

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

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## 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

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**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.

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