Advances in critical care management of hepatic failure and insufficiency

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Background: **Chronic liver disease is becoming an increasingly frequent diagnosis for patients in the intensive care setting with such diagnoses as symptomatic ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, or fulminant hepatic failure.**

Objective: **To review frequent diagnoses for patients with chronic liver disease admitted to the intensive care unit and discuss current concepts in management and investigational modalities.**

Results: **Patients with new-onset ascites in the intensive care setting should undergo immediate ultrasound to rule out acute thrombosis. A transjugular intrahepatic portosystemic shunt is indicated when control of the refractory ascites or hepatic hydrothorax is required. In patients with hepatorenal syndrome, hemodialysis can be used as a bridge to liver transplantation. Otherwise, hepatorenal syndrome carries a high mortality. When hepatic encephalopathy is present, a precipitating cause should be sought and treated, if identified. Although bioartificial support systems are under active investigation, standard treatment for hepatic encephalopathy is lactulose and alteration of gut flora. Patients with fulminant hepatic failure should be stabilized and transferred to the intensive care unit of a liver transplant center and supported with appropriate airway management, close neurologic evaluation, glucose monitoring, and correction of coagulopathy when there is overt bleeding or an invasive procedure is planned. Intracranial pressure monitoring is recommended to maintain an adequate cerebral perfusion pressure of >60 mm Hg.**

Conclusion: **Review of the literature demonstrates that certain critically ill patients with chronic liver disease may benefit from invasive modalities such as transjugular intrahepatic portosystemic shunting, hemodialysis, and in some cases, liver transplantation, which may be offered only at tertiary care centers. (Crit Care Med 2006; 34[Suppl.]:S225–S231)**

KEY WORDS: liver; cirrhosis; intensive care unit; dialysis; fulminant; hepatic failure; ascites; hepatorenal; spontaneous bacterial peritonitis; transplant

Patients with liver disease represent an important population within in the intensive care unit (ICU) because these patients experience a particularly high morbidity and mortality among the critically ill. This article addresses advances in therapy and in specific management issues related to hepatic dysfunction the intensivist is commonly called on to treat in the ICU, including ascites, hepatorenal syndrome, hepatic encephalopathy, and fulminant hepatic failure.

Ascites

Cirrhotic patients admitted to the medical ICU have significant mortality, ranging from 40% to 90%. Ascites is the most common complication of cirrhosis (1) and is suspected based on a history of abdominal distension, early satiety, shortness of breath, and by physical examination, which may show "shifting dullness." However, the sensitivity and specificity of the physical examination ranges from 50% to 94% and from 29% to 82%, respectively, when compared with abdominal ultrasound (2). If ascites is suspected, abdominal ultrasound can help not only in confirming the diagnosis but also in localizing a site for paracentesis. Ultrasound-assisted abdominal paracentesis yields a higher success rate than when directed by physical examination alone (95% vs. 61%) (3).

Patients with ascites in the intensive care setting should undergo a diagnostic paracentesis to rule out infection and to obtain the serum-to-ascites albumin gradient. If the ascites is new in onset, immediate ultrasound should be obtained to rule out acute thrombosis affecting the patency of the portal and hepatic veins, as seen in acute Budd-Chiari syndrome or acute portal vein thrombosis.

Ascitic fluid analysis is required to determine the pathogenesis of ascites. The serum-to-ascites albumin gradient, calculated by subtracting the ascitic fluid albumin level from the serum albumin level, has been shown to be effective in differentiating portal hypertensive from nonportal hypertensive ascites (4). A serum-to-ascites albumin gradient of >1.1 g/dL is seen when portal hypertension is present, as with patients who have cirrhosis, Budd-Chiari syndrome, cardiac disease, portal vein thrombosis, myxedema, or liver metastasis. A serum-to-ascites albumin gradient of <1.1 g/dL suggests nonportal hypertensive pathogeneses, including malignancy, pancreatic disease, bile leak, infection, or nephrosis.

Ascitic fluid analysis should also include a cell count with differential and culture. In cirrhotic patients, spontaneous bacterial peritonitis is diagnosed when >250 neutrophils/mm^3 are found in the fluid sample (sensitivity, 85%; specificity, 93%; diagnostic accuracy, 95%) (5). Studies suggested that reagent strips may provide a more rapid diagnosis of spontaneous bacterial peritonitis (6), although additional confirmatory studies are required before widespread acceptance of this technology (7). Spontaneous bacterial peritonitis has a 1-yr mortality of 40%, despite treatment with antibiot-

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ics (8). A polymicrobial culture raises the suspicion for intestinal perforation or abscess formation. Additional useful tests performed on ascitic fluid include: glucose, which is often elevated in the setting of malignancy or gut perforation; amylase, which may be elevated in pancreatic ascites; and lactate dehydrogenase, which may be low in cirrhosis but elevated in spontaneous bacterial peritonitis (9–11). Cytology can be obtained subsequently via large-volume paracentesis, if needed. If there is no obvious cause of ascites, a diagnostic laparoscopic examination may determine whether malignant or infectious peritoneal implantation is present.

The treatment of ascites is directed at the underlying pathogenesis. Common cirrhotic ascites can often be managed with diuretics and sodium restriction. The most successful diuretic regimen is a combination of spironolactone and furosemide (12). The goal of sodium restriction should be to limit intake to 2000 mg/day (13). Recent evidence suggests octreotide, administered in combination with midodrine, may improve both renal and systemic hemodynamics in patients with ascites (14). Whereas rapid diuresis can precipitate hepatorenal syndrome and should be avoided, large-volume paracentesis (>5 L) has been shown to be safe and effective, regardless of the cause of ascites. When performing large-volume paracentesis in patients with cirrhosis, an infusion of 6–8 g of albumin per liter removed prevents the development of paracentesis-induced circulatory dysfunction often associated with large fluid shifts (13). Cirrhotics treated with diuresis should have their electrolytes and kidney function closely monitored.

If there are >250 neutrophils/mm^3 in an ascitic fluid sample, empirical antibiotics should be administered expeditiously for a diagnosis of spontaneous bacterial peritonitis (15). A third-generation cephalosporin such as cefotaxime is most frequently employed in this setting (16, 17). Some authors recommend similar therapy in patients with clinical suspicion of spontaneous bacterial peritonitis, even if the ascitic fluid count is <250 neutrophils/mm^3 (15). If spontaneous bacterial peritonitis is diagnosed, albumin infusion and antibiotics have been shown to prevent hepatorenal syndrome. 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 (18). Patients with more advanced liver disease or impaired renal function may benefit the most (16).

The insertion of a transjugular intrahepatic portosystemic shunt can be employed for treatment of refractory ascites. A low-resistance channel is created between the hepatic vein and the intrahepatic portion of the portal vein via angiographic placement of a metal stent, allowing portal blood to bypass the liver and return to systemic circulation. Transjugular intrahepatic portosystemic shunt insertion lowers the rate of ascites recurrence and the risk of developing hepatorenal syndrome when compared with paracentesis plus albumin administration in patients with refractory ascites (19). Although the transjugular intrahepatic portosystemic shunt is fairly successful in the treatment of ascites, a recent meta-analysis concluded that it can also be associated with the development of increased encephalopathy and offers no survival benefit (20).

The Model for End-stage Liver Disease (MELD) score is a prospectively developed and validated scoring system for chronic liver disease that utilizes a patient's serum bilirubin, creatinine, and international normalized ratio for prothrombin time to predict survival. Several on-line calculators are readily available: http://www.unos.org/resources/MeldPeldCalculator.asp?index=98. A MELD score of >15 is effective at predicting a significant risk of hepatic decompensation, encephalopathy, and subsequent poor survival of patients undergoing transjugular intrahepatic portosystemic shunt placement (21). In general, a MELD score of <15 would correspond to a candidate with a bilirubin at <3 mg/dL, an international normalized ratio of <2, creatinine of <2 mg/dL, and less than grade II encephalopathy. However, when the management of ascites is critical, such as in the case of 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 MELD score (22).

Hepatic hydrothorax is usually right sided, but may be bilateral, and is seen when ascitic fluid tracks up into the thorax through defects in the diaphragm, potentially causing respiratory embarrassment. Although usually evident in addition to ascites, it can develop in its absence. Radionuclide scintigraphy can be used to confirm the passage of ascitic fluid across the diaphragm (23). Treatment of hepatic hydrothorax includes usual ascitic care, including salt restriction and diuretics. Therapeutic thoracentesis with albumin replacement may be helpful. However, tube thoracostomy should be avoided. Chest tube drainage is often persistent, making tube removal difficult and increasing the risk of infection. Transjugular intrahepatic portosystemic shunt has been shown to be an effective alternative in the management of refractory hydrothorax (24).

Hepatorenal Syndrome

Hepatorenal syndrome is the development of renal failure in a patient with advanced liver disease. Hepatorenal syndrome carries a high mortality; therefore, early diagnosis is crucial. The new liver allocation scheme for transplantation prioritizes patients with hepatorenal syndrome. Hemodialysis can be used as a bridge to liver transplantation, which offers the best option for long-term survival.

Hepatorenal syndrome is characterized by impaired renal function, abnormalities in the arterial circulation, and activity of the endogenous vasoactive system (25). It is the consequence of a reduction in renal perfusion induced by severe hepatic dysfunction. Hepatorenal syndrome is classified into two types: type I is more serious and is defined as a doubling of initial serum creatinine to >2.5 mg/dL or a 50% reduction of the initial 24-hr creatinine clearance to a level of <20 mL/min in <2 wks. Type II hepatorenal syndrome does not have a rapidly progressive course, displaying an insidious increase in serum creatinine or a reduction in creatinine clearance over several months. The prevalence of hepatorenal syndrome in patients with end-stage cirrhosis ranges between 7% and 15% (26). Predictive factors include sodium and H_2O retention (indicated by a urinary sodium of <5 mEq/L and dilutional hyponatremia), low mean arterial blood pressure, poor nutrition, reduced glomerular filtration rate, high plasma renin activity, and esophageal varices.

Diagnostic criteria for hepatorenal syndrome established by the International Ascites Club include the following: creatinine of >1.5 mg/dL or 24-hr creatinine clearance of <40 mL/min; absence of shock, infection, or fluid losses; no improvement in renal function after di-

uretic withdrawal and expansion of plasma volume with 1.5 L of plasma expander; proteinuria of <500 mg/day; and no evidence of parenchymal or obstructive renal disease (27). Before making the diagnosis, reversible prerenal azotemia, such as secondary to bacterial infection or drugs such as nonsteroidal anti-inflammatory drugs or aminoglycosides, should be ruled out.

Besides MELD, the severity of chronic liver failure can also be assessed by the Child–Turcotte-Pugh classification system. The Child–Turcotte-Pugh system is based on serum bilirubin, serum albumin, prothrombin time, in addition to more subjectively assessed variables such as ascites, and encephalopathy (Table 1). Although the Child–Turcotte-Pugh system does not correlate with the development of hepatorenal syndrome, both the Child–Turcotte-Pugh and the MELD scores have been found to be predictive of survival in patients with hepatorenal syndrome (28, 29). Nevertheless, survival of patients with hepatorenal syndrome is very poor, with a 60% mortality at 2 wks for type I patients.

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. Intravenous administration of clonidine has been shown to lower renal vascular resistance and increase the glomerular filtration rate by as much as 25%, an effect unfortunately not able to be sustained with oral therapy (30). Liver transplantation offers the best treatment, as it resolves circulatory and renal dysfunction and provides a 5-yr posttransplantation survival rate of 70% (31). About 5% of patients progress to end-stage renal disease after transplantation and require hemodialysis. Unfortunately, few patients with hepatorenal syndrome undergo liver transplantation because of the small donor pool and long waiting lists.

The combination of midodrine and octreotide may be effective in the treatment of hepatorenal syndrome by lessening hyperdynamic circulation without compromising glomerular filtration rate, as compared with octreotide alone, which does not improve systemic hemodynamics and worsens glomerular filtration rate (14). Midodrine is a systemic vasoconstrictor, whereas octreotide inhibits endogenous vasodilator release. In a study of 13 patients with hepatorenal syndrome, three of the five patients who received midodrine (2–4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and octreotide (100 to 200 μg subcutaneously three times daily) survived to discharge, whereas seven of the eight patients who received dopamine died (32). Significant improvements in renal function were seen in the midodrine/octreotide group, whereas there was a nonsignificant trend toward renal function deterioration in the dopamine group. Although this observation awaits confirmation in a larger study, given the overall poor prognosis of this syndrome, consideration can be given to employing this approach in selected patients with hepatorenal syndrome.

Patients with refractory ascites treated with a transjugular intrahepatic portosystemic shunt may have a lower prevalence of developing hepatorenal syndrome and be less likely to progress from type II to type I hepatorenal syndrome (19). Many patients with hepatorenal syndrome, however, are too ill to undergo transjugular intrahepatic portosystemic shunt placement. Patients with a MELD score of >18 should probably not undergo transjugular intrahepatic portosystemic shunt placement because these patients have a median predicted survival of ≤3 months after the procedure (33).

The molecular absorbent recirculating system (MARS), a form of extracorporeal albumin dialysis, has also been proposed as a modality for the treatment of hepatorenal syndrome. This is an artificial liver support system in which blood is dialyzed against an albumin-enriched dialysate to facilitate removal of albumin-bound toxins and of bilirubin, aromatic amino acids, and H_2O-soluble substances (34). MARS is one of several bioartificial liver support systems that have been or are being developed. Currently, MARS is commercially available only in Europe. In the United States, additional trials are being conducted to provide safety data for obtaining Food and Drug Administration device approval.

A prospective, randomized, controlled trial of MARS was performed to determine the effect of a MARS on 30-day survival in 13 patients with type I hepatorenal syndrome compared with standard medical treatment (35). The patients treated with five daily MARS sessions, each lasting 6–8 hrs, displayed significant decreases in bilirubin and creatinine compared with the nontreatment group. All conventionally treated patients were dead by day 7, but there were two survivors at 30 days among eight MARS patients. Larger trials are needed to assess the efficacy and safety of MARS in hepatorenal syndrome.

Table 1. Child-Turcotte-Pugh classification of liver disease severity

	Points Assigned[a]		
Parameter	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	≤2	2–3	>3
Albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds over control	1–3	4–6	>6
INR	<1.7	1.8–2.3	>2.3
Encephalopathy	None	Grades 1–2	Grades 3–4

INR, international normalized ratio.

[a]A total score of: 5–6 is grade A, 1- and 2-yr patient survival of 100% and 85%, respectively; 7–9 is grade B, 1- and 2-yr patient survival of 80% and 60%, respectively; and 10–15 is grade C, 1- and 2-yr patient survival of 45% and 35%, respectively.

Hepatic Encephalopathy

Hepatic encephalopathy occurs in patients with portal hypertension and cirrhosis. When severe, hepatic encephalopathy should be managed in the ICU. Hepatic encephalopathy involves a wide range of neuropsychiatric changes in patients with significant liver dysfunction, ranging from subtle cognitive abnormalities to coma (36). Different grades for hepatic encephalopathy are listed in Table 2. There are three clinical patterns for hepatic encephalopathy (37). Type A is related to acute liver failure. Type B occurs in the setting of normal liver histology and the presence of a hepatic vascular bypass, such as portocaval shunting. Type C hepatic encephalopathy is due to cirrhosis, entails the majority of cases, and is the type most commonly seen in the ICU setting. Type C hepatic encephalopathy is divided into acute encephalopathy, which is usually spontaneous and a precipitant is identified, and chronic encephalopathy, which involves a recurrent and fluctuating course.

Table 2. Grading 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, sleeping but arousable	Yes	Abnormal
IV	Coma	No	Abnormal

Diagnosis is usually established based on a combination of laboratory abnormalities suggesting severe hepatic dysfunction and neurologic deficits. Although elevated blood ammonia levels can be present, they are not required for making a diagnosis. Early neurologic abnormalities include disturbance in sleep patterns such as insomnia or hypersomnia. Neurologic abnormalities seen in more advanced presentations include asterixis and hyperactive deep tendon reflexes. Focal neurologic signs may be detected in some patients during episodes of hepatic encephalopathy, with hemiplegia being the most common focal deficit seen (38).

The first step in evaluation and management of these patients is to identify and treat precipitating factors such as gastrointestinal bleeding, infection, alkalosis, hypokalemia, sedatives/tranquilizers, ingestion of dietary proteins, azotemia, and progressive hepatic dysfunction (39). The mainstay of treatment for hepatic encephalopathy is lactulose and alteration of gut flora. Lactulose, a nonabsorbable disaccharide, should be initiated and titrated to about four bowel movements a day. Lactulose is metabolized by gut flora, lowering colonic pH and thereby favoring ammonia elimination. Enteric flora modification with antibiotics, such as metronidazole or neomycin, is a second-line treatment, and can be used in combination with lactulose.

Management also includes supportive measures such as restoring electrolyte balance, fluid maintenance, aspiration precautions, and rapid sequence intubation for airway protection in grades 3–4 hepatic encephalopathy. 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 (40).

Flumazenil has been proposed as a possible therapeutic agent for hepatic encephalopathy based on the theory that "endogenous benzodiazepines" may be present in patients with hepatic encephalopathy (41). 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 (42). Meta-analyses suggested that flumazenil was associated with a significant improvement in encephalopathy compared with placebo; however, the benefit was short term and may have been confined to patients who otherwise had a favorable prognosis (43, 44). A longer-acting intravenous or oral formulation is not available. In patients in whom there is suspected benzodiazepine use, flumazenil clearly has utility; in other patients, its use is less clear.

Extracorporeal albumin dialysis also has been studied for the treatment of hepatic encephalopathy. Case series have evaluated this modality in about 60 patients with cirrhosis and hepatic encephalopathy (45). Neurologic improvement has been observed in the majority of patients. More recently, a randomized, controlled trial of extracorporeal albumin dialysis vs. usual supportive care was performed in 23 patients with acute-on-chronic liver failure. Bilirubin decreased and both renal dysfunction and hepatic encephalopathy improved in the treatment group. There was also improved 30-day survival in the treatment group (46). This suggests extracorporeal albumin dialysis may serve as an effective bridge to liver transplantation.

Finally, L-ornithine-L-aspartate administration has been shown to improve ammonia detoxification in several randomized trials in patients with hepatic encephalopathy (47). Significant improvements in neuropsychological testing, mental state grade, and portosystemic encephalopathy index have been described. L-Ornithine-L-aspartate has not been compared with lactulose alone or in combination and is not presently available in the United States.

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. Once a patient is diagnosed with fulminant hepatic failure, the patient should be stabilized and transferred to a liver transplant center, as liver transplantation offers the best long-term survival in patients likely to die of this condition (48). There the patient should be cared for in the ICU setting and supportive measures initiated, including close neurologic evaluation and glucose monitoring.

Temporally related definitions have been proposed to classify patients with fulminant hepatic failure as: hyperacute, <7 days; acute, 7–28 days; and subacute, 28 days to 6 months (49). The National Institutes of Health Acute Liver Failure Study Group reported the cause 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%) (50). Overall survival is poor without liver transplantation, with a reported mortality of 90–97% (51). The advent of liver transplantation and aggressive medical care in the ICU has improved the mortality rate (52).

Hepatic encephalopathy and severe coagulopathy are important features of fulminant hepatic failure (53). Severe coagulopathy often precedes the evolution of hepatic encephalopathy to coma. Patients can rapidly progress from mild hepatic encephalopathy to deep coma (Table 2) (54). As soon as the diagnosis is made, it is important to establish the cause. If there is no clear cause based on history, urine and serum toxicology screens should be ordered in addition to hepatitis serologies. Other tests that should be considered include ceruloplasmin, antinuclear antibodies, smooth-muscle antibodies, serum protein electrophoresis, and antibodies to cytomegalovirus and Epstein–Barr virus. Certain pathogeneses demand immediate specific treatment, including *N*-acetylcysteine for acetaminophen ingestion; penicillin for *Amanita* mushroom poisoning; delivery of the in-

fant in acute fatty liver of pregnancy; zinc and trientine therapy for Wilson's disease; transjugular intrahepatic portosystemic shunt, surgical decompression or thrombolysis in patients with acute Budd-Chiari; and acyclovir in patients with acute liver failure related to herpesvirus infection.

Management involves supportive measures including nutrition (amino acids, lipids, glucose, and essential elements), electrolyte balance, frequent glucose monitoring (more often than every 6 hrs), aspiration precautions, and fluid maintenance. Hypokalemia, hyponatremia, and hypophosphatemia are common. Hypoglycemia, seen in up to 45% of patients with fulminant hepatic failure, requires aggressive glucose administration, often with 10% dextrose via central venous access (55). Infection in patients with fulminant hepatic failure is a major source of mortality, as 44–80% of patients with fulminant hepatic failure develop bacterial infections. Empirical, broad-spectrum antibiotics should be initiated on clinical suspicion of infection (56). Fungal infections are also not uncommon in these patients, with rates as high as 32% having been reported (57). Acute renal failure frequently develops in fulminant hepatic failure. Renal failure is particularly high in the setting of acetaminophen ingestion, as it can directly damage the kidneys. Once renal failure is established, it often is irreversible and carries a grave prognosis. Renal replacement therapy is generally well tolerated and may provide a bridge to transplant (58).

The development of severe coagulopathy is due to the decreased synthesis of clotting factors II, V, VII, and IX and is manifested by a prolonged prothrombin time. However, 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 (59). The protocol is to infuse 80 μg/kg after infusion of 4 units of fresh frozen plasma. This can normalize prothrombin time for up to 6 hrs.

Neurologic evaluation, a critical guide to therapy, should be performed at least every 6 hrs. Medications with sedative properties should be avoided if possible. Patients with chronic liver failure should be continued on lactulose. The use of lactulose for acute liver failure differs widely in ICUs throughout the country, but a review of 23 liver transplant centers across the United States suggested that lactulose provided only a short-term survival advantage in this patient population (60).

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. An emergent head computed tomographic scan should be performed if there is a change in mental status or signs of increased intracranial pressure. The diagnosis may be difficult to establish as head computed tomographic scan is insensitive, being useful only to rule out hemorrhage. Clinical signs of cerebral edema, such as decerebrate posturing, systemic hypertension, and pupillary abnormalities, are unreliable and should not be used for clinical decision making. Cerebral edema often leads to intracranial hypertension and subsequent herniation of the cerebral uncus, cerebral ischemic injury, and death (61). 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 >60 mm Hg is crucial to maintain intact neurologic function (62). Direct intracranial pressure monitoring is recommended in patients suspected of cerebral edema or intracranial hypertension, with a target intracranial pressure of <20 mm Hg (63).

Intracranial pressure monitoring is recommended to maintain an adequate cerebral perfusion pressure of >60 mm Hg. The placement of extradural intracranial pressure monitors is considered safer than subdural catheters. Recombinant factor VIIa may be superior to fresh frozen plasma in temporarily reversing coagulopathy in those patients requiring intracranial pressure monitor placement (64). In general, sedation should be avoided so that mental status may be assessed. However, an agitated patient with grade III coma may require the use of short-acting benzodiazepines, the preferred agents (65). Although hyperventilation may also reduce cerebral edema, it is effective only for a few hours. Mannitol is first-line therapy for treating cerebral edema and intracranial hypertension, administered at 0.3–0.4 g/kg body weight. In patients with renal failure, mannitol may accumulate in astrocytes and cause increased rebound swelling (66). Thiopental may be used in this setting (250 mg over 15 mins). In one case series, seven patients with fulminant hepatic failure were administered propofol for deteriorating cerebral edema (67). Decreased intracranial pressure was seen in five patients, but 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 (68) or while transplantation is being performed (69).

Liver transplantation offers the best long-term survival, with an overall post-transplantation 1-yr survival of about 60% (70). 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 (Table 3) (71). These criteria include an arterial pH of <7.30 after adequate fluid resuscitation or the combination of a prothrombin time of >100 secs, a creatinine level of >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 meta-analysis investigated several prognostic criteria for de-

Table 3. King's College criteria for liver transplantation in acute liver failure

Acetaminophen	Nonacetaminophen
Arterial lactate >3.5, 4 hrs after resuscitation	INR of >6.5 (PT of >100 secs) or any three of the following:
Or	INR of >3.5 (PT of >50 secs)
pH of <7.3 or arterial lactate of >3.0, 12 hrs after resuscitation	Age of <10 or >40 yrs
Or	Serum bilirubin of >17.5 mg/dL
INR of >6.5 (PT of >100 secs)	Duration of jaundice of >7 days
Serum creatinine of >3.4 mg/dL	Pathogenesis: drug reaction

INR, international normalized ratio; PT, prothrombin time.

termining 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 to predict the need for liver transplantation (72). Arterial blood lactate of >3.5 mmol/L at 4 hrs 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 (73).

Because only a relatively small portion of liver is actually required to support hepatic function, another potential therapeutic alternative that is being investigated is auxiliary liver transplantation. In this technique, a partial liver graft is placed either adjacent to the patient's native liver or in the hepatic bed after a portion of the native liver has been removed. Theoretically, this graft may support the patient while the native liver regenerates so that ultimately the patient would not need chronic immunosuppression. Although case reports and small case series have reported success using this technique, the procedure is technically very difficult and has not been adequately evaluated in controlled trials (74).

Short-term extracorporeal hepatic support for patients with fulminant hepatic failure may ultimately serve to improve overall survival and provide support as a bridge to liver transplantation, but it remains experimental. Two types of systems are being investigated: cell- and non–cell-based systems. Extracorporeal albumin dialysis, such as MARS, is an example of non–cell-based systems. Whereas non–cell-based systems aim to adsorb toxins from the patient's blood, cell-based systems also are designed to provide hepatic synthetic support. A meta-analysis of artificial and bioartificial support systems for fulminant hepatic failure examined a total of eight 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) (75). 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 seemed to have an increased risk of bleeding associated with their use. However, a meta-regression suggested that patients with acute-on-chronic liver failure experienced a 33% reduction in mortality as opposed to those with simply acute liver failure. Another future option includes hepatocyte transplantation. In one series, three of six patients with fulminant hepatic failure survived between 14 and 52 days after transplantation of 10^{10} human hepatocytes (76). To date, no randomized, controlled studies have examined this therapeutic option.

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