Critically Ill Patients with End-Stage Liver Disease

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KEYWORDS

• Complications of end-stage liver disease • Critical illness • Hepatic encephalopathy • Gastrointestinal bleeding • Coagulopathy • Hepatorenal syndrome

KEY POINTS

- Patients with end-stage liver disease (ESLD) who require intensive care unit admission have high rates of mortality.
- Important complications encountered in critically ill ESLD patients include hepatic encephalopathy, gastrointestinal bleeding, bacterial peritonitis, hepatorenal syndrome, severe coagulopathy, and hepatic hydrothorax.
- Critically ill ESLD patients often present with multisystem organ dysfunction, and require prompt diagnosis of the underlying cause of acute decompensation and treatment initiation.

INTRODUCTION

Patients with end-stage liver disease (ESLD) who require intensive care unit (ICU) admission have high rates of mortality. Although less than 50% of these patients survive to hospital discharge, more than 90% of those patients who are successfully discharged from the hospital are still alive at 1 year.[1] This highlights the important role of high-quality critical care of these patients; if clinicians are able to get them through their hospital course, their intermediate-term mortality is surprisingly good.

Risk Stratification

The Model for End-Stage Liver Disease (MELD) score is probably the most useful scoring system for clinicians to rapidly obtain a gross estimate of baseline illness severity in ESLD patients.

- The MELD score was designed to predict 3-month survival, and examination of the curve reveals an inflection point in the curve between a score of 20 and 30 where mortality risk increases precipitously (**Fig. 1**).

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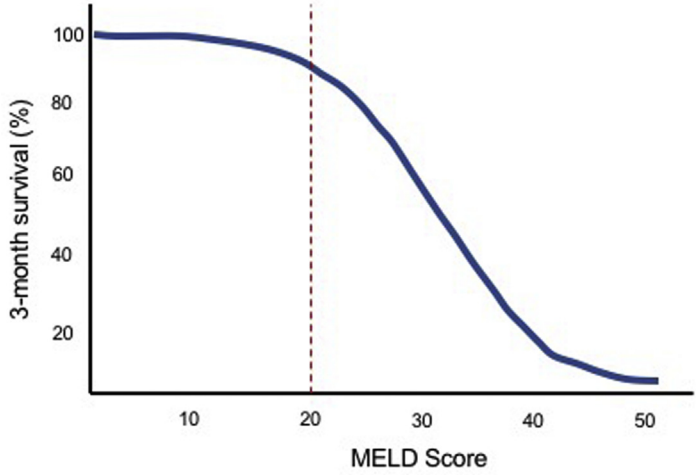

Fig. 1. The Model for End-Stage Liver Disease (MELD) system for clinicians. (*Adapted from* Teh SH, Nagorney DM, Stevens SR, et al. Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology 2007;132(4):1261 [Epub 2007 Jan 25]; with permission.)

- The variables used to calculate the score are readily available and include creatinine, international normalized ratio (INR), bilirubin, sodium, and renal replacement therapy.
- ESLD patients who are listed or being evaluated for transplant generally have previous MELD scores documented in the medical record, allowing the emergency clinician to easily obtain a global picture of the patient's overall trajectory.

Significance of Transplant Status

It is useful for the emergency provider to clarify the transplant status of a patient with ESLD. Transplant status may have implications for the approach taken in the acute care setting, as outlined in Table 1.

While the most common ICU-admitting diagnoses of ESLD patients are pneumonia, acute respiratory distress syndrome, and sepsis, this article focuses primarily on the most common complications specific to ESLD patients during critical illness.

Table 1
Significance of liver transplant status for the emergency provider

Listed for liver transplantation	The goal of the emergency physician is to provide aggressive care to support the patient the preoperative period
Undergoing liver transplant candidacy evaluation	The goal of the emergency physician is immediate stabilization and prevention of further complications to provide time for candidacy evaluation
Not a liver transplant candidate	In this case, the focus of the emergency physician should be on identifying reversible causes of an acute decompensation, and clarification of a goal of care early on; carefully consider the appropriateness of initiation of aggressive measures, particularly in the case of conditions such as hepatorenal syndrome or hepatopulmonary syndrome, which are associated with extremely high mortality, and for which liver transplantation is the only definitive management

HEPATIC ENCEPHALOPATHY

Pathophysiology

It is becoming increasingly understood that the pathophysiology of hepatic encephalopathy (HE) is complex, involving a wide range of pathologic processes including astrocyte edema and dysfunction, increased GABAergic tone, inflammatory cytokines, and depletion of acetylcholine.[2] Despite the growing understanding of the multifactorial pathophysiology of this disease, ammonia continues to be thought to play a central role. In the brain, ammonia and glutamate are converted into glutamine and the resultant high levels of glutamine then act as an osmolyte, causing astrocyte edema and neuronal dysfunction.

Emergency Critical Care Assessment

The severity of HE is graded clinically:

- *Grade I*: personality and/or mood changes, mild confusion, slurred speech, disordered sleep
- *Grade II*: lethargy, moderate confusion
- *Grade III*: marked confusion, incoherent speech, depressed level of consciousness but remains arousable
- *Grade IV*: comatose, unresponsive to pain

On examination, patients with severe HE may exhibit hyporeflexia or hyperreflexia, rigidity, myoclonus, ataxia, dilated pupils, and even transient decerebrate posturing.

There are 2 key questions that need to be answered when an ESLD patient presents with altered mental status:

1. Is HE the primary cause of the altered mental status?
2. What has precipitated the HE?

Patients with ESLD are at high risk for numerous disease states that may cause altered mental status (eg, sepsis, uremia, alcohol withdrawal, intracerebral hemorrhage). As such, an ESLD patient with altered mental status should not be presumed to have HE until other causes have been systematically considered and ruled out.

Precipitants of hepatic encephalopathy

Key precipitants of HE that may require diagnosis and treatment in the emergency setting are listed in **Table 2**.

Ammonia levels in hepatic encephalopathy

Although ammonia is thought to play a central role in the pathogenesis of HE, interpretation of individual serum ammonia levels is not straightforward, and HE remains a primarily clinical diagnosis.

- A normal or modestly elevated blood ammonia level does not rule out the diagnosis of HE.[3]
- An elevated ammonia level is not necessarily diagnostic of HE. Nearly two-thirds of ESLD patients with elevated ammonia levels have no evidence of HE.[4]
- Although studies have shown that ammonia level may correlate to some extent with the severity of HE, absolute levels substantially overlap among patients with differing clinical grades of HE. As such, it is not possible to clearly identify a particular threshold cutoff value for ammonia that rules in or rules out HE in a given patient; ammonia levels must be interpreted in clinical context, and therefore there is limited clinical utility in obtaining ammonia levels in these patients.

Table 2
Precipitants of hepatic encephalopathy

Medication noncompliance	This is a frequent precipitant of hepatic encephalopathy. It is important to investigate the *reason* for medication noncompliance to rule out additional underlying pathology (ie, as altered mental status due to a distinct cause or intractable vomiting). Other precipitants that require specific treatment should be systematically considered even in cases when medication noncompliance is suspected as the primary precipitating cause
Gastrointestinal bleeding	Worsening hyperammonemia in this context is probably the result of a large blood protein load being broken down in the gastrointestinal tract
Hypokalemia	Hypokalemia causes potassium efflux from the intracellular space to the extracellular space with resultant intracellular influx of hydrogen; the ensuing intracellular acidosis in renal tubular cells increases the renal production of ammonia
Alkalosis	Alkalosis facilitates entry of ammonia into the central nervous system by increasing the conversion of ammonium (NH_4^+) into ammonia (NH_3), which, as an uncharged particle, can more easily cross the blood-brain barrier
Dehydration	This often occurs in the setting of aggressive diuresis in ESLD patients with ascites and peripheral edema; the resultant contraction alkalosis (often seen in conjunction with hypokalemia) is a common precipitant of hepatic encephalopathy
Sepsis	Inflammatory cytokines are thought to enhance ammonia-induced neurotoxicity
Constipation	Increasing the transit time through the gastrointestinal tract increases the amount of ammonia that may be absorbed
Alcohol or benzodiazepines	Short-term use of alcohol and benzodiazepines has been found to significantly increase the risk of acute development of hepatic encephalopathy

Emergency Critical Care Management

There are 3 key management principles for patients presenting with HE:

1. Airway management
2. Correct precipitating causes
3. Correct hyperammonemia

Airway management

Airway assessment should be performed immediately.

- Patients with grade IV HE often need intubation for airway protection.
- Even in patients who do not require immediate intubation for airway protection, it must be considered whether it is necessary to control the airway to initiate prompt treatment. The most important factor is whether the patient is alert and cooperative enough to safely take oral lactulose.
- Although there are some data showing that rectal lactulose is superior to tap water enemas in HE,[5] there are no high-quality data on the comparative efficacy of oral versus rectal lactulose, so it is unclear whether oral and rectal lactulose may be used interchangeably. Administering lactulose via a nasogastric tube is also an option, but it is unclear to what degree this truly mitigates the risk of aspiration.

Once intubated, sedation requirements in ESLD patients with severe HE tend to be relatively minimal.

- Propofol is a good choice because of its short duration of action, extrahepatic metabolism, and beneficial effects on intracranial pressure.
- Midazolam should be avoided given the potential for exacerbating the encephalopathy, as should large doses of opiates.
- Of note, even in patients without acute HE, both benzodiazepines and opiates should be administered at minimal doses or avoided altogether because their use in these patients is associated with significant morbidity in ESLD.

Correction of precipitating causes

Any precipitating causes that have been identified should be corrected.

- Dehydration-induced HE usually responds well to fluid resuscitation and correcting hypokalemia and hypomagnesemia. Albumin is the preferred resuscitation fluid, given recent evidence that it may improve outcomes in HE.[6]
- Gastrointestinal bleeding should be identified and treated, with blood product transfusion as needed.
- Patients with suspected sepsis should be administered broad-spectrum antibiotics, and their intravascular volume status optimized.

Correction of hyperammonemia

The final step in the treatment of HE is initiation of measures to correct hyperammonemia. Given the difficulty in identifying a single threshold cutoff value that may be generalized to rule out HE, these measures should be initiated in ESLD patients if there is a high clinical suspicion for HE regardless of ammonia levels (**Box 1**).

- Lactulose should be initiated at 20 g orally, and dosing should be titrated to achieve 3 to 4 soft stools per day. A 2016 Cochrane review concluded that there is moderate-quality evidence that lactulose reduces mortality as well as serious complications.[7]
- Rifaximin should be simultaneously initiated at 400 to 550 mg orally. A meta-analysis of 19 trials concluded that the addition of rifaximin appears to significantly reduce mortality in HE.[8]

Box 1
Key points: hepatic encephalopathy

Assessment

- Is HE the primary cause of altered mental status?
- If so, what has precipitated the HE?

Key precipitants of HE: gastrointestinal bleeding, sepsis, hypokalemia, dehydration (usually caused by overdiuresis), constipation, and alcohol/benzodiazepine use.

Blood ammonia levels cannot be used in a straightforward manner to rule in or rule out the diagnosis of HE.

Management

- Airway management
- Correct precipitating causes (correction of bleeding, volume resuscitation, electrolyte repletion, antibiotics, control of hemorrhage)
- Correct hyperammonemia (lactulose + rifaximin)

VARICEAL UPPER GASTROINTESTINAL BLEEDING

Pathophysiology

Among ESLD patients presenting with upper gastrointestinal bleeding (GIB), variceal bleeding is the underlying cause in approximately 60% of patients.[9] The outcomes for patients with variceal bleeding are closely correlated with the severity of liver disease, and mortality rates as high as 40% in patients with the most severe disease.[10]

Esophageal varices are a consequence of portal hypertension.

- Portal hypertension initially occurs in response to hepatic vascular bed distortion.
- Splanchnic vasodilatation occurs in response to increased resistance to portal blood flow, precipitating sodium and water retention, which further exacerbates portal hypertension.
- The development of portal-collateral circulation is a direct result of portal hypertension, with a minimum threshold hepatic venous pressure gradient of greater than 10 mm Hg for the development of esophageal varices.

Emergency Critical Care Assessment

Patients with variceal hemorrhage typically present with hematemesis and/or melena, but the clinician should be alert for occult bleeding episodes in patients presenting with altered mental status or shock. Large volumes of blood may collect in the upper gastrointestinal tract before the patient begins to have active hematemesis, and as such upper GIB should remain on the differential even in the absence of an overt history of bleeding. A disproportionately elevated blood urea nitrogen level may be a clue to an occult upper GIB.

Mortality resulting from acute massive hemorrhage has improved significantly with the advent of endoscopic variceal band ligation. A significant proportion of the mortality associated with variceal bleeding episodes is in fact due to complications that develop secondary to bleeding and massive transfusion as opposed to mortality caused by hemorrhagic shock during the acute bleeding episode. It is not unusual for multiple complications to develop simultaneously. Major complications include:

- Aspiration pneumonia
- Sepsis
- HE
- Renal failure

Emergency Critical Care Management

There are 3 primary goals of management during an acute episode of variceal bleeding:

1. Hemodynamic stabilization and blood product resuscitation
2. Treatment and prevention of complications
3. Hemorrhage control

Hemodynamic stabilization and blood product resuscitation

- In the setting of acute bleeding in the hemodynamically stable patient, a transfusion threshold of hemoglobin greater than 7 seems to be safe and is in fact associated with a lower risk of rebleeding than higher transfusion thresholds.[11]

- In the patient with evolving hemodynamic instability or massive exsanguinating bleeding, the patient's hemodynamics and ongoing assessment of end-organ perfusion should guide blood product resuscitation as opposed to a hemoglobin target.
- It is important to closely monitor these patients to avoid overtransfusion. Significant volume overload can be particularly problematic in the context of acute variceal bleeding because of the potential for rebound portal hypertension and resultant rebleeding.[12]

Treatment and prevention of complications

Although prophylactic intubation in a general population of patients with an upper GIB has not been shown to improve outcomes—and may in fact be associated with increased rates of hospital acquired pneumonia—early intubation should be pursued in patients with altered mental status and/or massive bleeding.

Bacterial infection is commonly found in the ESLD patient with acute variceal bleeding.[13] It remains unclear whether infection tends to precipitate bleeding or whether bleeding tends to precipitate infection, or both.

- Endotoxin released during bacterial infection can result in increased portal pressure via activation of endothelin activation and vasoconstrictive cyclooxygenases.[14]
- Increased bacterial translocation and complement deficiencies have been noted in ESLD patients during acute bleeding episodes.[13]

Irrespective of the direction of this effect, administration of prophylactic antibiotics in ESLD patients with variceal bleeding has been shown to significantly reduce the incidence of sepsis, rebleeding events, duration of hospitalization, and mortality.[15]

- Given the increasing rates of quinolone resistance, ceftriaxone 1 g is the preferred antibiotic choice, and should be initiated before endoscopy.

Hemorrhage control

Primary treatment of acute variceal bleeding is endoscopic variceal band ligation. Endoscopy should be done as soon as possible in a patient with clinically significant bleeding, and should not be delayed for more than 12 hours after presentation, as per the 2016 American Association for the Study of Liver Disease guidelines.[16]

There is also a supportive role for vasoactive medications to achieve hemostasis (**Box 2**).

- Use of octreotide or somatostatin has been associated with decreased length of stay in hospital and transfusion requirements,[17] and combination therapy with octreotide or somatostatin and band ligation has been shown to improve rates of successful hemorrhage control compared with band ligation alone, although no effect was found on mortality.[18]
- Octreotide (50 μg bolus followed by a drip at 50 μg/h) is the preferred vasoactive agent to potentiate hemorrhage control in ESLD patients with variceal bleeds. Given the high prevalence of nonvariceal bleeds in this population, it is reasonable to administer pantoprazole while awaiting endoscopy.
- Balloon tamponade can be performed as a temporizing measure, and the emergency physician should acquire familiarity with the equipment and the detailed steps required to successfully perform this relatively rare intervention in an emergent situation.

Box 2
Key points: variceal bleeding

Hemodynamic stabilization and blood product resuscitation

- Guided by hemodynamics and perfusion indices
- Close monitoring to avoid overtransfusion

Treatment and prevention of complications

- Complications arising from bleeding and massive transfusion contribute significantly to mortality from active hemorrhage: aspiration pneumonia, sepsis, acute-on-chronic liver failure, HE, and renal failure
- Early intubation, antibiotics

Hemorrhage control

- Octreotide
- Endoscopic variceal ligation
- Balloon tamponade as a temporizing measure

COAGULOPATHY AND HEMORRHAGE

Pathophysiology

Patients with ESLD are in a state of hemostasis disequilibrium whereby susceptibility to both bleeding and clotting may be increased, with the relative balance different for each patient.

- Patients with severe liver disease should not be assumed to be "autoanticoagulated" or at risk of bleeding based on standard coagulation testing, which does not give a full picture of the complex interplay of the simultaneously ongoing procoagulant and anticoagulant changes in these patients.

Coagulopathy in ESLD is multifactorial:

- *Decreased platelet number and function*. Thrombocytopenia results from a combination of splenic sequestration and decreased hepatic thrombopoietin production.
- *Decreased production of clotting factors*. The liver is responsible for production of almost all clotting factors, and ESLD patients may have severely diminished levels of clotting factors.
- *Increased fibrinolysis*. Systemic fibrinolysis occurs in up to 50% of patients with ESLD and corresponds to the degree of liver dysfunction. Hyperfibrinolysis promotes premature clot dissolution, and the associated consumption of clotting factors interferes with clot formation.
- *Poor nutritional status*. In a subset of patients with liver disease, particularly those actively using alcohol and/or with poor baseline nutritional status, vitamin K deficiency can further exacerbate deficiencies of vitamin K–dependent clotting factors.

Emergency Critical Care Assessment

Assessment of coagulopathy

The best way to assess coagulopathy in ESLD patients is viscoelastic testing, including thromboelastography (TEG) or thromboelastometry (ROTEM), which give a global picture of clot kinetics that represents the true state of their coagulopathy better than traditional measures such as INR.

- Numerous studies have shown that management of bleeding in ESLD patients guided by viscoelastic testing, as opposed to standard assays, significantly decreases the amount of product given without worsening outcomes, and in some cases has even been associated with improved outcomes.[19–21]

Emergency Critical Care Management

In any actively bleeding ESLD patient, the clinician should monitor platelets and fibrinogen levels, as well as following global assay of hemostasis such as TEG or ROTEM, when available.

- The decision of which products to administer should be based on the deficiencies identified on viscoelastic testing that are contributing to impaired clot formation rather than a single laboratory measurement.
- Management decisions should be unaffected by results of prothrombin time/INR and activated partial thromboplastin time testing. If there is significant ongoing hemorrhage and the clinician does not have access to thromboelastography, a 1:1:1 transfusion strategy is reasonable.
- Cryoprecipitate should be administered to maintain a fibrinogen level $\geq$100 mg/dL.
- Platelets should be administered to maintain a platelet count greater than 50,000 for active, severe, or CNS bleeding.
- Platelet dysfunction may be evaluated to some degree by viscoelastic testing. If there is severe ongoing bleeding and platelet function is thought to be impaired, the clinician may consider platelet transfusion independent of platelet count.

Avoid overtransfusion

- The pathophysiology of hemorrhage in ESLD is complex. The increased propensity to bleeding is not fully explained by the various abnormalities of hemostasis seen on laboratory testing, and hemodynamic dysregulation consequent to portal hypertension may be at least as relevant as coagulopathy.[22]
- The clinician must carefully weigh the benefits of giving additional blood products in an attempt to optimize coagulopathy against the potential for increasing portal pressure, especially in a patient with varices, even if these are not the site of acute bleeding.

Prothrombin complex concentrate and recombinant factor VIIa PCC

Therapies such as PCC and rFVIIa should generally be avoided in ESLD patients.

- These products are quite costly and have not been shown to meaningfully affect outcomes.
- Recall that ESLD patients may also be expected to have prothrombotic tendencies. PCC and rFVII carry a greater thrombotic risk, and how that plays out in a given patient may be unpredictable.

Vitamin K

Vitamin K should be administered to patients at risk of vitamin K deficiency.

- Risks for vitamin K deficiency include poor nutritional status, active alcohol use, cholestatic disease, active diarrheal disease, or prolonged antibiotic use.
- If it is unknown whether the patient has any of these risk factors, it is reasonable to give vitamin K in the acutely bleeding patient.

- For major bleeding episodes, a single dose of 10 mg of vitamin K should be given as a slow infusion no faster than 1 mg/min.

Hypocalcemia

Hypocalcemia can become a significant problem during massive transfusion in ESLD patients (**Box 3**).

- In healthy patients, the half-life of citrate, which binds to calcium, is only a few minutes; however, in the setting of severe hepatic dysfunction compounded by hypotension, hypothermia, and acidosis, the metabolism of citrate can be fairly prolonged.
- It is important to trend ionized calcium levels and give adequate calcium repletion during massive transfusion.
- Evidence suggests that calcium gluconate does not require hepatic metabolism and is as effective as calcium chloride even in patients with absent liver function.[23]

SEPSIS AND BACTERIAL PERITONITIS

Pathophysiology

ESLD patients have greater susceptibility to bacterial infections than the general population and also have a higher risk of sepsis-associated mortality.

- The response to infection in patients with ESLD is often associated with dramatic cytokine imbalances characterized by a disproportionate inflammatory response, and consequent increased risk for the development of septic shock.
- In ESLD patients with sepsis, the resulting hemodynamic failure is more marked, partially because of the severe vasoplegia patients often exhibit at baseline.

Bacterial peritonitis is a frequent cause of sepsis in these patients that is not generally seen outside this population.

- ESLD predisposes to the development of bacterial peritonitis resulting from bacterial overgrowth and microbiome disturbances caused by altered intestinal motility, as well as increased intestinal permeability.

Emergency Critical Care Assessment

ESLD patients with bacterial infections may not present classically. Use of lactate to assess severity and trajectory of early sepsis may be challenging because of significant impairments in lactate clearance. However, acute increase in serum lactate level

Box 3
Key points: coagulopathy

- Pathologically rebalanced hemostasis → both bleeding and thrombosis are increased
- ESLD with or without coagulation abnormalities should not be assumed to be "autoanticoagulated"
- Risks of bleeding and thrombosis are not reflected in the conventional indices, and blood product administration should not be based on these indices, especially in the absence of acute bleeding
- Management of active bleeding in ESLD patients should ideally be guided by viscoelastic testing, which has been shown to significantly decrease the amount of product as well as improving outcomes
- Hypocalcemia can become a significant problem during massive transfusion in ESLD patients, and calcium should be closely monitored and aggressively repleted

is associated with very high mortality rates in the population,[24] and emergency physicians should *not* reflexively attribute an elevated lactate to underlying liver disease in the acute phase of care.

Bacterial peritonitis should be suspected in patients with ESLD who develop fever, abdominal pain, altered mental status, abdominal tenderness, or hypotension.

- The abdominal examination in patients with bacterial peritonitis can be deceptively benign. Ascites can prevent the development of classic peritoneal signs by creating a separation between the visceral and parietal peritoneum.

Primary versus secondary bacterial peritonitis

Although secondary bacterial peritonitis only represents approximately 5% of cases, it is critical to distinguish between the two as early as possible.

- The mortality of secondary bacterial peritonitis approaches 100% if treatment consists only of antibiotics without appropriate surgical intervention.[25]
- The mortality of primary bacterial peritonitis is approximately 80% if a patient receives an unnecessary exploratory laparotomy.[26]

Primary bacterial peritonitis is confirmed by a polymorphonuclear cell count in the ascitic fluid of $\geq$250 cells/mm^3.

Secondary bacterial peritonitis may be associated with perforation peritonitis, but also with other processes such as an intra-abdominal abscess. Secondary spontaneous bacterial peritonitis (SBP) should be suspected when a least 2 of the following ascitic fluid findings are present:

- Total protein greater than 1 g/dL
- Glucose less than 50 mg/dL
- Lactate dehydrogenase greater than upper limit for serum

In addition, cultures showing a polymicrobial infection or a Gram stain demonstrating numerous different bacterial forms are strongly suggestive of intestinal perforation and secondary bacterial peritonitis.

Patients in whom there is a suspicion of secondary bacterial peritonitis should undergo an emergency computed tomography scan of the abdomen.

Emergency Critical Care Management

The vast majority of bacterial peritonitis cases are primary (**Box 4**).

Box 4
Key points: sepsis and bacterial peritonitis

- ESLD patients are more prone to infection and also more likely to have severe hemodynamic sequelae attributable to infection
- Initial diagnostic workup should focus on differentiating primary and secondary SBP
- Secondary SBP is only 5% of all SBP, but mortality approaches 100% if this diagnosis is missed
- Mortality is low if treatment was started before shock or acute renal failure

Treatment

- Cefotaxime 2 g intravenously every 8 hours
- Albumin (1.5 g/kg within 6 hours of diagnosis and 1 g/kg body weight on day 3)
- Pressor support $\pm$ octreotide if renal failure has already developed

Antibiotics

The infection-related mortality from SBP is relatively low with appropriate treatment, and mortality is close to zero for patients in whom treatment was initiated before the development of shock or renal failure.[27]

- In patients with fever, abdominal tenderness, or altered mental status, treatment should be started as soon as ascitic fluid and blood cultures have been obtained.
- In patients without these findings, it is reasonable to wait until the results of the ascitic fluid cell counts are available.
- Cefotaxime 2 g intravenously every 8 hours is the preferred treatment of SBP because it has been shown to produce excellent ascitic fluid levels. Ceftriaxone may also be used at 2 g every 24 hours.

Albumin

Renal failure develops in up to 40% of patients with SBP, and portends a significantly worse prognosis.[28]

- Albumin infusion in patients with SBP has been associated with a significant decrease in the incidence of renal impairment (8% vs 31%) and a significant reduction in mortality (16% vs 35%).[29]
- Albumin 1.5 g/kg should be given within 6 hours of diagnosis of SBP if any of the following criteria are met:
  - Creatinine is >1 mg/dL
  - Blood urea nitrogen is >30 mg/dL
  - Bilirubin is >4 mg/dL

HEPATIC HYDROTHORAX

Pathophysiology

Hepatic hydrothorax refers to a pleural effusion in a patient with decompensated liver failure that is not secondary to a cardiopulmonary, malignant, or other primary process.

- A hepatic hydrothorax is generated when negative intrathoracic pressure during inspiration promotes the passage of ascitic fluid from the abdominal cavity into the pleural space via small diaphragmatic defects.
- Diaphragmatic defects are frequently found in the right hemidiaphragm because the left hemidiaphragm is more muscular and thicker than the right. There have been case reports of patients with confirmed hepatic hydrothorax without the presence of clinically significant ascites,[30] presumably because most of the fluid ends up in the pleural space rather than the peritoneal space.

Similar to SBP in patients with abdominal ascites, approximately 15% of patients with hepatic hydrothorax may develop spontaneous bacterial empyema when the pleural effusion is seeded with bacteria spreading directly from the abdominal cavity.[31] Approximately one-half of cases of spontaneous bacterial empyema (SBEM) are associated with SBP, and the pathogens tend to be the same as those associated with SBP. Unlike SBP, SBEM is associated with high mortality rates, approaching 40%.[31]

Emergency Critical Care Assessment

Patients with hepatic hydrothorax can present with severe symptoms with relatively small volumes (~500 mL) present.

- Patients with hepatic hydrothorax commonly present with shortness of breath, pleuritic chest pain, cough, fatigue, and hypoxemia.
- Hepatic hydrothorax develops on the right in approximately 80% of patients, on the left in approximately 15% of patients and bilaterally in approximately 5% of patients.
- Occasionally patients may present with hemodynamic instability resulting from a tension hydrothorax.

SBEM should be suspected in patients with hepatic hydrothorax who also present with fever, encephalopathy, and/or unexplained acute kidney injury. Diagnostic criteria for SBEM include:

- Positive pleural fluid culture AND polymorphonuclear (PMN) cell count greater than 250 cells/mm^3
- Negative pleural fluid culture AND PMN count greater than 500 cells/mm^3
- No evidence of pneumonia on a chest imaging study

Emergency Critical Care Management

Patients who are severely symptomatic should undergo a therapeutic thoracentesis.

- Care should be taken to limit fluid removal to 1 to 2 L on initial thoracentesis, owing to concerns of precipitating negative pressure pulmonary edema, or even hepatorenal syndrome (HRS).

Patients presenting with SBEM should be administered ceftriaxone 2 g every 24 hours, with levofloxacin as an alternative agent in penicillin-allergic patients.

Occasionally chest tube placement may be necessary in patients with SBEM with frank pus or loculations; however, chest tubes should *not* be placed routinely for the treatment of hepatic hydrothorax (**Box 5**).

- Chest tube placement in these patients can result in massive protein and electrolyte losses, and there is no clear end point for chest tube removal because of continuous reaccumulation of fluid.
- Chest tube placement in ESLD patients with hepatic hydrothorax has been associated with numerous complications including infection, renal failure, empyema, bleeding, and an increased risk of mortality.

Box 5
Key points: hepatic hydrothorax

- Generally in the right hemithorax, but may also occur on the left or bilaterally
- Patients with hepatic hydrothorax may develop spontaneous bacterial empyema (SBEM), which is associated with a very high mortality rate
- Consider a diagnostic thoracentesis to rule out SBEM in patients with fever, encephalopathy, sepsis, and/or unexplained worsening renal function
- Treat SBEM with ceftriaxone 2 g every 24 hours
- Patients who are severely symptomatic should undergo therapeutic thoracentesis followed by diuretics
- Chest tubes should *not* be placed for the treatment of hepatic hydrothorax
- Placement of chest tubes in patients with hepatic hydrothorax → massive protein and electrolyte depletion, infection, renal failure, empyema, and bleeding, and is associated with increased mortality

HEPATORENAL SYNDROME

Pathophysiology

HRS arises from the progressive systemic vasodilation superimposed on profound renal vasoconstriction in patients with ESLD.

- Portal hypertension leads to profound splanchnic vasodilation, which ultimately leads to progressively worsening vasoplegia and a hyperdynamic circulation, thought to be predominantly mediated by nitric oxide dysregulation.
- These changes result in a decrease in effective arterial circulating volume, stimulating compensatory activation of the rennin-angiotensin-aldosterone system, ultimately leading to intense renal vasoconstriction and hypoperfusion.
- Resultant renal ischemia then increases production of intrarenal vasoconstrictors, further compromising renal hemodynamics and function.

Emergency Critical Care Assessment

HRS is just one of many possible causes of acute renal failure in patients with ESLD and is a diagnosis of exclusion that carries a very poor prognosis, with a 3-month mortality approaching 60%.[32]

- Mortality is significantly lower in ESLD patients with acute renal failure that is secondary to prerenal causes. Volume depletion, as may occur frequently in these patients with overly aggressive diuresis, can closely mimic HRS.

HRS is characterized by:

- Rising serum creatinine
- Oliguria
- Normal urine sediment
- Zero or minimal proteinuria
- Urine Na less than 10 mEq/L

Because HRS can be difficult to differentiate from prerenal causes of acute renal failure, the diagnosis also requires failure of improvement with fluid resuscitation and discontinuation of any nephrotoxic agents.

Emergency Critical Care Management

Critically ill patients with HRS should be treated with norepinephrine in combination with albumin.[33]

- Although the only definitive treatment of HRS is liver transplantation, vasopressors appear to improve rates of HRS reversal (34%–44% vs 9%–13%).[34] Previously, terlipressin was considered the vasopressor of choice; however, recent evidence has shown that norepinephrine has similar efficacy with fewer adverse events.[35] In patients who are critically ill, norepinephrine should be administered to elevate the mean arterial pressure to 10 to 15 mm Hg above baseline.
- In patients with HRS who are not critically ill and do not otherwise require ICU admission, octreotide plus midodrine should be initiated.
- Albumin is given for at least 3 days as an intravenous bolus (~1 g/kg per day). A recent meta-analysis found a dose-response relationship between 100-g increments of albumin dose and survival; over a cumulative dose range of 200 to 600 g, 30-day survival increased from 43% to 59%.[36]

ESLD patients who develop HRS and require dialysis have an extremely poor prognosis unless they are listed for liver transplantation.

Box 6
Key points: hepatorenal syndrome

- HRS is a diagnosis of exclusion
- Prognosis for acute kidney injury (AKI) caused by HRS is significantly worse than for other causes of AKI in ESLD patients

Renal replacement therapy (RRT) should be offered as a bridge to patients awaiting liver transplantation.

- Continuous RRT may be preferred in patients who are unlikely to hemodynamically tolerate intermittent hemodialysis and in patients with HE

Treatment of HRS

- Albumin 1 g/kg/d × 2 days PLUS either norepinephrine in patients who are critically ill OR octreotide and midodrine for patients who do not otherwise require ICU admission

- Provision of renal replacement therapy (RRT) should be offered as a bridge to patients awaiting liver transplantation or those undergoing liver transplant evaluation.
- Provision of long-term RRT is generally not indicated in ESLD except as a trial while awaiting return of renal function.

Hemodialysis is frequently difficult to perform in patients with HRS (**Box 6**).

- The combination of baseline vasoplegia and hypoalbuminemia makes ESLD patients poorly tolerant of rapid fluid shifts and, as such, continuous RRT may be a better tolerated modality, particularly in patients in whom HRS is precipitated by sepsis or upper GIB.

SUMMARY

Critically ill ESLD patients routinely and rapidly develop multiorgan system dysfunction. Although these patients are profoundly ill in the acute phase, they have relatively good intermediate-term outcomes if they can survive to hospital discharge. In the emergency department, clinicians should focus on identification and correction of underlying causes of acute decompensation while anticipating and preventing downstream complications. Pathophysiology and management pearls for critical illness specific to ESLD described in this article can help emergency department physicians achieve these goals.

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