

# Update in Nonpulmonary Critical Care

## Advances in Critical Care Hepatology

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Liver disease is a major source of morbidity and mortality in the intensive care unit (ICU). Cirrhotic patients admitted to the medical ICU have increased mortality (40 to 90%) and a poor prognosis (1). This article addresses specific management issues for conditions the intensivist is often called on to treat, including fulminant hepatic failure, complications of chronic liver disease such as ascites and hepatorenal syndrome, and sepsis-induced liver dysfunction.

### FULMINANT HEPATIC FAILURE

Fulminant hepatic failure is a clinical syndrome characterized by the rapid onset of hepatic encephalopathy in conjunction with a marked decline in hepatic synthetic function within 28 days of the onset of symptoms in those without a history of chronic liver disease (2). The National Institutes of Health Acute Liver Failure Study Group reported the etiology of fulminant hepatic failure in 308 patients as follows: acetaminophen hepatotoxicity (39%), idiosyncratic drug reaction (13%), hepatitis B (6%), hepatitis A (6%), and indeterminate cause (17%) (3). Overall survival is poor without liver transplantation, with a reported mortality of 90 to 97% (4). The advent of liver transplantation and aggressive medical care in the ICU has improved the mortality rate (5).

### Diagnosis

Hepatic encephalopathy and severe coagulopathy are the hallmark features of fulminant hepatic failure (6). Severe coagulopathy often precedes evolution of hepatic encephalopathy to coma. Patients with fulminant hepatic failure can rapidly progress from mild hepatic encephalopathy to deep coma (Table 1) (7). As soon as the diagnosis is made, it is important to establish the cause. Certain etiologies demand immediate specific treatment, including *N*-acetylcysteine for acetaminophen ingestion, penicillin for *Amanita* mushroom poisoning, delivery of the infant in acute fatty liver of pregnancy, or zinc and trientine therapy for Wilson's disease. Patients should be admitted to the ICU and transferred to a transplantation center, given that liver transplantation is the only effective therapy for this devastating disease (8).

### Management

Management starts with supportive measures including nutrition (amino acids, lipids, glucose, and essential elements), electrolyte balance, frequent glucose monitoring (< every 6 hours), aspira-

tion precautions, and fluid maintenance. Neurologic evaluation, a critical guide to therapy, should be performed at least every 6 hours. The presence of severe coagulopathy, due to the decreased synthesis of clotting Factors II, V, VII, and IX, is manifested by a prolonged prothrombin time. Current recommendations are to correct coagulopathy with fresh frozen plasma intravenously only when overt bleeding occurs or when an invasive procedure is planned. Recombinant Factor VIIa has been shown to be safe and effective in reversing the coagulopathy in patients with fulminant hepatic failure (9). The protocol is to infuse 80  $\mu$ g/kg after infusion of 4 units of fresh frozen plasma. This can normalize prothrombin time for up to 6 hours. Hypoglycemia, seen in up to 45% of patients with fulminant hepatic failure, requires aggressive glucose administration, often with 10% dextrose via central venous access (10).

Infection in patients with fulminant hepatic failure is a major source of mortality, as 44 to 80% of patients with fulminant hepatic failure develop bacterial infections. Empiric, broad-spectrum antibiotics should be initiated on clinical suspicion of infection (11).

Cerebral edema is a common complication of fulminant hepatic failure, occurring in up to 80% of patients with Grade IV coma, but requires a high level of clinical suspicion. The diagnosis may be difficult to establish as head computed tomography scan is insensitive, being useful only to rule out hemorrhage, and clinical signs of cerebral edema, such as decerebrate posturing, systemic hypertension, and pupillary abnormalities, are typically observed only in advanced disease. Cerebral edema often leads to intracranial hypertension and subsequent herniation of the cerebral uncus, cerebral ischemic injury, and death (12). Intracranial hypertension can also cause a reduction in the cerebral perfusion pressure (mean arterial pressure minus intracranial pressure), which may produce cerebral ischemia. A cerebral perfusion pressure of more than 60 mm Hg is crucial to maintain intact neurologic function (13).

Direct intracranial pressure monitoring is recommended in patients suspected of cerebral edema or intracranial hypertension, with a target intracranial pressure of less than 20 mm Hg (14). The placement of extradural intracranial pressure monitors is considered safer than subdural catheters. Recombinant Factor VIIa can reverse coagulopathy in those patients requiring intracranial pressure monitor placement (15), and may prove preferable to fresh frozen plasma if additional studies are confirmatory. The patient's head should be elevated 10 to 20°. Maneuvers that increase intracranial pressure, such as tracheal suction or high positive end-expiratory pressure, should be avoided. Use of sedation is usually avoided so that mental status may be assessed. However, an agitated patient with Grade III coma may require the use of short-acting benzodiazepenes, the preferred agents (16). Mannitol is first-line therapy for treating cerebral edema and intracranial hypertension, administered at 0.3 to 0.4 g/kg body weight. In patients with renal failure, mannitol may accumulate in astrocytes and cause increased rebound swelling (17). Thiopental may be used in this setting (250 mg over 15 minutes). Hyperventilation may also reduce cerebral edema, but it is effective only for a few hours.

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TABLE 1. GRADES OF HEPATIC ENCEPHALOPATHY

Grade	Mental Status	Asterixis	Electroencephalogram
I	Euphoria/depression Mild confusion Slurred speech Disordered sleep	Yes/No	Usually normal
II	Lethargy Moderate confusion	Yes	Abnormal
III	Marked confusion Incoherent	Yes	Abnormal
IV	Sleeping but arousable Coma	No	Abnormal

In one case series, seven patients with fulminant hepatic failure were given propofol for deteriorating cerebral edema (18). A decrease in intracranial pressure was seen in five patients. However, only three survived, with one undergoing liver transplantation. Additional studies are needed before a recommendation to use propofol in this setting can be made. Another therapeutic adjunct, moderate hypothermia to 32–33°C, may be useful in decreasing intracranial pressure as a bridge to liver transplantation (19), or while transplantation is being performed (20).

Liver transplantation offers the best long-term survival with an overall, posttransplantation 1-year survival of about 60% (21). Unfortunately, prediction of the need for transplantation remains problematic. The King's College Hospital criteria are the most widely used prognostic indicator for survival in fulminant hepatic failure (22). These criteria include an arterial pH of less than 7.30 after adequate fluid resuscitation, or the combination of a prothrombin time greater than 100 seconds, a creatinine level greater than 3.3 mg/dl, and Grade III or IV encephalopathy. These criteria exhibit a sensitivity, specificity, positive predictive value, and negative predictive value of 55, 94, 87, and 78%, respectively. A metaanalysis investigated several prognostic criteria for determining the need for liver transplant in acetaminophen-induced fulminant hepatic failure including King's College criteria, pH, prothrombin time, Factor V levels, and creatinine, but found that none of these was sufficiently sensitive in predicting the need for liver transplantation (23). Arterial blood lactate greater than 3.5 mmol/L 4 hours after presentation to the hospital has been shown to have a sensitivity of 67%, a specificity of 95%, a positive likelihood ratio of 13%, and a negative likelihood ratio of 35% for survival in acetaminophen-induced fulminant hepatic failure (24).

#### Advances in Artificial and Bioartificial Support Systems

Short-term extracorporeal support for patients with fulminant hepatic failure may ultimately serve to improve overall survival and provide support as a bridge to liver transplantation, but remains experimental. A metaanalysis of artificial and bioartificial support systems for fulminant hepatic failure examined a total of 8 randomized controlled trials, involving 139 patients, and found no improvement in mortality compared with standard supportive care (relative risk, 0.95; 95% confidence interval, 0.71–1.29) (25). In addition, the interventions were not found to be useful as a bridge to liver transplantation (relative risk, 0.60; 95% confidence interval, 0.29–1.23). The support systems appeared to have an increased risk of bleeding associated with their use. A future option is hepatocyte transplantation. In one series, three of six patients with fulminant hepatic failure survived between 14 and 52 days after transplantation of 10<sup>10</sup> human hepatocytes (26). To date, no randomized, controlled studies have examined this therapeutic option.

#### Summary Recommendations

Once the diagnosis is made, all necessary supportive measures should be employed in an ICU setting. Neurologic evaluation and glucose monitoring should be performed frequently. Coagulopathy should be corrected when there is overt bleeding or an invasive procedure is planned. An emergent head computed tomography scan should be performed if there is a change in mental status or signs of increased intracranial pressure. Intracranial pressure monitoring is recommended to maintain an adequate cerebral perfusion pressure of greater than 60 mm Hg. Currently, liver transplantation offers the best long-term survival in patients likely to die of fulminant hepatic failure.

#### ASCITES

The cause of ascites is frequently determined by diagnostic paracentesis. The serum-to-ascites albumin gradient has been shown to be effective in differentiating portal hypertensive from nonportal hypertensive ascites (27). A serum-to-ascites albumin gradient greater than 1.1 suggests it is portal hypertension due to cirrhosis, Budd-Chiari syndrome (hepatic vein or inferior vena cava thrombosis), cardiac disease, portal vein thrombosis, myxedema, or liver metastasis. A serum-to-ascites albumin gradient less than 1.1 suggests nonportal hypertensive ascites due to malignancy, pancreatic disease, bile leak, infections, or nephrosis.

When portal hypertensive ascites is confirmed, an abdominal ultrasound should be performed to evaluate portal and hepatic veins. Rapid recognition is required for acute Budd-Chiari syndrome, acute portal vein thrombosis, and myxedema, to administer specific therapies. In cirrhotic patients, paracentesis is diagnostic of spontaneous bacterial peritonitis when more than 250 neutrophils/mm<sup>3</sup> are found in the ascitic fluid sample (sensitivity, 85%; specificity, 93%; diagnostic accuracy, 95%) (28). Studies suggested that reagent strips may provide a more rapid diagnosis of spontaneous bacterial peritonitis (29), although additional confirmatory studies are required before widespread acceptance (30). Spontaneous bacterial peritonitis has a 1-year mortality of 40% despite treatment with antibiotics (31). A polymicrobial culture raises the suspicion for intestinal perforation or abscess formation. In the setting of nonportal hypertensive ascites, ascitic fluid amylase, bilirubin, and cultures are important determinates of etiology. Cytology can be obtained subsequently via large-volume paracentesis. If there is no obvious etiology, a diagnostic laparoscopic examination may determine malignant or infectious peritoneal implantation.

#### Management

The treatment is directed to the cause of the ascites. Common cirrhotic ascites is managed with diuretics and sodium restriction. Although rapid diuresis can precipitate hepatorenal syndrome and should be avoided, large-volume paracentesis (greater than 5 L) has been shown to be safe and effective, regardless of the etiology of ascites. When performing large-volume paracentesis in patients with cirrhosis, an infusion of 6 to 8 g of albumin per liter removed prevents the development of hemodynamic embarrassment often associated with large fluid shifts (32). In the setting of greater than 250 neutrophils/mm<sup>3</sup> in the ascitic fluid sample, empiric antibiotics should be considered expeditiously (33); a third-generation cephalosporin is most frequently employed in this setting (34, 35). Some recommend similar therapy in patients with clinical suspicion of spontaneous bacterial peritonitis even if the ascitic fluid count is less than 250 neutrophils/mm<sup>3</sup> (33). In the setting of spontaneous bacterial peritonitis intravenous albumin at 1.5 g/kg of body weight at the time of diagnosis, followed by 1 g/kg on Day 3, was effective in preventing hepatorenal syndrome in one unblinded, randomized

study (36); the greatest benefit may have been noted in patients with more advanced liver disease or impaired renal function (34). A Model for End-stage Liver Disease score greater than 15 is effective at predicting a significant risk of hepatic decompensation, encephalopathy, and subsequent poor survival of patients undergoing transjugular intrahepatic portosystemic shunt (37). In general, candidates would exhibit bilirubin at less than 3 mg/dl, an international normalized ratio of less than 2, creatinine less than 2 mg/dl, and less than Grade II encephalopathy. However, when the management of ascites is critical, such as ventral hernia rupture or hepatic hydrothorax causing persistent respiratory failure, a transjugular intrahepatic portosystemic shunt can be placed to help control ascites, regardless of the model for end-stage liver disease score (38). In contrast to an earlier study in which the use of albumin was less regular (39), a more recent randomized trial found no survival benefit with transjugular intrahepatic portosystemic shunt when compared with paracentesis with albumin administration (40). Although ascites recurred less often, overall cost and the development of severe hepatic encephalopathy were greater in the transjugular intrahepatic portosystemic shunt group.

Hepatic hydrothorax, usually right sided, may be seen when ascitic fluid tracks up into the thorax through defects in the diaphragm, and can cause respiratory embarrassment. Treatment of hepatic hydrothorax is usual ascitic care, including salt restriction and diuretics. Thoracentesis may be performed therapeutically with albumin replacement. Tube thoracostomy should be avoided, as drainage is usually persistent, making tube removal difficult and increasing the risk of infection. In refractory hydrothorax, a transjugular intrahepatic portosystemic shunt has been shown to be an effective alternative (41).

### Summary Recommendations

Patients with ascites in the intensive care setting should undergo diagnostic paracentesis to rule out infection and to obtain the serum-to-ascites albumin gradient. Treatment depends on the underlying etiology of the ascites. Large-volume paracentesis (more than 5 L) is generally safe in patients with cirrhosis, when given albumin to prevent hypotension. If spontaneous bacterial peritonitis is diagnosed, albumin infusion and antibiotics have been shown to prevent hepatorenal syndrome. A transjugular intrahepatic portosystemic shunt is indicated when control of the ascites or hepatic hydrothorax is important for management of the critically ill patient.

## HEPATORENAL SYNDROME

Hepatorenal syndrome occurs in patients with chronic liver disease and advanced hepatic failure. Hepatorenal syndrome is characterized by impaired renal function, abnormalities in the arterial circulation, and activity of the endogenous vasoactive system (42). Hepatorenal syndrome is classified into two types: Type I involves a doubling of initial serum creatinine to greater than 2.5 mg/dl or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 ml/minute in less than 2 weeks. Type II hepatorenal syndrome does not have a rapidly progressive course, involving an insidious increase in serum creatinine or a reduction in creatinine clearance over several months. Reversible prerenal azotemia, such as secondary to bacterial infection or drugs such as nonsteroidal antiinflammatory drugs or aminoglycosides, should be ruled out. The incidence of hepatorenal syndrome in patients with end-stage cirrhosis ranges between 7 and 15% (43). Predictive factors are sodium and water retention (indicated by a urinary sodium of less than 5 mEq/L and dilutional hyponatremia), low mean arterial blood pressure, poor nutrition, reduced glomerular filtration rate, high

plasma renin activity, and esophageal varices. The degree of liver failure assessed by the Child–Pugh classification does not correlate with the development of hepatorenal syndrome. Survival of patients with hepatorenal syndrome is poor, with a 60% mortality at 2 weeks for Type I patients.

Diagnostic criteria for hepatorenal syndrome established by the International Ascites Club include the following: creatinine greater than 1.5 mg/dl or 24-hour creatinine clearance less than 40 ml/minute; absence of shock, infection, or fluid losses; no improvement in renal function after diuretic withdrawal and expansion of plasma volume with 1.5 L of plasma expander; proteinuria less than 500 mg/day; and no evidence of parenchymal or obstructive renal disease (44).

### Management

Patients with hepatorenal syndrome should be managed by monitoring of urine output, patient weight, blood pressure, evaluation and replacement of electrolytes, and the institution of emergent procedures such as dialysis. Liver transplantation offers the best treatment, as it resolves circulatory and renal dysfunction and provides a 5-year posttransplantation survival rate of 70% (45). About 5% of patients progress to end-stage renal disease after transplantation and require hemodialysis. Few patients with hepatorenal syndrome undergo liver transplantation because of the small donor pool and long waiting lists.

### Advances in Treatment

Patients with refractory ascites treated with a transjugular intrahepatic portosystemic shunt may have a lower incidence of developing hepatorenal syndrome, and be less likely to progress from Type I to Type II hepatorenal syndrome (40). The molecular absorbent recirculating system has been proposed as a modality for the treatment of hepatorenal syndrome. Blood is dialyzed against an albumin-enriched dialysate to facilitate removal of albumin-bound toxins as well as bilirubin, aromatic amino acids, and water-soluble substances (46). A prospective, randomized controlled trial was performed to determine the effect of a molecular absorbent recirculating system on 30-day survival in 13 patients with Type I hepatorenal syndrome compared with standard medical treatment (47). All conventionally treated patients were dead by Day 7, but there were two survivors at 30 days among eight molecular absorbent recirculating system patients. There were five daily molecular absorbent recirculating system sessions, each lasting 6–8 hours, with significant decreases in bilirubin and creatinine in the treatment group. Larger trials are needed to assess the efficacy and safety of the molecular absorbent recirculating system for hepatorenal syndrome.

The combination of peripheral vasoconstrictors and plasma volume expanders has been utilized in an attempt to reverse the extreme vasodilation and decreased effective blood volume characteristic of hepatorenal syndrome. Terlipressin at 0.5 mg every 4 hours, plus albumin at a dosage of 1 g/kg the first day and 20–40 g/day thereafter, was associated with a marked reduction in serum creatinine, with survival and reversal of hepatorenal syndrome in 5 of 12 patients in one randomized trial (48). Terlipressin is not currently available in the United States.

### Summary Recommendations

Hepatorenal syndrome occurs in the setting of chronic liver disease and carries a high mortality. Early diagnosis is crucial. Hemodialysis can be used as a bridge to liver transplantation, which offers the best option for long-term survival. The new liver allocation scheme for transplantation prioritizes patients with hepatorenal syndrome. New treatments such as the molecular absorbent recirculating system and vasoconstrictors may provide

new options for the otherwise scarce armamentarium available to patients with hepatorenal syndrome.

## HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy involves a wide range of neuropsychiatric changes in patients with significant liver dysfunction (49). Different grades for hepatic encephalopathy are listed in Table 1. There are three clinical patterns for hepatic encephalopathy (50). Type A is related to acute liver failure as discussed above. Type B occurs in the setting of normal liver histology and the presence of a hepatic vascular bypass, such as portocaval shunting. Type C, due to cirrhosis, involves the majority of cases. Type C hepatic encephalopathy is divided into acute encephalopathy, which usually is spontaneous and a precipitant is identified, and chronic encephalopathy, which involves a recurrent and fluctuating course. Management issues discussed below pertain to acute Type C hepatic encephalopathy, the type commonly seen in the ICU setting.

### Management

Management includes supportive measures such as nutrition (amino acids, lipids, glucose, and essential elements), restoring electrolyte balance, fluid maintenance, and aspiration precautions, including rapid sequence intubation for Grade 3–4 hepatic encephalopathy. Intravenous lidocaine, given at 1 mg/kg, may be given to decrease laryngoscopy-induced intracranial pressure elevation, although this remains controversial in other settings (51). Precipitating factors, such as gastrointestinal bleeding, infection, alkalosis, hypokalemia, sedatives/tranquilizers, dietary proteins, azotemia, and progressive hepatic dysfunction, should be identified and treated (52). Empiric treatment with lactulose, a nonabsorbable disaccharide, should be initiated and titrated to about four bowel movements a day. Enteric flora modification with antibiotics, such as metronidazole or neomycin, is a second-line treatment, and can be used in combination with lactulose. A low-protein diet is required only in patients not improving with the above-described measures. The utility of blood ammonia levels in tracking changes in the depth of hepatic encephalopathy remains controversial (53).

“Endogenous benzodiazepines” may be present in patients with hepatic encephalopathy (54). Antagonism of such compounds with flumazenil has been proposed. In a trial of 560 patients with hepatic encephalopathy and changes in mental status, intravenous flumazenil improved mental status in 15% of patients, compared with 3% of placebo-treated control subjects (55). Metaanalyses suggested that flumazenil was associated with a significant improvement in encephalopathy compared with placebo, although the benefit was short term and may have been confined to patients who otherwise had a favorable prognosis (56, 57). Flumazenil has a role in the treatment of hepatic encephalopathy when there is suspected benzodiazepine use (52). A longer acting intravenous or oral formulation is not available.

### Advances in Treatment

The molecular absorbent recirculating system also has been studied for the treatment of hepatic encephalopathy, but to date no randomized controlled trials have been performed. Case series have evaluated this modality in about 60 patients with cirrhosis and hepatic encephalopathy (58). Neurologic improvement has been observed in the majority of patients, and the molecular absorbent recirculating system has served as an effective bridge to liver transplantation. L-Ornithine-L-aspartate administration has been shown to improve ammonia detoxification in several randomized trials in patients with hepatic encephalopathy (59). Significant improvements in neuropsychological testing, mental

state grade, and portosystemic encephalopathy index have been described. This agent is not presently available in the United States.

### Summary Recommendations

Hepatic encephalopathy occurs in patients with portal hypertension and cirrhosis. In the majority of cases a precipitant is identified, prompting appropriate therapy. The mainstay of treatment for hepatic encephalopathy is lactulose and alteration of gut flora. An ongoing multicenter, randomized study in the United States will determine whether the molecular absorbent recirculating system is effective for the treatment of severe hepatic encephalopathy.

## HEPATIC DYSFUNCTION IN SEPSIS

Acute-phase proteins generated by the liver during sepsis contribute to the procoagulant, antifibrinolytic state believed important in the development of multiple organ dysfunction syndrome and host survival (60, 61). Primary hepatic dysfunction results from hepatocellular injury, ostensibly due to poor perfusion during shock. This clinical entity, called ischemic hepatitis, occurs in the period immediately after shock and resuscitation, and is manifested by transaminase elevation, decreased lactate clearance, and often hypoglycemia (62). Cholestatic jaundice also occurs in the setting of sepsis, primarily in children and gram-negative infections (63). Hyperbilirubinemia develops in sepsis, particularly in the setting of bacteremia; in one series 34% of bacteremic patients had a total serum bilirubin level equal to or greater than 2.0 ml/dl (64). Bilirubin is elevated disproportionately to elevations in serum alkaline phosphatase and aspartate aminotransferase. Hyperbilirubinemia precedes positive blood cultures in one third of cases.

Patients with cirrhosis often manifest hyperdynamic circulation and coagulopathy, and may be mistakenly diagnosed as having sepsis with disseminated intravascular coagulation. High cardiac output, low systemic vascular resistance, and vasodilation-induced hypotension are seen with invasive hemodynamic monitoring (65). Accelerated intravascular coagulation and fibrinolysis, involving hyperfibrinolysis, intravascular coagulation, and thrombocytopenia, occurs in about 30% of cirrhotic patients as a function of increased disease severity. In addition, decreased synthesis of clotting factors and inhibitors results in prothrombin time prolongation. The diagnosis of disseminated intravascular coagulation in cirrhotic patients is aided by the presence of appropriate clinical circumstances, progressive worsening of thrombocytopenia and clotting times from baseline values, and a disproportionate reduction in Factor V or a decreased level of Factor VIII (66).

### Summary Recommendations

Liver abnormalities in sepsis include ischemic hepatitis, cholestasis, and hyperbilirubinemia. The differentiation of sepsis from the hyperdynamic circulation of cirrhosis (67) with accelerated intravascular coagulation and fibrinolysis may prove clinically problematic and depends on a careful analysis for the presence of infection.

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