Time-Sensitive Interventions in Hospitalized Patients With Cirrhosis

Zachary Sherman, M.D.,* Amin Soltani, M.D.,* Peter Steel, M.B.B.S., M.A.,† and Arun Jesudian, M.D.‡

BACKGROUND

Despite the development of evidence-based quality metrics for cirrhosis care, the in-hospital mortality rate among patients with decompensated cirrhosis remains high at approximately 10%.1 Many critical diagnostic and therapeutic interventions for hospitalized patients with cirrhosis have time-dependent efficacy (Table 1). This article reviews these interventions and the data that support their importance.

Paracentesis in Patients with Ascites

Given the high risk for spontaneous bacterial peritonitis (SBP), diagnostic paracentesis is recommended in all hospitalized patients with cirrhosis and ascites, even in the absence of symptoms. Retrospective analyses of the Nationwide Inpatient Sample revealed that only 51% to 61% of hospitalized patients with cirrhosis underwent paracentesis, but for those who did, the in-hospital mortality rate was reduced by 24% to 29%.2,3 Multicenter retrospective analysis of patients with cirrhosis and ascites demonstrated that delays in paracentesis (>12 hours) after admission accounted for a 2.7-fold increase in in-hospital mortality.4 Furthermore, each hour delay in paracentesis was associated with a 3.3% inpatient mortality rate increase. These findings support the prioritization of early (<12 hours) diagnostic paracentesis in any hospitalized patient with cirrhosis and ascites.

Antibiotics in Patients with SBP

SBP in patients with cirrhosis is extremely concerning given the significant risk for development of hepatorenal syndrome (HRS) and associated mortality rates as high as 40%. Once diagnosed (by ascites fluid neutrophils >250 cells/mm³ and/or positive culture), appropriate SBP therapy consists of broad-spectrum antibiotics in all patients, as well as high-dose albumin at days 1 and 3, particularly in those with creatinine concentration >1 mg/dL, blood urea nitrogen level >30 mg/dL, or total bilirubin

Abbreviations: EGD, esophagogastroduodenoscopy; GI, gastrointestinal; HRS, hepatorenal syndrome; ICU, intensive care unit; OHE, overt hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt. From the *Department of Medicine, Weill Cornell Medicine, New York, NY; †Department of Emergency Medicine, Weill Cornell Medicine, New York, NY; and ‡Division of Gastroenterology and Hepatology, Weill Cornell Medicine, New York, NY.

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level >4.0 mg/dL. Although no prospective studies have investigated the timing of initiation of antibiotics in SBP, a retrospective cohort study of 126 patients with cirrhosis with SBP-associated septic shock demonstrated that those who survived were more likely to have been administered antibiotics earlier (median [range] 1.8 [1.1-5.2] versus 9.5 [3.9-14.3] hours; \( P < 0.001 \)), with each hour delay in antibiotic treatment increasing mortality by 1.86 times. Both national and international consensus guidelines recommend prompt initiation of empiric antibiotic therapy at diagnosis of SBP by ascites cell count without waiting for culture data.5,7

## TREATMENT OF HRS

Development of rapidly progressive type 1 HRS is associated with potentially irreversible acute kidney injury and poor short-term survival in the absence of liver transplantation. Once identified, pharmacological treatment with vasoconstrictor therapy and albumin infusion is essential to maximize the likelihood of reversing type 1 HRS. Where available, terlipressin is the vasoconstrictor of choice given its efficacy in reversing HRS.5 If terlipressin is unavailable, a combination of midodrine and octreotide is recommended.5 However, if there is no clinical response or if intensive care unit (ICU) care is accessible, norepinephrine infusion is preferred because it exhibits similar efficacy to terlipressin.8 No prospective studies have examined the relationship between timing of HRS therapy initiation and outcomes. In a post hoc analysis of 56 patients treated for type 1 HRS with terlipressin, the only variable that predicted HRS reversal was baseline serum creatinine.9 A similar analysis demonstrated that lower creatinine and higher urine output at baseline correlated with increased rates of HRS reversal in patients receiving terlipressin.10 In addition, there have been several small studies that have shown that transjugular intrahepatic portosystemic shunt (TIPS) may improve renal function and possibly reduce mortality in HRS.11 Earlier initiation of HRS therapy, prior to the development of severe renal dysfunction, and consideration of TIPS may improve the likelihood of HRS reversal.

## INTERVENTIONS FOR SUSPECTED VARICEAL BLEEDING

The objective of care in acute upper gastrointestinal (GI) hemorrhage in patients with cirrhosis is to control bleeding and prevent early rebleeding and 6-week mortality.12
In addition to assessing for adequate respiratory function and circulation, evaluation for ICU admission is advised. The in-hospital mortality rate from variceal bleeding is as high as 20%, related to the risks for hemorrhagic shock and infection, both at presentation and later during the hospitalization. Vasoactive medications, such as octreotide, have been shown to reduce both transfusion requirements and all-cause mortality. Prophylactic antibiotics have been shown to reduce the risk for infection, rebleeding, and death. For these reasons, consensus guidelines recommend both vasoactive medications and an antibiotic, such as ceftriaxone, be administered immediately in the patient with cirrhosis and upper GI bleed. Esophagogastroduodenoscopy (EGD) should then be performed as soon as possible within 12 hours of presentation. In patients presenting with hematemesis, early EGD in less than 12 hours was associated with lower 6-week rebleeding rates and mortality. In addition, patients who are at high risk for treatment failure may benefit from TIPS within 72 hours, because this has been shown to reduce rebleeding and mortality. Early vasoactive medications, antibiotics, EGD, and consideration of TIPS have all been shown to reduce in-hospital mortality from variceal bleeding and should be implemented as soon as possible.

**FIG 1** Algorithm for time-sensitive interventions in hospitalized patients with cirrhosis.

**INTERVENTIONS FOR OVERT HEPATIC ENCEPHALOPATHY**

Overt hepatic encephalopathy (OHE) is among the most common reasons for admission in patients with decompensated cirrhosis. Consensus guidelines recommend a four-pronged approach at presentation that consists of: (1) initiation of care for patients with altered consciousness; (2) exclusion of alternative causes of altered mental status; (3) identification of precipitating factors and their correction; and (4) commencement of empirical hepatic encephalopathy treatment. Patients with high-grade OHE who are unable to protect their airway might require endotracheal intubation and ICU transfer. Early exclusion of precipitating factors, such as infection, bleeding, and electrolyte disturbances, is of the utmost importance because most episodes of OHE are attributable to a precipitant, and many of these can be life-threatening. Data regarding time-sensitive interventions for OHE are lacking. One study showed that administration of six or more cups of lactulose within the first 24 hours of admission was associated with a significantly shorter length of stay by 2.36 days. The addition of rifaximin to lactulose is indicated for the prevention of recurrent episodes of OHE. Further research is needed.
to fully elucidate the relationship between timing of initiation of OHE therapy and clinical outcomes.

**CONCLUSION**

Hospitalized patients with cirrhosis are a vulnerable population at high risk for complications and death. We have reviewed several interventions that, when done expeditiously, have been shown to improve outcomes in this population (Fig. 1). Despite this, multiple studies demonstrate that adherence to these consensus recommendations and best practices for inpatient cirrhosis care remains suboptimal. We recommend institutions invest in the educational and operations infrastructure necessary to adhere to these evidence-based guidelines to optimize the care of these patients.

**CORRESPONDENCE**

Zachary Sherman, M.D., Department of Medicine, Weill Cornell Medicine, 525 E 68th Street, Box 130, Room M-532, New York, NY 10065. E-mail: zms9001@med.cornell.edu

**REFERENCES**


