with refractory variceal UGIB.<sup>42–50</sup>

## COAGULOPATHY

### When should VTE prophylaxis be given in patients with DC?

#### Recommendation

The timing of VTE prophylaxis initiation should not differ from patients without DC, regardless of standard coagulation test results. In cases of clinical uncertainty, normal or hypercoagulable VET may be an appropriate trigger to initiate prophylaxis. Anti-factor Xa monitoring is not recommended.

#### Discussion

Patients with DC are at risk for thrombosis as well as bleeding. Cirrhosis-related international normalized ratio (INR) elevation and thrombocytopenia classically led to a presumption of hypocoagulability, resulting in underutilization of VTE prophylaxis and exclusion of patients from key prophylaxis and treatment trials.<sup>51</sup> In actuality, reductions in liver-derived procoagulants are offset by reductions in anticoagulants as well as increases in endothelial-derived procoagulants, leading to a fragile net hypercoagulable state.<sup>52–53</sup> As such, the incidence of deep vein thrombosis is 50%–70% higher in patients with cirrhosis.<sup>54–55</sup> Importantly, the most common VTE event in DC is portal vein thrombosis, which can lead to reduced hepatic perfusion, increased variceal pressure, worsening hepatic decompensation, and technical issues with future transplantation.<sup>56</sup>

Studies of VTE prophylaxis in DC are largely retrospective and conflicting, but overall suggest that prophylactic anticoagulation does increase bleeding events.<sup>57</sup> Bleeding complications may be more common with unfractionated as compared with low molecular weight heparin (LMWH); thus LMWH is a reasonable agent of choice outside of renal failure.<sup>58</sup> Due to lower endogenous anti-Xa activity in DC, anti-Xa level monitoring underestimates heparin effects and may lead to overanticoagulation and is not recommended.<sup>59</sup> For mechanistic reasons, VET has limitations in the assessment of the true hemostatic

potential of patients with cirrhosis. The finding of a normal or hypercoagulable VET-based reaction time is a reasonable trigger to initiate VTE prophylaxis, recognizing a lack of data specifically addressing this approach.<sup>60</sup>

### Should thrombocytopenic patients with DC receive empiric platelet transfusion prior to procedures?

#### Recommendation

Empiric platelet transfusions are not indicated for periprocedural correction of thrombocytopenia, unless VET indicates a functional platelet deficit.

#### Discussion

Thrombocytopenia is common in DC, related to splenic sequestration and decreased thrombopoietin levels. However, platelet function is also simultaneously augmented by elevated von Willebrand Factor (vWF) and increased circulating activated platelets.<sup>61–62</sup> The American Gastroenterological Association recommends platelet transfusion to correct the platelet count to  $>50\,000$  only in the setting of high-risk procedures or active bleeding, while the AASLD recommends no routine preprocedural correction.<sup>63–64</sup> If high risk is anticipated 2–10 days in advance, thrombopoietin agonists are an emerging option to avoid transfusion.<sup>65</sup> The use of desmopressin (DDAVP) outside of clear uremic platelet dysfunction is mechanistically unappealing, given the already increased circulating levels of vWF. Several studies of VET-guided algorithms for both periprocedural as well as variceal bleeding transfusion algorithms suggest that VET-guided platelet transfusion is associated with similar or reduced blood product transfusion without increased risk of bleeding.<sup>66</sup>

## HEPATIC ENCEPHALOPATHY

### What are the best practices in management of hepatic encephalopathy?

#### Recommendation

Ammonia levels should be obtained to exclude or implicate HE as an etiology of altered mental status, but not to follow its progression or response to therapy. Initial treatment should include non-absorbable disaccharides and rifaximin.

#### Discussion

HE complicating DC is associated with a 1-year mortality of  $\geq 50\%$ , and has a varied clinical presentation ranging from disorientation to coma.<sup>67</sup> In 70%–80% of cases, a precipitating event such as surgery, infection, or GI hemorrhage precedes these changes.<sup>45</sup> HE is a clinical diagnosis that can be difficult to establish definitively in the ICU given the abundance of alternative etiologies. Neurological changes can be mimicked by alternate conditions such as delirium which need to be considered prior to establishing a diagnosis of HE. Cerebral CT should be obtained to rule out other pathology such as subarachnoid or subdural hemorrhage, stroke and edema. Electroencephalography changes are non-specific but useful to rule out seizures.

Ammonia levels do not correlate with clinical severity of HE; however, a normal ammonia level has a negative predictive value of 80%, suggesting an alternative cause of mental status changes.<sup>68</sup> Blood samples should be drawn without tourniquet, placed on ice, and immediately sent to the laboratory. Monitoring ammonia levels as a response to therapy is not recommended. Ammonia levels are unlikely to normalize and often will remain elevated after resolution of an episode of HE.<sup>69</sup> The response to therapy should be assessed on a clinical basis.<sup>70</sup>

Lactulose, a non-absorbable disaccharide, has been shown to improve resolution of HE episodes and survival.<sup>71</sup> The dose of lactulose should be titrated to achieve two to three bowel movements per day, being administered hourly until the first bowel movement.<sup>72</sup> Enema formulations are available. L-ornithine l-aspartate can be considered when lactose intolerance exists and has been shown to have equivalent efficacy when compared with disaccharide therapy, but is not yet available in the USA.<sup>73</sup> The addition of rifaximin should be considered when the clinical response to lactulose is poor. Rifaximin in combination with lactulose demonstrated greater efficacy than either alone in treating HE with a higher probability of resolution, shorter hospital length of stay, and improved survival.<sup>74</sup> Rifaximin can also be given for primary prophylaxis of hepatic encephalopathy after gastrointestinal hemorrhage.<sup>75</sup> Polyethylene glycol is an osmotic laxative that has been shown in small studies to be effective in the treatment of HE but requires further validation.<sup>76</sup> Flumazenil therapy has been shown to improve encephalopathy but not impact mortality.<sup>77</sup> Probiotics have not shown improvement when compared with placebo.<sup>78</sup> The non-ureic nitrogen scavengers have promising early data but future studies are required.<sup>79</sup>

## NUTRITION

### How should nutritional support and hypoglycemia be managed in the patient with DC in the ICU?

#### Recommendation

Early enteral nutrition is preferred for patients with DC. Protein restriction is not beneficial. Hypoglycemia should be managed with frequent blood glucose measurements and dextrose if needed.

#### Discussion

Critically ill patients with DC require careful nutritional and metabolic management. Due to hepatocellular dysfunction, derangements in carbohydrate, protein, and lipid metabolism are commonly encountered and may manifest as impaired gluconeogenesis, impaired lactate clearance, and protein catabolism.<sup>80</sup> Furthermore, comorbidities such as ascites, alterations in gastrointestinal motility, and GIB may further complicate nutrition management. Protein and caloric malnutrition as well as trace element deficiency are common in DC, affecting >60% of patients.<sup>81 82</sup>

Early enteral nutrition should be provided to patients with DC unless there are clear contraindications. Enteral nutrition via a nasojunal or nasogastric tube is appropriate for those patients unable to take nutrition orally. Standard enteral feeding formulas should be offered. Dietary protein restriction, historically advocated to limit production of ammonia and associated hepatic encephalopathy, is not beneficial.<sup>83 84</sup> Patients with DC suffer from concomitant protein calorie malnutrition and diets high in protein are actually associated with improved mental status and outcomes.<sup>83 84</sup> Patients should be provided a daily protein intake of 1.2–2.0 g/kg of dry body weight.<sup>84 85</sup> Branched-chain amino acid formulas offer no benefit over standard tube feed formulas. Parenteral nutrition may be considered second-line treatment in patients unable to receive enteral nutrition or for those not meeting caloric needs with enteral nutrition.

Hypoglycemia can occur in patients with DC due to depletion in hepatic glycogen stores, impaired gluconeogenesis due to hepatocyte loss, and hyperinsulinemia.<sup>86</sup> Continuous infusion of 5% dextrose can mitigate hypoglycemia, although this can lead to volume overload. Therefore, more frequent glucose checks with goal-directed glucose therapy may be beneficial. In more

severe cases of hypoglycemia, 20% or 50% dextrose boluses may be used.<sup>87</sup> Frequent blood glucose checks (every 2 hours) should be performed to monitor response to therapy. Hypoglycemia, an ominous sign in the patient with DC, has been identified as a prognostic factor for poor outcomes.<sup>81 88</sup> The 30-day mortality rate for patients with hypoglycemia and DC may be as high as 30%.<sup>88</sup>

## PROGNOSIS

### What tools can aid in estimation of outcomes for patients with DC in the ICU?

#### Recommendation

Clinical scores including the MELD, Acute-on-Chronic Liver Failure (ACLF) criteria, and the Chronic Liver Failure-Sequential Organ Failure Assessment (SOFA) (CLIF-SOFA) can be used to predict outcomes in DC. Biomarkers including cystatin C, copeptin, procalcitonin, and C reactive protein are under investigation to predict outcomes in DC but are not recommended for routine use at this time.

#### Discussion

Acute decompensation of liver disease is associated with organ failure and high mortality. Determining which patients will go on to develop progressive organ dysfunction leading to death is difficult. Previous work has demonstrated that patients with chronic liver disease with progressive organ failure, specifically defined by elevated INR, need for hemodialysis, or mechanical ventilation have the highest rates of mortality.<sup>89</sup> Commonly used prognostication scores include Child-Pugh score or MELD score.<sup>41 90–92</sup> However, several other scoring systems have been developed to aid in the determination of acute decompensation. ACLF based on the European Association for the Study of the Liver (EASL)-CLIF Consortium criteria has been identified to predict patients with an acute deterioration of liver function in patients with cirrhosis due to superimposed liver injury or extrahepatic precipitating factors, including infections.<sup>93</sup> Patients meeting these criteria have an expected mortality of 65% or higher compared with ~10% in patients that do not.<sup>94</sup> The North American Consortium for the Study of End-Stage Liver Disease criteria is noted to outperform the EASL-CLIF in the prediction of 7-day mortality, which may demonstrate futility.<sup>41</sup> In addition, a modification of SOFA has been developed, termed CLIF-SOFA. This score has been proposed as an adjunct to predicting outcome and mortality. The CLIF-SOFA score has been validated to predict outcomes in several studies in patients with DC, with scores that correlate to predicted mortality.<sup>94 95</sup>

Prediction is not limited to clinical classifications. Recently, biomarkers including the microbiome have been investigated to help predict the development of AKI, hepatic encephalopathy, infection, and muscle wasting in patients with DC.<sup>41 96</sup> Specifically, serum cystatin C, a biomarker for renal function, can help predict both the development of DC and hepatorenal syndrome in patients with chronic liver disease.<sup>97</sup> Additionally, copeptin, a stable cleavage product of arginine vasopressin, is predictive of short-term survival of patients with DC.<sup>98</sup> Similar to other conditions, levels of procalcitonin and C reactive protein are associated with the development of infection and poor outcome in patients with both DC and chronic liver failure.<sup>96</sup> Overall, these biomarkers have only recently been proposed as adjuncts to predicting and prognosticating outcomes and mortality in patients suffering from ACLF. Further studies are needed to validate these initial studies.

## Author affiliations

<sup>1</sup>Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

<sup>2</sup>Department of Surgery, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA

<sup>3</sup>Department of Surgery, San Francisco General Hospital and Trauma Center, San Francisco, California, USA

<sup>4</sup>Department of Surgery, UCSF Fresno, Fresno, California, USA

<sup>5</sup>Surgery, Yale University School of Medicine, New Haven, Connecticut, USA

<sup>6</sup>Department of Surgery, Yale New Haven Hospital, New Haven, Connecticut, USA

<sup>7</sup>Surgery, University of Mississippi Medical Center, Jackson, Mississippi, USA

<sup>8</sup>Department of Surgery, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

<sup>9</sup>Department of Surgery, Maine Medical Center, Portland, Oregon, USA

<sup>10</sup>Department of Gastroenterology, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA

<sup>11</sup>Department of Surgery, Inova Fairfax Hospital, Falls Church, Virginia, USA

**Contributors** All authors were involved in the design, research, and writing of this guideline, as well as critical revision of the manuscript. AS and CPM performed the final revisions of the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## ORCID iDs

Anupamaa Seshadri <http://orcid.org/0000-0001-8432-7518>

Samuel P Carmichael II <http://orcid.org/0000-0003-0237-4244>

Joseph Cuschieri <http://orcid.org/0000-0003-1456-6841>

Krista L Kaups <http://orcid.org/0000-0002-0823-6902>

Christopher P Michetti <http://orcid.org/0000-0002-3744-0603>

## REFERENCES

- GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet Gastroenterol Hepatol* 2020;5:245-66.
- Weiss E, Paugam-Burtz C, Jaber S. Shock etiologies and fluid management in liver failure. *Semin Respir Crit Care Med* 2018;39:538-45.
- Vora RS, Subramanian RM. Hypotension in cirrhosis. *Clin Liver Dis* 2019;13:149-53.
- Maynard E. Decompensated cirrhosis and fluid resuscitation. *Surg Clin North Am* 2017;97:1419-24.
- Davenport A, Argawal B, Wright G, Mantzoukis K, Dimitrova R, Davar J, Vasianopoulou P, Burroughs AK. Can non-invasive measurements aid clinical assessment of volume in patients with cirrhosis? *World J Hepatol* 2013;5:433-8.
- Martin ND, Codner P, Greene W, Brasel K, Michetti C. Contemporary hemodynamic monitoring, fluid responsiveness, volume optimization, and endpoints of resuscitation: an AAST critical care Committee clinical consensus. *Trauma Surg Acute Care Open* 2020;5:e000411.
- Davenport A, Ahmad J, Al-Khafaji A, Kellum JA, Genyk YS, Nadim MK. Medical management of hepatorenal syndrome. *Nephrol Dial Transplant* 2012;27:34-41.
- Premkumar M, Kajal K, Kulkarni AV, Gupta A, Divyaveer S. Point-Of-Care echocardiography and hemodynamic monitoring in cirrhosis and acute-on-chronic liver failure in the COVID-19 era. *J Intensive Care Med* 2021;36:511-23.
- SCCM. *Critical care ultrasound course Handbook*.
- Marik PE. Fluid responsiveness and the six guiding principles of fluid resuscitation. *Crit Care Med* 2016;44:1920-2.
- Premkumar M, Rangegowda D, Kajal K, Khumuckham JS. Noninvasive estimation of intravascular volume status in cirrhosis by dynamic size and collapsibility indices of the inferior vena cava using bedside echocardiography. *JGH Open* 2019;3:322-8.
- Biancofiore G, Critchley LAH, Lee A, Bindi L, Bisà M, Esposito M, Meacci L, Mozzo R, DeSimone P, Urbani L, et al. Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. *Br J Anaesth* 2009;102:47-54.
- Morgan B. Central Venous/Mixed Venous Oxygen Saturation. *Critical Care Trauma Centre*. 2018. <https://www.lhsc.on.ca/critical-care-trauma-centre/central-venous/mixed-venous-oxygen-saturation>.
- Funk GC, Doberer D, Kneidinger N, Lindner G, Holzinger U, Schneeweiss B. Acid-Base disturbances in critically ill patients with cirrhosis. *Liver Int* 2007;27:901-9.
- Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med* 2018;378:819-28.
- Vipani A, Lindenmeyer CC, Sundaram V. Treatment of severe acute on chronic liver failure: management of organ failures, investigational therapeutics, and the role of liver transplantation. *J Clin Gastroenterol* 2021;55:667-76.
- Han X, Davis AM, Parker WF. Managing adult acute and acute-on-chronic liver failure in the ICU. *JAMA* 2021;326:1964-5.
- European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69:406-60.
- Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, Levantesi F, Airoldi A, Boccia S, Svegliati-Baroni G, et al. Long-Term albumin administration in decompensated cirrhosis (answer): an open-label randomised trial. *Lancet* 2018;391:2417-29.
- Solà E, Solé C, Simón-Talero M, Martín-Llahí M, Castellote J, García-Martínez R, Moreira R, Torrens M, Márquez F, Fabrellas N, et al. Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. *J Hepatol* 2018;69:1250-9.
- Northup PG, Friedman LS, Kamath PS. AGA Clinical Practice Update on Surgical Risk Assessment and Perioperative Management in Cirrhosis: Expert Review. *Clin Gastroenterol Hepatol* 2019;17:595-606.
- Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, Wong F, Kim WR, Diagnosis KWR. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American association for the study of liver diseases. *Hepatology* 2021;74:1014-48.
- Telem DA, Schiano T, Divino CM. Complicated hernia presentation in patients with advanced cirrhosis and refractory ascites: management and outcome. *Surgery* 2010;148:538-43.
- Fagan SP, Awad SS, Berger DH. Management of complicated umbilical hernias in patients with end-stage liver disease and refractory ascites. *Surgery* 2004;135:679-82.
- Vinet E, Perreault P, Bouchard L, Bernard D, Wassef R, Richard C, Létourneau R, Pomier-Layrargues G. Transjugular intrahepatic portosystemic shunt before abdominal surgery in cirrhotic patients: a retrospective, comparative study. *Can J Gastroenterol* 2006;20:401-4.
- Aryan M, McPhail J, Ravi S, Harris P, Allamneni C, Shoreibah M. Perioperative transjugular intrahepatic portosystemic shunt is associated with decreased postoperative complications in decompensated cirrhotics undergoing abdominal surgery. *Am Surg* 2022;88:1613-20.
- Jain D, Mahmood E, V-Bandres M, Feysa E. Preoperative elective transjugular intrahepatic portosystemic shunt for cirrhotic patients undergoing abdominal surgery. *Ann Gastroenterol* 2018;31:330-7.
- Philip M, Thornburg B. Preoperative transjugular intrahepatic portosystemic shunt placement for extrahepatic abdominal surgery. *Semin Intervent Radiol* 2018;35:203-5.
- Kulkarni AV, Kumar P, Sharma M, Sowmya TR, Talukdar R, Rao PN, Reddy DN. Pathophysiology and prevention of Paracentesis-induced circulatory dysfunction: a Concise review. *J Clin Transl Hepatol* 2020;8:42-8.
- Newman KL, Johnson KM, Cornia PB, Wu P, Itani K, Ioannou GN. Perioperative evaluation and management of patients with cirrhosis: risk assessment, surgical outcomes, and future directions. *Clin Gastroenterol Hepatol* 2020;18:2398-414.
- Odom SR, Gupta A, Talmor D, Novack V, Sagy I, Evenson AR. Emergency hernia repair in cirrhotic patients with ascites. *J Trauma Acute Care Surg* 2013;75:404-9.
- Fagioli S, Bruno R, Debernardi Venon W, Schepis F, Vizzutti F, Toniutto P, Senzolo M, Caraceni P, Salerno F, Angeli P, et al. Consensus conference on tips management: techniques, indications, contraindications. *Dig Liver Dis* 2017;49:121-37.
- Fuster J, Llovet JM, Garcia-Valdecasas JC, Grande L, Fondevila C, Vilana R, Palacin J, Tabet J, Ferrer J, Bruix J, et al. Abdominal drainage after liver resection for hepatocellular carcinoma in cirrhotic patients: a randomized controlled study. *Hepatogastroenterology* 2004;51:536-40.
- Liu C-L, Fan S-T, Lo C-M, Wong Y, Ng IO-L, Lam C-M, Poon RT-P, Wong J. Abdominal drainage after hepatic resection is contraindicated in patients with chronic liver diseases. *Ann Surg* 2004;239:194-201.
- Simonetto DA, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. *BMJ* 2020;370:m2687.
- Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International club of ascites (ICA) consensus document. *J Hepatol* 2019;71:811-22.
- Kaewput W, Thongprayoon C, Dumancas CY, Kanduri SR, Kovvuru K, Kaewput C, Pattharanitima P, Petnak T, Lertjitbanjong P, Boonpheng B, et al. In-Hospital mortality



- of hepatorenal syndrome in the United States: nationwide inpatient sample. *World J Gastroenterol* 2021;27:7831–43.
- 38 Liu S, Meng Q, Xu Y, Zhou J. Hepatorenal syndrome in acute-on-chronic liver failure with acute kidney injury: more questions requiring discussion. *Gastroenterol Rep* 2021;9:505–20.
- 39 Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, Gonzalez SA, Mumtaz K, Lim N, Simonetto DA, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med* 2021;384:818–28.
- 40 Song T, Rössle M, He F, Liu F, Guo X, Qi X. Transjugular intrahepatic portosystemic shunt for hepatorenal syndrome: a systematic review and meta-analysis. *Dig Liver Dis* 2018;50:323–30.
- 41 Bajaj JS, Leary JGO, Lai JC, Wong F, Long MD, Wong RJ, Kamath PS. *Acute-On-Chronic liver failure clinical guidelines*, 2022:1–28.
- 42 Rajwani K, Fortune BE, Brown RS. Critical care management of gastrointestinal bleeding and ascites in liver failure. *Semin Respir Crit Care Med* 2018;39:566–77.
- 43 Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet* 2021;398:1359–76.
- 44 Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American association for the study of liver diseases. *Hepatology* 2017;65:310–35.
- 45 Chandna S, Zarate ER, Gallegos-Orozco JF. Management of decompensated cirrhosis and associated syndromes. *Surg Clin North Am* 2022;102:117–37.
- 46 PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group, Young PJ, Bagshaw SM, Forbes AB, Nichol AD, Wright SE, Bailey M, Bellomo R, Beasley R, Brickell K, et al. Effect of stress ulcer prophylaxis with proton pump inhibitors vs Histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: the peptic randomized clinical trial. *JAMA* 2020;323:616–26.
- 47 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver/Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, Krag A, Laleman W, Gines P. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69:406–60.
- 48 Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma. *JAMA* 2015;313:471–82.
- 49 Nevens F, Bittencourt PL, Coenraad MJ, Ding H, Hou M-C, Laterre P-F, Mendizabal M, Ortiz-Olvera NX, Vorobioff JD, Zhang W, et al. Recommendations on the diagnosis and initial management of acute variceal bleeding and hepatorenal syndrome in patients with cirrhosis. *Dig Dis Sci* 2019;64:1419–31.
- 50 Laine L, Barkun AN, Saltzman JR, Martel M, Leontiadis GI. ACG clinical guideline: upper gastrointestinal and ulcer bleeding. *Am J Gastroenterol* 2021;116:899–917.
- 51 Cohen AT, Tapson VF, Bergmann J-F, Goldhaber SZ, Kakkak AK, Deslandes B, Huang W, Zayaruzny M, Emery L, Anderson FA, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008;371:387–94.
- 52 Tripodi A, Primignani M, Lemma L, Chantarangkul V, Mannucci PM. Evidence that low protein C contributes to the procoagulant imbalance in cirrhosis. *J Hepatol* 2013;59:265–70.
- 53 Bos S, van den Boom B, Kamphuisen PW, Adelmeijer J, Blokzijl H, Schreuder T, Lisman T. Haemostatic profiles are similar across all aetiologies of cirrhosis. *Thromb Haemost* 2019;119:246–53.
- 54 Ambrosino P, Tarantino L, Di Minno G, Paternoster M, Graziano V, Petitto M, Nasto A, Di Minno MND. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. *Thromb Haemost* 2017;117:139–48.
- 55 Dabbagh O, Oza A, Prakash S, Sunna R, Saetle TM. Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease. *Chest* 2010;137:1145–9.
- 56 Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, Zecchini R, Gitto S, Petta S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology* 2012;143:1253–60.
- 57 Turco L, de Raucourt E, Valla D-C, Villa E. Anticoagulation in the cirrhotic patient. *JHEP Rep* 2019;1:227–39.
- 58 Ha NB, Regal RE. Anticoagulation in patients with cirrhosis: caught between a Rock-Liver and a hard place. *Ann Pharmacother* 2016;50:402–9.
- 59 Fuentes A, Gordon-Burroughs S, Hall JB, Putney DR, Monsour HP. Comparison of anti-Xa and activated partial thromboplastin time monitoring for heparin dosing in patients with cirrhosis. *Ther Drug Monit* 2015;37:40–4.
- 60 Lisman T. Interpreting hemostatic profiles assessed with viscoelastic tests in patients with cirrhosis. *J Clin Gastroenterol* 2020;54:389–91.
- 61 Hugenholtz GCG, Adelmeijer J, Meijers JCM, Porte RJ, Stravitz RT, Lisman T. An imbalance between von Willebrand factor and ADAMTS13 in acute liver failure: implications for hemostasis and clinical outcome. *Hepatology* 2013;58:752–61.
- 62 Raparelli V, Basili S, Carnevale R, Napoleone L, Del Ben M, Nocella C, Bartimoccia S, Lucidi C, Talerico G, Riggio O, et al. Low-Grade endotoxemia and platelet activation in cirrhosis. *Hepatology* 2017;65:571–81.
- 63 O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA clinical practice update: coagulation in cirrhosis. *Gastroenterology* 2019;157:34–43.
- 64 Northrup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, Lisman T, Valla DC, Disorders VL. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American association for the study of liver diseases. *Hepatology* 2021;73:366–413.
- 65 Khemichian S, Terrault NA. Thrombopoietin receptor agonists in patients with chronic liver disease. *Semin Thromb Hemost* 2020;46:682–92.
- 66 Nguyen G, Lejeune M, Crichton B, Frere C. Hemostasis testing in patients with liver dysfunction: advantages and caveats. *World J Gastroenterol* 2021;27:7285–98.
- 67 Rudler M, Weiss N, Bouzbib C, Thabut D. Diagnosis and management of hepatic encephalopathy. *Clin Liver Dis* 2021;25:393–417.
- 68 Nicolao F, Efrati C, Masini A, Merli M, Attili AF, Riggio O. Role of determination of partial pressure of ammonia in cirrhotic patients with and without hepatic encephalopathy. *J Hepatol* 2003;38:441–6.
- 69 Mallet M, Weiss N, Thabut D, Rudler M. Why and when to measure ammonia in cirrhosis? *Clin Res Hepatol Gastroenterol* 2018;42:505–11.
- 70 Haj M, Rockey DC. Ammonia levels do not guide clinical management of patients with hepatic encephalopathy caused by cirrhosis. *Am J Gastroenterol* 2020;115:723–8.
- 71 Gluud LL, Vilstrup H, Morgan MY. Nonabsorbable disaccharides for hepatic encephalopathy: a systematic review and meta-analysis. *Hepatology* 2016;64:908–22.
- 72 Olson JC, Karvellas CJ. Critical care management of the patient with cirrhosis awaiting liver transplant in the intensive care unit. *Liver Transpl* 2017;23:1465–76.
- 73 Butterworth RF, McPhail MJW. L-Ornithine L-aspartate (LoLA) for hepatic encephalopathy in cirrhosis: results of randomized controlled trials and meta-analyses. *Drugs* 2019;79:31–7.
- 74 Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol* 2013;108:1458–63.
- 75 Higuera-de-la-Tijera F, Servín-Caamaño AI, Salas-Gordillo F, Pérez-Hernández JL, Abdo-Francis JM, Camacho-Aguilera J, Alla SN, Jiménez-Ponce F. Primary prophylaxis to prevent the development of hepatic encephalopathy in cirrhotic patients with acute variceal bleeding. *Can J Gastroenterol Hepatol* 2018;2018:3015891.
- 76 Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350--electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. *JAMA Intern Med* 2014;174:1727–33.
- 77 Goh ET, Andersen ML, Morgan MY, Gluud LL. Flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy. *Cochrane Database Syst Rev* 2017;7:CD002798.
- 78 Dalal R, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. *Cochrane Database Syst Rev* 2017;2:CD008716.
- 79 Weiss N, Tripson S, Lodey M, Guiller E, Junot H, Monneret D, Mayaux J, Brisson H, Mallet M, Rudler M, et al. Treating hepatic encephalopathy in cirrhotic patients admitted to ICU with sodium phenylbutyrate: a preliminary study. *Fundam Clin Pharmacol* 2018;32:209–15.
- 80 Bischoff SC, Bernal W, Dasarathy S, Merli M, Plank LD, Schütz T, Plauth M. ESPEN practical guideline: clinical nutrition in liver disease. *Clin Nutr* 2020;39:3533–62.
- 81 Plauth M, Bernal W, Dasarathy S, Merli M, Plank LD, Schütz T, Bischoff SC. ESPEN guideline on clinical nutrition in liver disease. *Clin Nutr* 2019;38:485e521.
- 82 Tandon P, Raman M, Mourtzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. *Hepatology* 2017;65:1044e57.
- 83 Ge PS, Runyon BA. Treatment of patients with cirrhosis. *N Engl J Med* 2016;375:767–77.
- 84 Córdoba J, López-Hellín J, Planas M, Sabín P, Sanpedro F, Castro F, Esteban R, Guardia J. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol* 2004;41:38–43.
- 85 Lai JC, Tandon P, Bernal W, Tapper EB, Ekong U, Dasarathy S, Carey EJ. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guidance by the American association for the study of liver diseases. *Hepatology* 2021;74:1611–44.
- 86 Vilstrup H, Iversen J, Tygstrup N. Glucoregulation in acute liver failure. *Eur J Clin Invest* 1986;16:193e7.
- 87 Rueda M, Lipsett P. "Hepatic Failure". In: Martin ND, Kaplan LJ, eds. *Principles of adult surgical critical care*, 2016.
- 88 Hung T-H, Tseng C-W, Tsai C-C, Lee H-F. Prognosis of hypoglycemia episode in cirrhotic patients during hospitalization. *BMC Gastroenterol* 2021;21:319.
- 89 Chebl RB, Tamim H, Sadat M, Qahtani S, Dabbagh T, Arabi YM. Outcomes of septic cirrhosis patients admitted to the intensive care unit: a retrospective cohort study. *Medicine* 2021;100:e27593.
- 90 Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK. Systematic review: The model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Aliment Pharmacol Ther* 2005;22:1079–89.
- 91 Cholongitas E, Senzolo M, Triantos C, Samonakis D, Patch D, Burroughs AK. MELD is not enough--enough of MELD? *J Hepatol* 2005;42:475–7.
- 92 Tsochatzidis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014;383:1749–61.

- 93 Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V, Kamath PS. Acute-on chronic liver failure. *J Hepatol* 2012;57:1336–48.
- 94 Silva PESE, Fayad L, Lazzarotto C, Ronsoni MF, Bazzo ML, Colombo BS, Dantas-Correa EB, Narciso-Schiavon JL, Schiavon LL. Single-Centre validation of the EASL-CLIF Consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. *Liver Int* 2015;35:1516–23.
- 95 Jeong JH, Park IS, Kim DH, Kim SC, Kang C, Lee SH, Kim TY, Lee SB. CLIF-SOFA score and SIRS are independent prognostic factors in patients with hepatic encephalopathy due to alcoholic liver cirrhosis. *Medicine* 2016;95:e3935.
- 96 Iwasa M, Shigefuku R, Eguchi A, Tamai Y, Takei Y. Update on blood-based biomarkers for chronic liver diseases prognosis: literature review and institutional experience. *JGH Open* 2021;5:1250–6.
- 97 Markwardt D, Holdt L, Steib C, Benesic A, Bendtsen F, Bernardi M, Moreau R, Teupser D, Wendon J, Nevens F, *et al.* Plasma cystatin C is a predictor of renal dysfunction, acute-on-chronic liver failure, and mortality in patients with acutely decompensated liver cirrhosis. *Hepatology* 2017;66:1232–41.
- 98 Kerbert AJC, Verspaget HW, Navarro Àlex Amorós, Jalan R, Solà E, Bente D, Durand F, Ginès P, van der Reijden JJ, van Hoek B, *et al.* Copeptin in acute decompensation of liver cirrhosis: relationship with acute-on-chronic liver failure and short-term survival. *Crit Care* 2017;21:321.