Acute liver failure in adults: Management and prognosis

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INTRODUCTION

Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (international normalized ratio [INR] of ≥1.5) in a patient without cirrhosis or pre-existing liver disease [1,2]. While the time course that differentiates acute liver failure from chronic liver failure varies between reports, a commonly used cutoff is an illness duration of <26 weeks.

Acute liver failure may also be diagnosed in patients with previously undiagnosed Wilson disease, vertically acquired hepatitis B virus, or autoimmune hepatitis, in whom underlying cirrhosis may be present, provided the disease has been recognized for <26 weeks. On the other hand, patients with acute severe alcoholic hepatitis, even if recognized for <26 weeks, are considered to have acute-on-chronic liver failure since most have a long history of heavy drinking. The approach to such patients is discussed elsewhere. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis" and "Management of alcohol-associated steatosis and alcohol-associated cirrhosis".)

Acute liver failure has also been referred to as fulminant hepatic failure, acute hepatic necrosis, fulminant hepatic necrosis, and fulminant hepatitis. Untreated, the prognosis is poor, so timely recognition and management of patients with acute liver failure is crucial [3]. Whenever possible, patients with acute liver failure should be managed in an intensive care unit (ICU) at a liver transplant center.

This topic will review the management and prognosis of acute liver failure in adults. The etiology, clinical manifestations, and diagnosis of patients with acute liver failure are discussed separately. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

The discussion that follows is largely consistent with society guidelines from the American Association for the Study of Liver Diseases, the American College of Gastroenterology (ACG), and the European Association for the Study of Liver for the management of acute liver failure [1,2,4,5].

GENERAL MANAGEMENT

The general management of a patient with acute liver failure includes ensuring the patient is being cared for in the proper setting, monitoring for worsening liver failure, treating complications, and providing nutritional support.

Setting — Patients with acute liver failure should be managed in centers with an active liver transplantation program and expertise in caring for these patients [2]. Only 40 percent of patients with acute liver failure recover spontaneously, leaving many in need of liver transplantation, and even those who do eventually recover are often gravely ill. As a result, patients admitted to hospitals without a liver transplantation program should be transferred as soon as possible, since it can be hazardous to transfer patients later in the disease course because of severe coagulopathy and increased intracranial pressure [6]. This includes patients who do not yet appear to be gravely ill, such as those with an international normalized ratio (INR) ≥1.5 but with no or minimal (now referred to as covert) hepatic encephalopathy. If a patient has comorbid illnesses (eg, heart failure with reduced ejection, active or recent malignancy) that likely preclude liver transplantation, it is reasonable to discuss the appropriateness of transfer with a transplant hepatologist. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation", section on 'Contraindications'.)

We typically manage patients with acute liver failure in the intensive care unit (ICU), but it is possible for patients with grade I encephalopathy (table 1) to be managed on a general medical ward, provided that the environment is quiet and frequent neurologic checks (eg, every two hours) are performed. If there is progression of the patient's encephalopathy, or for patients presenting with grade II, III, or IV encephalopathy, management in an intensive care unit is indicated [2].

Stimulation can lead to increased intracranial pressure and should be minimized. Whenever possible, patients' rooms should be quiet, without audible monitors or alarms in the room, and

dimly lit. (See 'Cerebral edema' below.)

Laboratory testing — Serial laboratory tests are used to follow the course of a patient's liver failure and to monitor for complications. Serum aminotransferases and bilirubin should be monitored daily. More frequent monitoring (three to four times daily) should be performed for coagulation parameters, complete blood counts, metabolic panels, and arterial blood gasses. In particular, patients should be monitored and treated for hypoglycemia, hypokalemia, hypomagnesemia, and hypophosphatemia. We perform finger sticks to monitor blood glucose levels every six hours. We also monitor ammonia levels every four to six hours because an ammonia level >150 microg/dL has been associated with increased risk of cerebral herniation [1,7]. We monitor ammonia levels more frequently in patients with grade III and IV encephalopathy. Additionally, ammonia levels may increase with initiation of enteral feeding [5]. (See 'Metabolic abnormalities' below.)

Decreasing aminotransferase levels may indicate spontaneous recovery but could also signal worsening liver failure with loss of hepatocyte mass. In patients who are improving, the bilirubin and prothrombin time/INR will decline, whereas in those with worsening liver failure, the bilirubin and prothrombin time/INR will continue to rise. Because of the prognostic importance of the prothrombin time/INR, it is recommended that plasma only be used when there is a clear indication [2]. (See 'Bleeding prevention' below and "Hemostatic abnormalities in patients with liver disease", section on 'Bleeding' and "Hemostatic abnormalities in patients with liver disease", section on 'Invasive procedures'.)

Hemodynamic management — Hemodynamic derangements are common in patients with acute liver failure due to low systemic vascular resistance. In addition, patients may have intravascular volume depletion because of decreased oral intake and extravasation of fluid into the extra-vascular space. As a result, most patients will require fluid resuscitation initially. Patients who are hypotensive should be resuscitated with normal saline [2]. Patients who are acidotic can be resuscitated with half-normal saline with 75 mEq/L sodium bicarbonate. Dextrose should be added to crystalloid solutions in patients with hypoglycemia. However, it is important to avoid overhydration since it may worsen cerebral edema. (See "Maintenance and replacement fluid therapy in adults", section on 'Replacement fluid therapy'.)

Some patients may not respond adequately to fluid resuscitation may require vasopressor support. The goal is to maintain a mean arterial pressure of at least 75 mmHg or a cerebral perfusion pressure of at least 50 to 60 mmHg. Norepinephrine is often preferred because it is thought to best augment peripheral organ perfusion with less tachycardia and better preservation of splanchnic blood flow than other agents [8]. Vasopressin may be added in those who do not respond to norepinephrine to potentiate the effect of norepinephrine. (See

'Treatment of intracranial pressure elevation' below and "Use of vasopressors and inotropes", section on 'Norepinephrine'.)

As is seen in patients with septic shock, patients with acute liver failure may develop adrenal insufficiency. Thus, if hypotension persists despite volume repletion and vasopressor support, a trial of hydrocortisone is reasonable [9,10]. (See "Glucocorticoid therapy in septic shock in adults", section on 'Administration'.)

N-acetylcysteine — N-acetylcysteine is used for the treatment of acetaminophen toxicity, but it may be beneficial in other forms of acute liver failure. While additional studies are needed before this therapy can be routinely recommended for acute liver failure from causes other than acetaminophen toxicity, it is reasonable to give it to patients who are not candidates for liver transplantation, to patients in whom acetaminophen toxicity may be contributing to the liver failure (eg, a patient with acute hepatitis B who was taking acetaminophen for right upper quadrant pain), and to patients with an indeterminate cause for the acute liver failure. The empiric use of N-acetylcysteine may also be beneficial for patients taking medications that induce cytochrome P450 activity and for patients with chronic liver disease. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation", section on 'Clinical factors that may influence toxicity' and "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Acetaminophen and other hepatotoxins'.)

A placebo-controlled trial involving 173 patients with acute liver failure due to causes other than acetaminophen (mainly drug-induced liver injury, autoimmune hepatitis, hepatitis B virus, or indeterminate) found significantly higher transplant-free survival (40 versus 27 percent) in patients randomized to N-acetylcysteine [11]. The benefit appeared to be confined to patients with early stage hepatic encephalopathy.

Bleeding prevention — Patients with acute liver failure can develop severe coagulopathy and bleed due to the diminished capacity of the failing liver to synthesize coagulation factors. However, conventional indices of coagulation (eg, the international normalized ratio [INR]) are not helpful in determining a patient's bleeding risk. Because of this, patients who require an invasive procedure or who develop bleeding may need additional testing, such as a determination of fibrinogen levels, thromboelastography, or thromboelastometry, to guide management. The management of patients with liver disease who require an invasive procedure or develop bleeding is discussed in detail elsewhere. (See "Hemostatic abnormalities in patients with liver disease", section on 'Bleeding' and "Hemostatic abnormalities in patients with liver disease", section on 'Invasive procedures'.)

Prophylactic administration of fresh frozen plasma is not recommended since it has not been shown to influence mortality in a small randomized trial [12], can interfere with assessments of liver function, and may lead to fluid overload [13].

Because the most common site of bleeding is the gastrointestinal tract, patients should receive stress ulcer prophylaxis with an H2 blocker or proton pump inhibitor.

Infection surveillance and prevention — Patients with acute liver failure are at increased risk of infection and sepsis from a wide variety of causes, so an aggressive approach to diagnosing and treating infections is necessary. The most common sites of infection are the respiratory tract, the urinary tract, and the blood [14]. Localizing signs of infection, such as fever and sputum production, are frequently absent, and the only clue to an underlying infectious process may be worsening of encephalopathy or renal function.

Guidelines from the AASLD, EASL, and ACG suggest that all patients (including those without signs of infection) should have routine urine, sputum, and blood cultures, as well as chest radiographs to detect bacterial or fungal infection upon presentation [2,4,5]. It is reasonable to repeat surveillance cultures and radiographs every 48 to 72 hours. However, it is important to note that data are lacking regarding the value of such testing, and positive culture results in the absence of signs of infection may be due to colonization or contamination by bacterial or fungal organisms.

In addition to surveillance cultures, we suggest an evaluation for possible infection in patients with signs or symptoms suggesting infection (eg, fever, cough, sputum production) or deteriorating clinical status, particularly if there is worsening encephalopathy or worsening renal function. In addition to urine and blood cultures for bacterial or fungal infection and diagnostic chest radiographs, patients with ascites should undergo diagnostic paracentesis if ascites is present.

The role of prophylactic antibiotics is controversial. While a randomized trial with 59 patients with acute liver failure who were not infected at entry found that prophylactic antibiotics reduced the rate of infection, a survival benefit was not seen [15]. In a retrospective study of 1551 patients with acute liver failure, antimicrobial prophylaxis did not reduce the incidence of bloodstream infection (13 with prophylaxis versus 16 percent without) or mortality within 21 days (30 percent in both groups) [16].

Our approach to antibiotic prophylaxis is similar to that recommended by society guidelines. We do not give patients prophylactic antibiotics, but instead give them only if there is evidence of active infection, positive surveillance culture results, or clinical deterioration (progression to high-grade encephalopathy or evidence of systemic inflammatory response syndrome [SIRS])

[2]. In addition, having a low-index of suspicion for fungal infection is important because fungal infections are frequently encountered and are often diagnosed too late to be effectively treated [17]. We have a low threshold for initiating antifungal coverage for patients with signs of infection who are at increased risk for fungal infection, such as those who have had prolonged hospitalization, those receiving continuous venovenous hemodialysis, those receiving parenteral nutrition, and those who have been receiving an antibiotic or glucocorticoids. In our experience, many patients with acute liver failure meet these criteria.

If the decision is made to provide empiric broad spectrum antibiotic coverage, nephrotoxic antibiotics, particularly the aminoglycosides, and hepatotoxic antibiotics should be avoided. We often use piperacillin/tazobactam or a fluoroquinolone. In addition, surveillance cultures are not needed in patients receiving antibiotic prophylaxis.

Nutrition — Nutritional support is a vital component in the treatment of acute liver failure and should be initiated early. It is required to prevent catabolism of body stores of proteins and it may decrease the risk of gastrointestinal bleeding from stress ulceration in critically ill patients [18]. To prevent protein catabolism, severe protein restrictions should be avoided; a daily intake of 60 grams of protein is reasonable for most patients with acute liver failure. (See "Nutrition support in critically ill patients: An overview".)

In patients with grade I or II encephalopathy, oral or enteral feeding is usually sufficient to meet metabolic requirements [19]. Enteral feeding should be provided for patients with grade III or IV encephalopathy. Placement of a nasogastric tube can increase intracranial pressure (because of gagging) and should generally be performed only in patients who are intubated and sedated. If adequate enteral feeding cannot be provided, parenteral nutrition should be initiated.

Medications to avoid — In general, sedation should be avoided because patients with acute liver failure have a severely impaired ability to clear sedatives, and the effects of sedation may mask the signs of worsening encephalopathy or cerebral edema. However, in patients with severe agitation that cannot be managed in any other way, short-acting benzodiazepines in low doses may be given [2]. In patients who require sedative medications, benzodiazepines, barbiturates, and propofol, are preferable to opioids because opioids can decrease the seizure threshold. (See 'Hepatic encephalopathy' below and 'Cerebral edema' below.)

Because acute renal failure often complicates acute liver failure, nephrotoxic drugs should be avoided. In addition, intravenous contrast agents should be used with caution. (See "Contrast-associated and contrast-induced acute kidney injury: Clinical features, diagnosis, and management".)

Unhelpful treatments — A number of interventions have been studied that are unhelpful for acute liver failure and should generally not be used.

Such treatments include:

- Glucocorticoids, which increase the risk of sepsis [20].
- Hepatic regeneration therapy using insulin and glucagon [21].
- Charcoal hemoperfusion [22].
- Prostaglandin E, which appeared to have promise in uncontrolled studies [23], but was subsequently shown to be ineffective in controlled studies [24].

TREATMENT OF THE UNDERLYING CAUSE

For some causes of acute liver failure, such as acetaminophen toxicity, treatment aimed at the underlying cause may prevent the need for liver transplantation and decrease mortality. Because of this, quickly determining the cause of acute liver failure is crucial. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Determining the cause of acute liver failure'.)

Acetaminophen toxicity — N-acetylcysteine can dramatically improve the prognosis in patients with acetaminophen toxicity. Serious hepatotoxicity is uncommon and death extremely rare if N-acetylcysteine is administered within eight hours following acetaminophen overdose [25-27]. In patients who have developed acute liver failure, intravenous N-acetylcysteine decreases mortality and improves hepatic microcirculatory function. (See "Acetaminophen (paracetamol) poisoning in adults: Treatment".)

The threshold for giving N-acetylcysteine should be low, because patients with acetaminophen-induced acute liver failure may not have a clear history of acetaminophen overdose. As an example, doses as low as 4 g/day can cause hepatotoxicity in regular alcohol users [28]. Thus, N-acetylcysteine should not only be given to patients with a history suggestive of acetaminophen toxicity, but also for those with acute liver failure of unknown etiology. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation".)

Hepatitis B infection — Antiviral therapy with a nucleos(t)ide analogue may be beneficial in patients with acute liver failure from acute hepatitis B virus infection [29-31], though not all studies have shown a benefit [32]. However, even if not clearly beneficial for preventing the

need for liver transplantation, nucleos(t)ide analogues should be given to transplantation candidates to help prevent post-transplantation recurrence. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

Mushroom poisoning — In patients with *Amanita phalloides* ingestion, early administration of activated charcoal is recommended. Activated charcoal binds to amatoxin and is associated with improved survival when given early compared with supportive therapy alone, though whether it is beneficial once acute liver failure has developed is not clear. Additional therapies include administration of silibinin and penicillin G. (See "Amatoxin-containing mushroom poisoning (eg, Amanita phalloides): Clinical manifestations, diagnosis, and treatment", section on 'Management'.)

Budd-Chiari syndrome — Methods to restore hepatic drainage in patients with acute Budd-Chiari syndrome include transjugular intrahepatic portosystemic shunt placement, surgical decompression, or thrombolysis. (See "Budd-Chiari syndrome: Management", section on 'Management'.)

Herpes simplex virus infection — We initiate therapy for patients with suspected or documented herpes simplex virus (HSV) infection, while patients with acute liver failure from HSV hepatitis often lack the typical skin lesions. We have a low threshold for initiating HSV therapy. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Hepatitis'.)

Therapy consists of acyclovir (5 mg/kg every eight hours with adjustment as needed based on the patient's renal function) for at least seven days or until herpes simplex virus infection has been excluded. (See "Treatment and prevention of herpes simplex virus type 1 in immunocompetent adolescents and adults", section on 'Disseminated or visceral disease'.)

Wilson disease — Patients with acute liver failure due to Wilson disease typically require liver transplantation, though plasma exchange to remove copper may act as a temporizing measure. Although hemodialysis, peritoneal dialysis, and hemofiltration have also been used, plasma exchange with fresh frozen plasma replacement is often preferred since it can remove relatively large amounts of copper in a short period of time. There is no role for chelation therapy in the management of acute liver failure due to Wilson disease. (See "Wilson disease: Treatment and prognosis", section on 'Acute liver failure'.)

Autoimmune hepatitis — Whether administration of glucocorticoids can prevent the need for liver transplantation in patients with acute liver failure from autoimmune hepatitis is unsettled, and there is concern over septic complications in patients receiving glucocorticoids. (See "Management of autoimmune hepatitis", section on 'Patients with acute liver failure'.)

Our approach for patients who have an INR ≥1.5 but without hepatic encephalopathy is to give a trial of glucocorticoids (40 to 60 mg of prednisone or prednisolone per day for two weeks or less) while performing a transplant evaluation and closely monitoring the patient's clinical status and Model for End-stage Liver Disease (MELD) score, reserving liver transplantation for patients who develop encephalopathy. For patients who meet criteria for acute liver failure, we recommend proceeding directly to liver transplant evaluation without starting glucocorticoids [33]. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation", section on 'Pretransplantation evaluation' and "Model for End-stage Liver Disease (MELD)".)

Acute fatty liver of pregnancy — There is no specific medical treatment for acute fatty liver of pregnancy. As a result, the primary treatment is prompt (usually emergent) delivery once the mother has been stabilized. (See "Acute fatty liver of pregnancy".)

When the underlying cause is unknown — N-acetylcysteine is used for the treatment of acetaminophen toxicity, but it may be beneficial in other forms of acute liver failure. While additional studies are needed before this therapy can be routinely recommended for acute liver failure from causes other than acetaminophen toxicity, it is reasonable to give it to patients in whom acetaminophen toxicity may be contributing to the liver failure (eg, a patient with acute hepatitis B who was taking acetaminophen for right upper quadrant pain), and in patients with an indeterminate cause for the acute liver failure. (See 'N-acetylcysteine' above.)

MANAGEMENT OF COMPLICATIONS

Managing patients with acute liver failure requires a thorough understanding of the complications that may develop, including metabolic derangements, encephalopathy, cerebral edema, seizures, and renal failure.

Metabolic abnormalities — Common metabolic disturbances in acute liver failure include acid-base and electrolyte disorders. Acid-base disturbances are best managed by treating the underlying abnormality, such as infection or tissue hypoperfusion, and by administering treatments for toxins that may lead to acid-base disturbances and acute liver failure (eg, acetylcysteine for acetaminophen). Hypokalemia, hyponatremia, and hypoglycemia are often seen and require correction, whereas hypophosphatemia, while also common, typically does not require treatment.

Among the acid-base disorders, alkalosis is more common than acidosis in the early stages of acute liver failure and is frequently a mixed respiratory and metabolic abnormality [34]. Metabolic alkalosis may contribute to hepatic encephalopathy by facilitating ammonia entry

into the brain by promoting the conversion of ammonium (NH_4^+), a charged particle that cannot cross the blood-brain barrier, into ammonia (NH_3), which can. As acute liver failure progresses, patients typically develop metabolic acidosis (due to lactic acidosis) with respiratory alkalosis. (See "Simple and mixed acid-base disorders".)

The most common electrolyte disturbances are hypokalemia, hyponatremia, hypophosphatemia, and hypoglycemia:

- Hypokalemia is common in both fulminant and subfulminant hepatic failure. Several factors may contribute, including diuretic therapy and increased sympathetic tone, since activation of the beta-2 adrenergic receptors promotes the uptake of potassium by the cells. One effect of hypokalemia is to increase renal ammonia production, and hypokalemia should be corrected if present. (See "Clinical manifestations and treatment of hypokalemia in adults" and "Hypokalemia-induced kidney dysfunction", section on 'Increased ammonia production'.)

- Hyponatremia is more frequently seen in patients with subfulminant hepatic failure. Tissue hypoperfusion, leading to enhanced release of antidiuretic hormone, and impaired renal function combine to limit free water excretion. Hyponatremia should be treated, but care must be taken to avoid osmotic demyelination syndrome that may be seen with overly rapid correction. (See "Causes of hypotonic hyponatremia in adults" and "Overview of the treatment of hyponatremia in adults".)

- Hypophosphatemia is especially common in patients with acetaminophen-induced acute liver failure and those with intact renal function [35]. The presence of hypophosphatemia is good prognostic sign [36]. The fall in plasma phosphate is due to movement into the cells and may be related to the metabolic and synthetic demands of a regenerating liver. Most patients with hypophosphatemia are asymptomatic, and treatment of the hypophosphatemia is usually not required. (See "Hypophosphatemia: Causes of hypophosphatemia" and "Hypophosphatemia: Evaluation and treatment", section on 'Treatment'.)

- Hypoglycemia, which occurs in more than 40 percent of the patients with acute liver failure, results from both depletion of hepatic glycogen stores and impaired gluconeogenesis and has been associated with increased mortality [37,38]. The plasma glucose concentration should be monitored closely, and hypertonic glucose solutions should be administered as needed to keep the level above 65 mg/dL (3.6 mmol/L).

Hepatic encephalopathy — Hepatic encephalopathy is one of the defining characteristics of acute liver failure, although the precise mechanism remains unclear (table 1) [39]. The most

widely accepted theory is related to increased production of ammonia from nitrogenous substances within the gut lumen. No specific treatment for hepatic encephalopathy has been shown to improve overall outcomes. Severe protein restrictions in patients with acute liver failure promote protein catabolism and should be avoided.

Whereas lactulose is commonly used in patients with hepatic encephalopathy due to chronic liver disease, its use in acute liver failure is controversial. One study found a small increase in survival time among patients with acute liver failure who received lactulose [40]. However, there was no difference in the severity of encephalopathy or in overall outcomes. One concern with the use of lactulose is that it may lead to bowel distension that could result in technical difficulties during liver transplantation [2]. (See "Hepatic encephalopathy: Pathogenesis" and "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Neurologic examination' and "Hepatic encephalopathy in adults: Treatment" and 'Nutrition' above.)

We do not routinely treat patients with acute liver failure with lactulose. However, if lactulose is used, endotracheal intubation should be performed prior to its administration in patients with advanced (grade III or IV) encephalopathy.

Neomycin, which is sometimes used in the treatment of hepatic encephalopathy, should be avoided because it is nephrotoxic. In addition, while rifaximin has been studied for the treatment of hepatic encephalopathy in patients with chronic liver disease, its role in patients with acute liver failure is unclear. We do not use rifaximin for the treatment of hepatic encephalopathy in patients with acute liver failure. (See 'Medications to avoid' above and 'Acute renal failure' below.)

Continuous renal replacement therapy (CRRT) has been used successfully to remove ammonia, treat metabolic disturbances, and/or manage fluid balance in patients with acute liver failure [41,42]. In adults, CRRT has been associated with lower ammonia levels within three days of initiating therapy and with a lower risk of mortality [41]. In general, we have a low threshold for starting patients on CRRT early in the course of disease to manage metabolic disturbances including high ammonia levels and excess volume [4].

Cerebral edema — Cerebral edema is uncommon in patients with grade I or II encephalopathy, but it is present in 25 to 35 percent of those with grade III encephalopathy and in approximately 75 percent of those with grade IV encephalopathy [6,19]. The consequences of cerebral edema include intracranial pressure (ICP) elevation, brain ischemia and hypoxia, and brainstem herniation, which are the most common causes of death in acute liver failure [43-45]. Liver transplantation is the only definitive treatment for cerebral edema, though uncontrolled ICP

elevation is a contraindication to liver transplantation. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Neurologic examination'.)

The classic signs of ICP elevation include systemic hypertension, bradycardia, and irregular respirations (referred to as Cushing's triad). Neurologic manifestations may include increased muscle tone, hyperreflexia, and altered pupillary responses. However, early in the course of acute liver failure, these signs and symptoms may be absent or difficult to detect [6]. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Neurologic examination'.)

Intracranial pressure monitoring — Because of the devastating consequences of ICP elevation and the difficulty in accurately assessing for its presence based upon clinical examination alone, some suggest invasive means of monitoring ICP to guide management. However, severe complications from ICP monitoring may develop, such as infection and bleeding, and observational studies of patients undergoing ICP monitoring did not find differences in overall survival between those who received ICP monitoring and those who did not [46-48]. In the United States, approximately half of the liver transplantation programs routinely use ICP monitoring [48]. We generally use ICP monitoring in those at greatest risk for cerebral edema, namely patients with grade IV encephalopathy or in patients with grade III encephalopathy that is rapidly progressing. (See "Evaluation and management of elevated intracranial pressure in adults", section on 'ICP monitoring'.)

Intracranial pressure monitoring is used to follow:

- ICP
- Cerebral perfusion pressure
- Cerebral oxygen consumption

The cerebral perfusion pressure is the difference between mean arterial pressure and ICP. Cerebral oxygen consumption is a function of cerebral blood flow and the oxygen gradient between arterial and jugular venous blood.

Prior to catheter placement, a computed tomographic (CT) scan of the brain should be obtained. While CT scans do not provide a reliable assessment of ICP, they are useful to rule out other possible causes of rapidly altered mental status, such as intracranial hemorrhage [6]. Before an ICP monitor is placed, any existing coagulopathy should be corrected. (See 'Bleeding prevention' above.)

Four types of catheters have been used to measure ICP:

- Epidural catheters – placed outside the dura mater
- Subdural catheters – placed beneath the dura mater
- Parenchymal catheters – placed directly into the brain parenchyma
- Intraventricular catheters – placed within a cerebral ventricle

The advantage of epidural catheters compared with the others is that they are less invasive and therefore cause fewer complications during placement. Their main disadvantage is that their recordings are not as accurate or reliable as the more invasive catheters.

The major complications from ICP monitoring are infection and bleeding. A review of 262 patients demonstrated a lower complication rate with epidural catheters than with subdural or parenchymal/intraventricular catheters (4 versus 20 and 22 percent, respectively) [37]. Approximately 1 percent of patients died as a result of complications from the placement of epidural catheters compared with 4 to 5 percent from the placement of subdural and parenchymal catheters, respectively [37]. For these reasons, epidural catheters are the most widely used.

Transcranial Doppler ultrasound — Transcranial Doppler ultrasound is another method being studied for the detection of ICP elevation. It noninvasively measures the velocity of blood flow in the proximal cerebral circulation and can be used to estimate ICP based on characteristic changes in waveforms that occur in response to increased resistance to cerebral blood flow [49-52].

Preventing intracranial pressure elevation — Methods to prevent ICP elevation include minimizing patient agitation/stimulation, elevating the head of the patient's bed, maintaining optimal fluid balance, and prophylactic administration of hypertonic saline.

Patients should be placed in an environment with minimal sensory stimulation since stimulation can raise ICP. For the same reasons, attempts should be made to keep the patient from becoming agitated. Nasogastric tube placement can cause gagging and thus should generally be performed only in patients who are intubated and sedated. Similarly, endotracheal suction should be minimized. In most cases the head of the patient's bed should be elevated to 30 degrees. However, bed elevation can also reduce cerebral perfusion. Thus, experts have recommended not raising the head of the bed if the cerebral perfusion pressure cannot be maintained at an appropriate level (ie, 50 mmHg) with bed elevation [34,53]. (See 'Setting' above and "Evaluation and management of elevated intracranial pressure in adults", section on 'Position'.)

Overhydration can elevate ICP, whereas hypotension due to intravascular volume depletion can decrease cerebral perfusion pressure. Thus, the fluid status of patients with acute liver failure

should be closely monitored. (See 'Hemodynamic management' above.)

The induction of hypernatremia may decrease water influx into the brain and thereby reduce cerebral edema and ICP. A potential clinical benefit was suggested in a randomized trial involving 30 patients with acute liver failure and grade III or IV encephalopathy who were randomly assigned to receive standard treatment plus hypertonic saline infusion to maintain serum sodium levels of 145 to 155 mEq/L or standard treatment alone [54]. ICP decreased significantly relative to baseline over the first 24 hours in the treatment group, but not in controls. The incidence of ICP elevation was also significantly lower in the hypertonic saline group.

Our approach is to prophylactically manage patients who are at high risk of developing cerebral edema with hypertonic saline (3 percent), with a goal serum sodium of 145 to 150 mEq/L [5]. High-risk patients include patients with grade IV encephalopathy, high ammonia levels (>150 micromol/L), or acute renal failure, and patients who require vasopressor support. Care must be taken when treating patients with hypertonic saline because an overly rapid induction of hypernatremia can lead to neurologic symptoms.(See "Manifestations of hyponatremia and hypernatremia in adults".)

Treatment of intracranial pressure elevation — In patients with an elevated ICP, the goals of therapy are to reduce the ICP to below 20 to 25 mmHg and to maintain cerebral perfusion pressure above 50 to 60 mmHg [2,55]. Approaches to lowering the ICP include administration of hyperosmotic agents (eg, mannitol) and hyperventilation, though the benefits are often transient. Mannitol is our preferred first-line approach to treatment of a patient with an elevated ICP.

Hyperosmotic agents — Hyperosmotic agents are often transiently effective in reducing cerebral edema. A bolus of mannitol (0.5 to 1.0 g/kg) is typically the first-line therapy for patients with an elevated ICP [2]. In small series, mannitol was shown to correct episodes of ICP elevation and improve survival [56,57]. One or two additional boluses may be given if needed, provided the serum osmolality is <320 mOsm/L. Patients receiving mannitol should be monitored for hyperosmolarity and hypernatremia. (See "Evaluation and management of elevated intracranial pressure in adults", section on 'Mannitol'.)

Patients with acute liver failure commonly have compromised renal function and oliguria and may develop fluid overload with mannitol administration. In this setting, fluid should be removed via ultrafiltration or other continuous venous hemofiltration methods with a goal of removing three to five times the fluid volume of the infused mannitol [19,35]. (See "Complications of mannitol therapy".)

Hypertonic saline has been studied for the prevention of ICP elevation in patients with acute liver failure, but not for the treatment of ICP elevation once present. However, some transplant centers use hypertonic saline to treat ICP elevation in patients with renal failure.

Hyperventilation — Hyperventilation can be considered for patients with an ICP above 20 mmHg, but its effects are transient, and many patients spontaneously hyperventilate. We use hyperventilation for patients with impending herniation, but do not use it for the routine management of ICP elevation in the absence of impending herniation.

Decreasing the PaCO2 to 25 to 30 mmHg via hyperventilation restores cerebrovascular autoregulation, resulting in vasoconstriction and a reduction in the ICP. However, in addition to the effects being temporary, there is concern that hyperventilation may worsen cerebral edema by causing cerebral ischemia [58,59]. In a randomized trial, hyperventilation did not reduce the incidence of cerebral edema or ICP elevation, but it did appear to delay the onset of cerebral herniation [60]. (See "Evaluation and management of elevated intracranial pressure in adults", section on 'Hyperventilation'.)

Barbiturates — If other measures to treat severe ICP elevation fail, a barbiturate coma should be induced with pentobarbital or thiopental. Our approach is to give a pentobarbital bolus of 3 to 5 mg/kg intravenously. Barbiturates decrease ICP, but may also result in systemic hypotension and thus decrease cerebral perfusion pressure. Because barbiturate clearance is markedly reduced in the setting of acute liver failure, neurologic assessment will not be possible for prolonged periods of time.

Treatments that do not work — While glucocorticoids such as dexamethasone are used in the management of ICP elevation related to brain tumors and some central nervous system infections, small randomized trials and observational studies have shown them to not be beneficial in patients with ICP elevation due to acute liver failure [56,61,62]. Because of a lack of efficacy, combined with a concern for infection, glucocorticoids should **not** be administered for the treatment of ICP elevation in patients with acute liver failure.

Experimental therapies — Other therapies to prevent or treat cerebral edema and ICP elevation continue to be studied.

Induction of hypothermia — Hypothermia decreases cerebral edema in animal models of liver failure, providing a rationale for study in humans [63]. A 2010 systematic review identified five case series with a total of 35 patients that together suggested a benefit of moderate hypothermia combined with ICP monitoring with regard to ICP, cerebral perfusion pressure, and cerebral blood flow [64]. However, more recent studies have had variable results. The following illustrate findings from individual reports:

- An initial report in humans included seven patients with uncontrolled ICP elevation in whom a core body temperature of 32 to 33°C was achieved using cooling blankets [65]. Four patients who were candidates for liver transplantation survived after an average of 13 hours of hypothermia prior to liver transplantation. Their mean ICP decreased from 45 to 16 mmHg and their mean cerebral perfusion pressure increased from 45 to 70 mmHg during hypothermia. Three patients who were unsuitable for liver transplantation died upon rewarming.

- A subsequent study included 14 patients with acute liver failure who had ICP elevations that were unresponsive to standard medical therapy [66]. The patients' core temperatures were reduced to 32 to 33°C using cooling blankets. Thirteen patients were successfully bridged to liver transplantation with a median of 32 hours of cooling. The mean ICP before cooling was 37 mm Hg and was reduced to 16 mm Hg within four hours of cooling. Mean arterial pressure and cerebral perfusion pressure increased, and the need for inotropic support was reduced.

- Another study performed after the systematic review included 97 patients with acute liver failure who had grade III or grade IV hepatic encephalopathy and underwent therapeutic hypothermia (core temperature reduction to 32 to 35°C) and 1135 patients with acute liver failure and grade III or IV encephalopathy who did not undergo therapeutic hypothermia [67]. Outcomes were similar between those treated with hypothermia and those who were not, including 21-day overall survival (62 versus 60 percent) and transplant-free survival (45 versus 39 percent).

Despite the potential benefits, hypothermia can also increase the risk of infection, cardiac dysrhythmias, and bleeding, all of which are known complications of acute liver failure [68]. As a result, more experience is required before this therapy can be routinely recommended. However, it is a reasonable option as a bridge to transplantation in patients who have failed other treatments, including barbiturate-induced coma. (See 'Barbiturates' above.)

Indomethacin — Indomethacin (25 mg IV over one minute) has been used in patients with elevated ICP refractory to other therapeutic modalities. It exerts its effects by causing cerebral vasoconstriction and can acutely decrease ICP [69,70]. While there are not enough data to recommend its use routinely, indomethacin can be considered in patients with an elevated ICP that fails to respond to standard treatment.

Seizures — Seizure activity in patients with acute liver failure is common but may be difficult to detect if patients are intubated and receiving paralytics. In the control arm of one trial, 7 of 22 patients (32 percent) had subclinical seizure activity detected by electroencephalogram (EEG)

[71]. In patients who require sedation, we use sedatives with anti-seizure activity. In patients who do not require sedation, we obtain routine (daily) EEGs to monitor for seizure activity. In addition, we will obtain an EEG in patients with clinical evidence of seizure activity.

Seizures in patients with acute liver failure should be treated promptly because seizure activity increases ICP and may cause cerebral hypoxia. Consensus recommendations suggest treatment with phenytoin, since patients with acute liver failure have a severely impaired ability to clear sedatives [2]. Patients who are refractory to phenytoin should receive short acting benzodiazepines.

Trials examining prophylactic phenytoin have had variable results regarding seizure prevention, though none has shown a survival benefit:

- One trial included 40 patients with acute liver failure who were randomly assigned to receive prophylactic phenytoin (15 mg/kg by slow intravenous infusion at a rate not exceeding 50 mg/min, followed by 100 mg doses at eight-hour intervals) or to serve as controls [71]. Subclinical seizure activity was observed less often in the group receiving phenytoin (15 versus 32 percent). Autopsy examinations were available in 19 patients and showed signs of cerebral edema less often in patients who had received phenytoin (22 versus 70 percent). However, a survival advantage was not detected with prophylactic phenytoin.

- No benefit from prophylactic phenytoin was observed in a second randomized trial involving 42 patients with acute liver failure [72]. Cerebral edema developed in 16 patients in the phenytoin group versus 15 in the control group. Similarly, seizures occurred in a similar proportion of patients (23 versus 25 percent, respectively). There was no overall mortality benefit.

These data do not support a role for prophylactic phenytoin in the treatment of acute liver failure.

Acute renal failure — Acute renal failure complicates acute liver failure in approximately 30 to 50 percent of patients [19,35,73]. The frequency of acute renal failure is higher (up to 75 percent) for etiologies of acute liver failure that are known to independently damage the kidneys, such as acetaminophen intoxication [14,55]. Once renal failure develops, it is usually progressive and is associated with a poor prognosis without liver transplantation [74,75].

Measures to preserve renal function include ensuring arterial perfusion by maintaining an adequate systemic blood pressure, identifying and treating infections promptly, and avoiding the use of nephrotoxic agents. If acute renal failure develops, continuous renal replacement

therapies, such as continuous venovenous hemofiltration, are better tolerated than intermittent modes of hemodialysis with regard to stability in cardiovascular and intracranial parameters [4,76]. (See "Continuous kidney replacement therapy in acute kidney injury", section on 'Indications'.)

Pulmonary complications — Pulmonary edema and pulmonary infections are encountered in approximately 30 percent of patients with acute liver failure [19]. Mechanical ventilation may be required to ensure adequate oxygenation. However, extreme caution must be used with positive end-expiratory pressure in patients with acute liver failure since it can worsen cerebral edema [19]. (See "Positive end-expiratory pressure (PEEP)".)

LIVER TRANSPLANTATION

The decision to proceed with liver transplantation depends upon the probability of spontaneous hepatic recovery. The goal is to differentiate patients who are likely to benefit from liver transplantation from those who are likely to recover spontaneously. In addition to optimizing organ allocation, correctly identifying patients likely to benefit from liver transplantation avoids life-long immunosuppression in patients who would have recovered without transplantation. In the United States and Europe, patients with acute liver failure who require transplantation are given the highest priority on the transplantation list. Of those who receive a transplant, one-year survival rates following liver transplantation are greater than 80 percent [77].

In addition to determining whether a patient is likely to recover spontaneously from acute liver failure, it is important to determine if the patient has contraindications to transplantation, such as severe cardiopulmonary disease or malignancy outside of the liver. In addition, in cases of intentional overdose, whether the patient is at high risk for future self-destructive behavior needs to be considered. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

Probability of spontaneous recovery — As a general rule, the most important factors for predicting the outcome in acute liver failure are the degree of encephalopathy (table 1), the patient's age, and the cause of the acute liver failure. These factors in part reflect the importance of the severity of the hepatic injury and the likelihood of reversal of the underlying process either spontaneously or with specific therapy (eg, N-acetylcysteine in acetaminophen toxicity).

Spontaneous recovery is more likely with lower grades of encephalopathy [74]:

- Grade I to II – 65 to 70 percent

- Grade III – 40 to 50 percent
- Grade IV – <20 percent

Patients younger than 10 or older than 40 years of age may have a lower likelihood of spontaneous recovery compared with patients between these ages. The importance of the etiology of the acute liver failure was demonstrated in a study of 308 patients with acute liver failure [78]. The short-term (three-week) transplant-free survival rate overall was 43 percent. The transplant free survival rate was ≥50 percent in patients with acute liver failure due to acetaminophen, hepatitis A, ischemia, or pregnancy-related acute liver failure. On the other hand, it was <25 percent for those whose liver failure was due to hepatitis B, autoimmune hepatitis, Wilson disease, Budd-Chiari syndrome, cancer, or an indeterminate cause.

Several other variables, such as the prothrombin time/INR and arterial ammonia levels, have been used to predict the probability of recovery, but their predictive accuracy has not been well established [7,55,79-82]. Liver histology has not proven to be accurate for predicting outcome and is only used in cases of diagnostic uncertainty [83]. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Liver biopsy'.)

Prognostic models — Several models have been developed for predicting the outcome in patients with acute liver failure to try to identify patients who are likely to benefit from liver transplantation [84-95]. The King's College Criteria are the most widely used for selecting patients for liver transplantation [74]. In addition, the Model for End-Stage Liver Disease (MELD) score, which is used to predict mortality in patients with chronic liver disease, has also been applied to patients with acute liver failure. Other scores that may also predict mortality in patients with acute liver failure include the Sequential Organ Failure Assessment (SOFA score) [90,91], the Clichy criteria [93,94], and the Acute Liver Failure Study Group (ALFSG) index [95].

King's College Criteria — The King's College Criteria were developed in a cohort of 588 patients with acute liver failure who were managed medically between 1973 and 1985 [74]. Recommendations for liver transplantation in acute liver failure were proposed based upon their outcomes (table 2).

The predictors are different based on the etiology of the acute liver failure (acetaminophen versus other causes). In patients with acute liver failure due to acetaminophen, recovery may be observed even in patients who have evidence of severe hepatocellular necrosis and synthetic dysfunction.

In acetaminophen-induced acute liver failure, there are two broad criteria for referral for orthotopic liver transplantation:

- An arterial pH of less than 7.30, irrespective of grade of encephalopathy **or**
- Grade III or IV encephalopathy with **both** a prothrombin time (PT) greater than 100 seconds and a serum creatinine concentration greater than 3.4 mg/dL (301 micromol/L)

For other causes of acute liver failure, referral for orthotopic liver transplantation is indicated for:

- A PT greater than 100 seconds, irrespective of the grade of encephalopathy **or**
- Any **three** of the following:
  - Age less than 10 or greater than 40 years
  - Unfavorable disease etiology, such as non-A, non-B viral hepatitis, idiosyncratic drug reactions, Wilson disease
  - Duration of jaundice before development of encephalopathy greater than seven days
  - PT greater than 50 seconds
  - Serum bilirubin greater than 18 mg/dL (308 micromol/L)

It should be noted that PT values may not be directly comparable across different laboratories because of use of different tissue factors.

The accuracy of the King's College Criteria has been evaluated in several studies and systematic reviews [96-99]:

- One systematic review of 14 studies of acetaminophen-induced liver failure estimated the overall sensitivity and specificity of the criteria for predicting mortality were 58 and 95 percent, respectively [96].
- In another study that included 145 patients with acute liver failure who were not transplanted, the positive and negative predictive values for mortality in those with acetaminophen toxicity were 88 and 65 percent, respectively [97]. The corresponding values for patients with other causes of acute liver failure were 79 and 50 percent, respectively. These values are slightly lower than the original King's College cohort. The relatively low negative predictive values indicate that these criteria are better able to predict patients with a poor prognosis than those with a good prognosis.
- Another systematic review of 18 studies of non-acetaminophen induced liver failure estimated a sensitivity for predicting mortality of 68 percent (95% CI 59-77 percent) and a specificity of 82 percent (95% CI 75-88 percent) [98]. Specificity was highest in studies of patients with high-grade hepatic encephalopathy (93 percent), and overall test characteristics were best in older studies. A possible explanation for this finding is that

improvements in the care of patients with acute liver failure have modified the performance of the criteria.

Model for End-stage Liver Disease (MELD) score — MELD is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) (calculator 1 and calculator 2). It was originally developed to predict survival following transjugular intrahepatic portosystemic shunt placement, but it has also been used to predict survival among patients with acute liver failure [89,100-103]. (See "Model for End-stage Liver Disease (MELD)".)

In a study of 91 patients with non-acetaminophen-related acute liver failure, the MELD score was compared with the King's College Criteria [100]. The King's College Criteria had a sensitivity and specificity for mortality of 88 and 71 percent, respectively. Similar results were obtained when a MELD score of 32 or higher was used to predict mortality (sensitivity of 79 percent and specificity of 71 percent).

Liver support — A number of approaches to perform the functions of the liver in an attempt to delay or obviate the need for liver transplantation in patients with acute liver failure continue to be studied. Among the most promising are artificial hepatic assist devices, auxiliary liver transplantation, a liver dialysis system, and xenotransplantation.

Artificial hepatic assist devices — Attempts have been made to develop an artificial hepatic assist device for acute liver failure that would operate on the same basic principles as hemodialysis for renal failure. However, developing a machine that performs the functions of the liver is inherently more difficult than developing one that performs the excretory functions of the kidneys because the liver performs a large number of diverse and vital synthetic functions. Results in patients treated with these systems have largely been disappointing and the systems are not widely available. As a result, they are generally not used in the management of patients with acute liver failure.

Support systems designed to treat patients with liver failure fall into two main categories, non-cell-based systems, including plasmapheresis, plasma exchange, albumin dialysis, and charcoal-based hemadsorption, and systems that incorporate living hepatocytes or hepatic tissue, also known as bioartificial liver support systems [104-108].

A systematic review that pooled 12 randomized controlled trials (with a total of 483 patients) using various bioartificial support systems concluded that overall they had no significant effect on mortality compared with standard medical therapy [109,110]. However, a meta-regression suggested that their effect depended upon the type of liver failure. A 33 percent reduction in

mortality was observed in patients with acute-on-chronic liver failure (RR 0.67, 95% CI: 0.51 to 0.90), while no significant benefit was detected in those with acute liver failure.

An extracorporeal liver replacement device, the molecular adsorbent recirculating system (MARS), is used for the treatment of drug overdoses, poisoning and hepatic encephalopathy and has also been studied in acute liver failure. (See "Amatoxin-containing mushroom poisoning (eg, Amanita phalloides): Clinical manifestations, diagnosis, and treatment", section on 'Elimination enhancement'.)

In a study 27 patients who received MARS therapy for different indications (ie, acute liver failure from severe liver trauma or toxic ingestion, or as a bridge to transplantation for massive hepatic necrosis), the overall patient survival rate was 60 percent [111].

Hepatocyte transplantation — Transplantation of hepatocytes is also under investigation and is discussed separately. (See "Hepatocyte transplantation".)

Auxiliary liver transplantation — Auxiliary liver transplantation involves placement of a reduced-size liver graft adjacent to the patient's native liver (auxiliary heterotopic liver transplantation) or in the hepatic bed after a portion of the native liver has been removed (auxiliary orthotopic liver transplantation). A potential advantage is that this procedure may support the patient while the native liver regenerates, obviating the need for chronic immunosuppression [55,112]. In addition, because only a relatively small portion of liver is required, the graft can be obtained from a donor liver that is being used for a standard orthotopic liver transplantation or from a living-related donor, thereby increasing the number of available organs. There are also reports of auxiliary liver grafts being reused in second recipients with chronic liver disease [113]. If the native liver recovers, the graft can be removed and transplanted into a second patient. While auxiliary liver transplantation shows promise, the procedure is technically difficult, and has not been adequately evaluated in controlled clinical trials.

While living donor liver transplantation (LDLT) has been reported for treating adults with acute liver failure, we do not typically use LDLT for such patients because of high MELD scores and the extensive donor selection process that is required prior to living donation [114]. (See "Living donor liver transplantation in adults".)

Xenotransplantation — Xenotransplantation (transplantation of a nonhuman organ) has been attempted for the treatment of acute liver failure. Prior to 1992, only 33 xenotransplantations had been performed in humans [55]. The longest graft survival was only nine months. Despite the initial disappointing results, this approach is being reevaluated, in

part because of advances in immunosuppression and the ability to manipulate donor antigen expression [115-119].

Other experimental approaches — Granulocyte colony-stimulating factor (G-CSF) has been studied for the treatment of acute-on-chronic liver failure (ACLF). The theory behind the approach is that mobilization of bone marrow-derived stem cells with G-CSF may promote hepatic regeneration. In a randomized trial with 47 patients with ACLF, 23 were assigned to receive G-CSF 5 mcg/kg subcutaneously daily for five days and then every three days for a total of 12 doses, and 24 were assigned to receive placebo [120]. None of the patients had decompensated liver disease prior to the onset of ACLF. Patients treated with G-CSF had a higher actuarial probability of survival at 60 days than those treated with placebo (66 versus 26 percent) and were less likely to develop hepatorenal syndrome (19 versus 71 percent), hepatic encephalopathy (19 versus 66 percent), or sepsis (14 versus 41 percent). None of the patients who survived underwent emergent liver transplantation.

High-volume plasma exchange has also been tried in patients with acute liver failure [121-123]. It is theorized that plasma exchange may have beneficial effect by removing plasma cytokines and adhesion molecules, replacing plasma factors, and modulating the immune system. In a randomized trial with 182 patients with acute liver failure, there was no difference between those treated with high-volume plasma exchange and those who received standard medical care alone in the primary endpoint of liver transplantation-free survival during hospitalization (26 and 36 percent, respectively; p = 0.17) [121]. However, the group who received high-volume plasma exchange did have higher overall hospital survival (59 versus 48 percent; hazard ratio after stratifying for liver transplantation 0.56, 95% CI 0.36-0.86).

PROGNOSIS

Overall, survival rates in patients treated for acute liver failure are greater than 60 percent [78,124]. Approximately 55 percent of patients will survive without needing a liver transplantation [124].

The prognosis of patients who are listed for transplantation is variable and cannot always be predicted accurately. An illustrative study from the United States included 308 patients with acute liver failure, of whom 67 percent survived [78]. Of 135 patients who had been listed for transplantation, 66 percent received a transplantation, 22 percent died while awaiting transplantation, and 12 percent recovered without transplantation. In other series, death rates among patients listed for transplantation are as high as 40 percent [125,126].

Following liver transplantation, the one-year survival rate is approximately 80 percent [77]. The majority of deaths among patients who undergo liver transplantation are due to neurologic complications or sepsis and occur within three months of the transplantation [2].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute liver failure".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Liver transplant (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **General principles** – The general management of patients with acute liver failure includes ensuring the patient is being cared for in the proper setting, monitoring for worsening liver failure, treating complications, and providing nutritional support. (See 'General management' above.)

  Patients with acute liver failure should be managed at a liver transplant center in the intensive care unit (ICU) whenever possible. Transfer to a liver transplant center should not delay initiation of diagnostic testing or therapy. (See 'Setting' above.)

- **Laboratory monitoring** – Serial laboratory tests are used to follow the course of a patient's liver failure and to monitor for complications. Serum aminotransferases and bilirubin should be monitored daily. More frequent monitoring (three to four times daily) should be performed for coagulation parameters, complete blood counts, metabolic panels, and arterial blood gasses. We perform finger sticks to monitor blood glucose levels every six hours. (See 'Laboratory testing' above.)

- **Management of complications**

  - **Hepatic encephalopathy** – Lactulose has not been shown to improve overall outcomes, and it may lead to bowel distension that could result in technical difficulties during liver transplantation. However, if lactulose is used, endotracheal intubation should be performed prior to its administration in patients with advanced (grade III or IV) encephalopathy. (See 'Hepatic encephalopathy' above.)

Continuous renal replacement therapy (CRRT) is also an option for removing ammonia in addition to managing other metabolic disturbances and fluid balance.

  - **Cerebral edema** – In patients at high risk for developing cerebral edema (ie, patients with grade IV encephalopathy or with grade III encephalopathy that is rapidly progressing), we suggest using intracranial pressure (ICP) monitoring (when expertise in such monitoring is available) to guide treatment for cerebral edema, rather than basing treatment decisions on the clinical signs of cerebral edema (**Grade 2C**). Early in the course of acute liver failure, signs and symptoms of cerebral edema may be absent or difficult to detect. Complications of cerebral edema include ICP elevation and brainstem herniation. However, ICP monitoring has not been shown to increase overall survival and is associated with complications such as infection and bleeding. (See 'Cerebral edema' above.)

    General measures to prevent ICP elevation include minimizing stimulation, maintaining appropriate fluid balance, and elevating the head of the patient's bed. For patients who are at high risk of developing cerebral edema, we also suggest prophylactic treatment with hypertonic saline (3 percent), with a goal serum sodium of 145 to 150 mEq/L (**Grade 2C**). High-risk patients include patients with grade IV encephalopathy, high ammonia levels (>150 micromol/L), or acute renal failure, and patients who require vasopressor support. (See 'Preventing intracranial pressure elevation' above.)

    In patients with ICP elevation, we suggest initial treatment with a bolus of mannitol (0.5 to 1.0 g/kg) rather than hyperventilation therapy (**Grade 2C**). One or two additional boluses may be given if needed, provided the serum osmolality is <320 mOsm/L. The

goals of therapy are to maintain the ICP below 20 to 25 mmHg and the cerebral perfusion pressure above 50 to 60 mmHg. Patients receiving mannitol should be monitored for hyperosmolarity and hypernatremia. (See 'Hyperosmotic agents' above.)

- **Prognosis** – Approximately 40 percent of patients with acute liver failure will recover spontaneously with supportive care. Prognostic models have been developed to help identify patients who are unlikely to recover spontaneously, because the decision to proceed with liver transplantation depends in part upon the probability of spontaneous hepatic recovery. Of those who receive a transplantation, one-year survival rates are greater than 80 percent. (See 'Liver transplantation' above and 'Prognosis' above.)

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Topic 3570 Version 40.0

GRAPHICS

Grading system for hepatic encephalopathy

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

EEG: electroencephalogram.

Graphic 62922 Version 2.0

King's College Hospital criteria for liver transplantation in acute liver failure

Acetaminophen-induced disease
Arterial pH <7.3 (irrespective of the grade of encephalopathy)
OR
Grade III or IV encephalopathy AND
Prothrombin time >100 seconds AND
Serum creatinine >3.4mg/dL (301 µmol/L)
All other causes of acute liver failure
Prothrombin time >100 seconds (irrespective of the grade of encephalopathy)
OR
Any **three** of the following variables (irrespective of the grade of encephalopathy)
1. Age <10 years or >40 years
2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
3. Duration of jaundice before onset of encephalopathy >7 days
4. Prothrombin time >50 seconds
5. Serum bilirubin >18 mg/dL (308 µmol/L)

Data from: O'Grady JG, Alexander GJM, Hayllar KM, et al. Gastroenterology 1989; 97:439.

Graphic 77717 Version 2.0

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