

## Acute Liver Failure

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Acute liver failure (ALF) is a potentially life-threatening condition that occurs in the setting of extensive injury to hepatocytes. Causes of ALF range from acetaminophen toxicity to viral hepatitis to other less common causes, including Wilson's disease, Budd-Chiari syndrome, and ingestion of toxins. Complications of ALF are multisystemic and can be associated with neurologic impairment, hematologic derangements, renal dysfunction, and metabolic abnormalities. ALF can be difficult to recognize and requires prompt critical decision making to remove the offending agent before the condition becomes potentially fatal. This article describes the case of a woman with ALF from unintentional acetaminophen toxicity. Clinical presentation and course of ALF are reviewed, and the importance of early recognition and intensive care monitoring are highlighted.

A 45-year-old Hispanic woman with a history of systemic lupus erythematosus, depression, recurrent pyelonephritis, pancreatitis, cholecystectomy, and chronic abdominal pain was admitted to a community hospital for worsening abdominal pain. She had previously been prescribed hydrocodone bitartrate/acetaminophen for chronic abdominal pain. Preoperative laboratory investigations revealed elevated alanine aminotransferase and aspartate aminotransferase levels to the 9000s U/L, an international normalized ratio of 2.5, and a platelet count of 93,000 cells/ $\mu$ L. She underwent emergent exploratory laparotomy for continued progressive abdominal pain. On postoperative day 2, she was transferred to another hospital for management of acute liver failure. Upon arrival, neurologic status worsened, necessitating intubation and mechanical ventilation for airway protection. The patient's hospital course was complicated by cerebral edema requiring intracranial pressure monitoring, acute renal failure, fever, and pleural effusion. Treatment was initiated with lactulose, continuous venovenous hemodialysis, and broad-spectrum antibiotics. Over the next several days, her neurologic status improved, renal failure resolved, and she was subsequently transferred from the medical intensive care unit to the general medicine floor for continued observation and medical care. On postoperative day 16, the patient was discharged home after recovering from acute liver failure following an accidental overdose of hydrocodone bitartrate/acetaminophen.

**A**cute liver failure (ALF) is a potentially life-threatening condition that occurs in the setting of extensive injury to hepatocytes that impairs the liver's ability to maintain normal function. Liver impairment is usually accompanied by evidence of coagulation

derangement and some degree of hepatic encephalopathy. In general, management of ALF centers on identifying and removing the offending agent, monitoring in the intensive care unit (ICU), and liver transplantation when indicated. This article reviews the pathophysiology, etiology, clinical manifestations, and management of ALF.

### DEFINITION

ALF is characterized by the presence of coagulopathy (international normalized ratio [INR]  $\geq$  1.5) and hepatic encephalopathy in the absence of preexisting chronic liver disease, with symptom onset within 26 weeks.<sup>1</sup> The term acute liver failure has evolved since the original term fulminant hepatic failure was proposed by Trey and Davidson.<sup>2</sup> The terms hyperacute, acute, and subacute hepatic failure were adopted later to classify hepatic failure based on the temporal onset of jaundice until the development of encephalopathy. To avoid confusion, only the term ALF will be used in this review.

### EPIDEMIOLOGY

ALF is relatively uncommon, with nearly 2800 cases diagnosed in the United States each year.<sup>3</sup> Drug-induced ALF, specifically acetaminophen toxicity, has surpassed viral hepatitis as the most common etiology in the United States and the United Kingdom.<sup>4,5</sup> In 2002, acetaminophen toxicity was the cause of liver failure in

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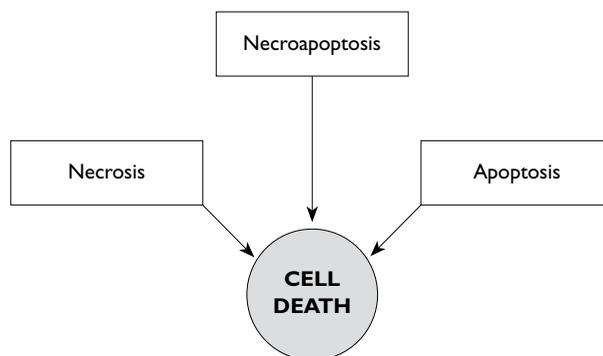
### TAKE HOME POINTS

- Acute liver failure (ALF) is characterized by the presence of coagulopathy (international normalized ratio  $\geq 1.5$ ) and encephalopathy in the absence of preexisting liver disease, with symptom onset within 26 weeks.
- Acetaminophen is the most common cause of ALF in the United States and the United Kingdom, but hepatitis A and B virus infections are leading causes in other parts of the world.
- The mechanism of hepatocellular death involves intricate cellular changes mediated by the mitochondrial permeability transition, which determines the pathway to cell death via a process that has been termed necroapoptosis.
- Diagnosis of ALF requires detailed history taking, physical examination, and pertinent laboratory studies.
- Management of ALF is centered on identifying and removing the offending agent, monitoring the patient, and liver transplantation, if appropriate.
- Liver transplantation is the only definitive therapy for ALF, provided a patient is an acceptable candidate.

39% (120 of 308) of patients, and nonacetaminophen and viral-related ALF accounted for 13% and 12% of cases, respectively.<sup>6</sup> Median age at diagnosis was 38 years, women were more often affected than men, and the incidence was greater among whites.<sup>6</sup> Hepatitis A and B are the most commonly identified causes of ALF in France and Japan,<sup>3</sup> while hepatitis E is a significant cause of ALF in India and Russia.<sup>1</sup> Mortality associated with ALF remains substantial, accounting for approximately 6% of deaths related to liver disease.<sup>3</sup> Earlier studies reported mortality rates near 85% before transplantation;<sup>7</sup> however, in the posttransplant era, 1-year survival rates are estimated at 60% to 80%.<sup>6,7</sup>

### PATHOPHYSIOLOGY

The liver is an essential organ with a number of major functions, including cellular metabolism, protein synthesis, and production of clotting factors. The principal mechanism involved in ALF is alterations in hepatic morphology, resulting in cell death either by cellular necrosis or apoptosis (**Figure 1**).<sup>8,9</sup> Necrosis occurs as a result of depletion of adenosine triphosphate (ATP) due to oxidative stress, which leads to a disruption



**Figure 1.** Mechanism of hepatocyte death in acute liver failure.

tion in cellular homeostasis and a loss of membrane integrity. These intricate intracellular changes promote remodeling of the plasma membrane and formation of balloon-like structures on the surface of the cell.<sup>10</sup> When subjected to stress, these structures can burst, triggering the release of cellular contents and culminating in an inflammatory response. In contrast, apoptosis involves receptor-mediated signaling pathways and the sequential activation of proteolytic caspases,<sup>8,9</sup> biochemical reactions for which ATP is essential. The intrinsic and extrinsic pathways are 2 main pathways that have been described in ALF-associated apoptosis.<sup>9</sup> The extrinsic pathway involves a class of death receptors on the cell surface that induce cell death via a receptor-ligand complex, prompting activation of the caspase cascade. The intrinsic pathway is characterized by the release of cytochrome c from the mitochondria, which occurs in response to oxidative stress. In the presence of ATP, cytochrome c activates the caspase cascade with the help of other proapoptotic factors.

A recent review suggests that necrosis and apoptosis may alternatively occur in response to the same inciting events mediated by the mitochondrial permeability transition in a process that has been termed *necroapoptosis*.<sup>9</sup> Mitochondrial permeability transition has been well described and is thought to be an important regulator in cell death. In response to physiologic stress, the mitochondrial membrane undergoes a series of events that leads to the opening of permeability transition pores. As a result, mitochondrial contents (eg, cytochrome c) are extruded into the intracellular medium and the pathway of necrosis or apoptosis ensues depending on the availability of ATP.

### ETIOLOGY

Acetaminophen toxicity is the most common identifiable cause of ALF in the United States, followed by other

**Table 1.** Causes of Acute Liver Failure

<b>Most common</b>
Acetaminophen
Drugs (isoniazid, statins, phenytoin [see Table 2])
Hepatitis A, B, D, and E viruses
<b>Others</b>
Toxins ( <i>Amanita phalloides</i> )
Cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, herpes simplex virus
Sepsis
Wilson's disease
Autoimmune hepatitis
Acute fatty liver of pregnancy
Metastatic carcinoma (ie, breast cancer, lymphoma)
Indeterminate
Herbs (eg, kava kava, germander, rattlesnake, gum thistle, comfrey, ragwort, valerian, tansy, skullcap, buckthorn, kombucha)

drug-related liver injury, viral hepatitis, autoimmune hepatitis, Wilson's disease, Budd-Chiari syndrome, toxins, and herbs (Table 1).<sup>4-6,11</sup>

**Acetaminophen Toxicity**

Arguably the most popular analgesic and antipyretic agent in the United States, acetaminophen (and acetaminophen-containing medications) are a common cause of ALF.<sup>4-6,11</sup> The recommended daily dose of acetaminophen is 4 g or less.<sup>6,12</sup> Amounts of acetaminophen in excess of 4 g/day have been shown to have a dose-dependent effect on hepatocytes, resulting in catastrophic liver damage, although ALF resulting from therapeutic doses of acetaminophen has been described as well.<sup>13</sup> The mechanism responsible for hepatocyte injury is thought to be related to the generation of N-acetyl-p-benzoquinone imine (NAPQI) when acetaminophen is metabolized by cytochrome P450 2E1 following ingestion. Acetaminophen overdose can deplete glutathione stores, allowing NAPQI to adhere to proteins that form adducts that mediate mitochondrial injury, ultimately leading to hepatocyte death.<sup>4,14</sup> Some evidence suggests that preexisting conditions such as alcohol abuse may influence the liver's susceptibility to lower doses of acetaminophen.<sup>15,16</sup> Unintentional overdose of acetaminophen is increasingly reported. According to 1 study, cases of accidental overdose of acetaminophen outnumbered cases of intentional overdose, and patients who accidentally overdosed tended to have a similar clinical course and survival outcomes when compared with patients with intentional overdose.<sup>5</sup> Findings from

**Table 2.** Selected Drugs Known to Cause Acute Liver Failure

Amoxicillin	Halothane	Ofloxacin
Carbamazepine	Ibuprofen	Phenytoin
Clavulanic acid	Imipramine	Pyrazinamide
Dapsone	Isoniazid	Rifampin
Diclofenac	Ketoconazole	Statins
Disulfiram	Lisinopril	Sulfonamides
Efavirenz	Metformin	Tetracycline
Erythromycin	Methyldopa	Valproic acid
Etoposide		

this study further suggest that when compared with all other causes of ALF, patients who had ingested acetaminophen, regardless of intent, had higher rates of spontaneous recovery and better outcomes.<sup>5</sup>

**Drug-Related Liver Failure**

In addition to acetaminophen, other frequently used medications have been shown to cause hepatic injury, including antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants (Table 2). Drug-induced ALF is often considered after known causes of ALF have been excluded. A significant number of these agents are idiosyncratic in nature, thus making it difficult to predict the risk for developing ALF after exposure. A recent review highlighting results from the Acute Liver Failure Study Group registry from 1998–2007 found that drug-induced liver failure was the cause of ALF in 119 of 1003 (12%) patients.<sup>17</sup> These patients had a spontaneous survival rate of 26% and a lower overall survival rate when compared with patients with other identifiable causes of ALF.<sup>17</sup>

**Viral Hepatitis**

The hepatotropic viruses are established causes of ALF.<sup>1</sup> In the United States, hepatitis A virus and hepatitis B virus (HBV) represent the most common viral causes (approximately 4% and 8%, respectively).<sup>1</sup> The incidence of hepatitis D virus–associated ALF is difficult to determine because it can occur as coinfection or superinfection with HBV. Pregnant women with acute hepatitis E virus infection are more vulnerable to developing ALF, and this is particularly more common in pregnant women in East Asia.<sup>18</sup> Other known but less frequent viral causes of ALF include cytomegalovirus, varicella-zoster virus, herpes simplex virus, and Epstein-Barr virus.<sup>1,4,18-21</sup>

**Other Causes**

Wilson's disease, Budd-Chiari syndrome, autoim-

**Table 3.** Clinical Clues to Acute Liver Failure in History and Physical Examination

Symptom/Feature	Possible Cause
Absence of jaundice	Acetaminophen ingestion
Intense jaundice	Wilson's disease (as a result of hemolysis)
Tender hepatomegaly with ascites	Budd-Chiari syndrome
Abdominal pain, vomiting, and diarrhea	<i>Amanita</i> toxin ingestion
Pregnant woman	Acute fatty liver of pregnancy

mune hepatitis, herbs, and toxins have been implicated as causes of ALF (Table 1).<sup>1</sup> Wilson's disease is a genetic disorder of abnormal copper metabolism. Patients typically present in the second decade of life with evidence of ALF that may be accompanied by hemolytic anemia with a precipitous elevation in indirect bilirubin.<sup>22</sup> Korman et al<sup>22</sup> reported that an increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio in combination with an alkaline phosphatase to total bilirubin ratio less than 4 was highly predictive of Wilson's disease in ALF. Wilson's disease has a high mortality rate in the absence of liver transplantation.<sup>22</sup> Budd-Chiari syndrome occurs as a result of hepatic venous outflow obstruction, and causes include hepatic vein thrombosis, malignancy, and polycythemia vera.<sup>23</sup> The classic presentation of Budd-Chiari syndrome includes hepatomegaly, abdominal pain, and ascites.<sup>23</sup> Autoimmune hepatitis occurs at all ages and is seen more frequently in women.<sup>24</sup> Diagnosis can be made based on the presence of autoantibodies and a liver biopsy that may demonstrate characteristic histologic findings of interface hepatitis and plasma cell infiltration.<sup>24</sup>

#### Acute Liver Failure of Unknown Etiology

It is not always possible to determine the cause of ALF. Ostapowicz et al<sup>6</sup> reported that 53 of 308 cases of ALF were indeterminate and that patients with an unidentifiable cause of ALF tended to have lower short-term survival rates in the absence of transplantation as compared with patients with more prevalent causes. Inability to identify the cause of ALF may be related to several factors, including insufficient history taking, availability of diagnostic studies at the time of presentation, and presence of unknown viral causes.<sup>11</sup>

#### APPROACH TO EVALUATION

The clinical presentation of ALF varies, and symptoms can range from mild gastrointestinal upset to generalized

malaise to confusion.<sup>1,4</sup> A detailed patient history is essential for identifying the cause of ALF. Physical examination is useful in evaluating for evidence of encephalopathy and chronic liver disease and may offer clues to the underlying cause of hepatic injury (Table 3).<sup>22,23,25-27</sup> The patient's mental status should be carefully assessed and monitored because neurologic status may subtly change and can progress rapidly to coma. Jaundice may not be apparent at the time of onset due to low serum bilirubin levels. Because patients may have preserved liver function despite having liver injury, bilirubin may not be elevated. However, serum bilirubin generally increases later in the course of ALF due to lack of liver metabolism. An abdominal examination may illicit tenderness. Because destruction of hepatocytes leads to release of cellular components into circulation, serum AST and ALT are invariably elevated. Other laboratory and serologic tests can be helpful in determining the cause of liver failure (Table 4). A disproportionate increase in bilirubin and alkaline phosphatase typically indicates hepatic injury at the level of the bile ducts. A liver biopsy may be useful in confirming the etiology when laboratory tests are inconclusive.<sup>28</sup> Transjugular liver biopsy is usually preferred over percutaneous biopsy to avoid bleeding complications.

The complications of ALF are multisystemic and can be associated with neurologic impairment, hematologic derangements, renal dysfunction, and metabolic abnormalities, as seen in the case patient.<sup>1,29</sup> The cascade of events in ALF can lead to multiorgan failure and has been associated with high mortality. Multiorgan failure precludes potential candidates from liver transplantation.

#### Hepatic Encephalopathy

Hepatic encephalopathy is a common complication in patients with ALF.<sup>30</sup> The mechanism of ALF-associated encephalopathy continues to be a topic of investigation. The altered sensorium that occurs in ALF is believed to be caused by abnormalities in the regulation of neurotransmitters.<sup>30,31</sup> Vaquero et al<sup>30</sup> have proposed that the underlying mechanism in the development of cerebral edema is strongly correlated with increased circulating ammonia and the production of glutamine accompanied by intracellular fluid shifts in response to an alteration in cellular osmolarity. These fluid shifts result in neuronal swelling and an increase in brain volume, which clinically manifests as increased intracranial pressure (ICP).<sup>30</sup> Dysautoregulation of cerebral blood flow has also become a point of interest in the pathogenesis of cerebral edema. Other confounding factors such as infection, release of toxins from liver necrosis, and

hyponatremia are believed to contribute to the pathogenesis of cerebral edema.<sup>30</sup> Compromised cerebral perfusion that results from cerebral edema and increased ICP can lead to irreversible brain damage. Particularly worrisome is the risk of uncal herniation and death. Computed tomography may be useful in identifying space-occupying lesions, but its utility in evaluating cerebral edema has not been validated.<sup>32,33</sup> Some patients may display clinical signs of encephalopathy only, without accompanying radiographic evidence of cerebral edema or increased ICP.<sup>32</sup>

### Coagulopathy

The liver synthesizes clotting factors responsible for regulating coagulation homeostasis during bleeding. A disturbance in the production of these clotting factors may lead to abnormal bleeding; however, clinically significant bleeding is seen in less than 20% of patients with ALF.<sup>29</sup> Sites of abnormal bleeding include the gastrointestinal tract, puncture wounds, and nasopharynx.<sup>29</sup> As a separate but related entity, thrombocytopenia is often observed in patients with ALF, and its causes include disseminated intravascular coagulopathy or a decrease in the synthesis of thrombopoietin.<sup>1,29</sup>

### Renal Failure

Renal failure is a common complication in ALF and is estimated to occur in more than 50% of patients with ALF.<sup>33</sup> The loss of renal function is multifactorial and may be directly related to the primary liver insult. The damage to the kidneys from acetaminophen typically leads to acute tubular necrosis (ATN).<sup>34</sup> Hypovolemia from reduced intravascular volume due to poor oral intake or cellular fluid shifts can also precipitate renal failure.<sup>35</sup> Additional consideration has been given to the vasodilatory effect of toxins from infection.<sup>35</sup>

### Infection

All patients with ALF are at risk for bacterial and fungal infections and should be monitored for signs of infection. In 1 study, bacterial infections were seen in nearly 80% of patients who developed ALF.<sup>36</sup> Staphylococcal and streptococcal bacteria were the most commonly identified organisms.<sup>36</sup> A similar study isolated *Candida albicans* in a significant number of patients.<sup>37</sup> This is particularly important because infections may preclude patients from liver transplantation, resulting in increased mortality.

### Metabolic Abnormalities

Because many biochemical processes (eg, gluconeogenesis, glycogenolysis) take place in the liver, a num-

**Table 4.** Initial Diagnostic Tests for Acute Liver Failure

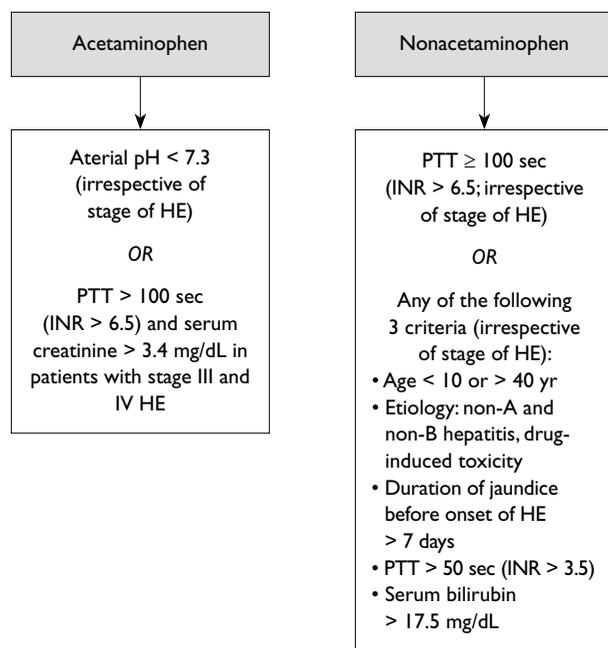
Complete blood count
Basic metabolic panel
Aspartate aminotransferase/alanine aminotransferase
Alkaline phosphatase
Bilirubin
Acute hepatitis panel (hepatitis A and B viruses)
Antinuclear antibody
Smooth muscle antibody
Amylase and lipase
Ceruloplasmin
Prothrombin time, partial thromboplastin time, international normalized ratio
Anti-liver/kidney microsomal antibody
Ammonia
HIV antibody
Serum acetaminophen
Serum and urine copper
Urine toxicology
Lactate dehydrogenase
β-hCG (females)

ber of metabolic derangements can be seen in patients with ALF. Hypoglycemia can cause altered mental status. A careful assessment must be performed as part of the physical examination to distinguish between the altered mental status associated with cerebral edema and that of hypoglycemia. This potential complication is often unrecognized but can be prevented with frequent monitoring. Other metabolic abnormalities may include hypokalemia, hypophosphatemia, and hypomagnesemia. Patients can also develop complicated acid-base disturbances. Both alkalosis and acidosis are known to occur.<sup>1</sup>

### Severity Assessment

Predicting recovery from ALF is challenging. Scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) and Model for End-Stage Liver Disease are used to grade the severity of illness in critically ill patients.<sup>38,39</sup> The APACHE scoring system utilizes a numeric score calculated from several physiologic parameters, with higher scores suggesting greater disease severity and higher rates of mortality.<sup>38</sup> Gc-globulin (vitamin D-binding protein) is a plasma protein that is synthesized in the liver that has been shown to have some value in predicting outcome in nonacetaminophen-related ALF.<sup>40</sup>

The decision to proceed with liver transplantation



**Figure 2.** King's College Hospital criteria. HE = hepatic encephalopathy; INR = international normalized ratio; PTT = prothrombin time. (Data from Polson J. Assessment of prognosis of acute liver failure. *Semin Liver Dis* 2008;28:218–25; Bernal W, Wendon J. Liver transplantation in adults with acute liver failure. *J Hepatol* 2004;40:192–7; and O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439–45.)

depends upon a comprehensive evaluation of ALF. Several prognostic models have been developed to identify patients who could benefit from liver transplantation.<sup>41</sup> The King's College Hospital Criteria (**Figure 2**) have a high specificity for predicting the outcome of ALF, although the sensitivity remains low.<sup>42</sup> Alternatively, the Clichy criteria, which employ clotting factor V, age, and degree of hepatoencephalopathy as predictors of outcome, have been considered in ALF.<sup>42</sup> The often unpredictable course of ALF reduces the utility of prognostic models, and further investigation of these models is warranted.<sup>41</sup>

## MANAGEMENT

To ensure optimal management of ALF, prompt recognition and early transfer to a transplant center are paramount. Efforts should focus on identifying and eliminating the offending agent, supportive care in an ICU setting, and liver transplantation when indicated. Several known causes of ALF require specific therapy directed at the insult responsible for hepatocellular injury (**Table 5**),<sup>1,4,22,25,43</sup> while other treatments should be targeted at the presenting complications of ALF (**Table 6**).

**Table 5.** Selected Therapies for Causes of Acute Liver Failure

Etiology	Therapy	Reference
Acetaminophen	N-acetylcysteine	Fontana <sup>4</sup>
Hepatitis B virus	Lamivudine	Tillmann et al <sup>43</sup>
Herpes simplex virus	Acyclovir	Polson and Lee <sup>1</sup>
Wilson's disease	Liver transplantation	Korman et al <sup>22</sup>
<i>Amanita</i> toxin	Penicillin/silibinin	Polson and Lee <sup>1</sup>
Fatty liver of pregnancy	Delivery	Castro et al <sup>25</sup>

The gold standard therapy for acetaminophen toxicity is N-acetylcysteine (NAC). Note that the Rumack-Matthew nomogram is not predictive of hepatic injury in chronic acetaminophen ingestion. Therefore, NAC is given regardless of the timing of acetaminophen overdose and should be continued until liver function recovers.<sup>4,14</sup> NAC is usually given intravenously but can be administered orally. Clinical trials are needed to compare the clinical efficacy of oral versus intravenous (IV) NAC preparations.

## Hepatic Encephalopathy and Cerebral Edema

As previously mentioned, hepatic encephalopathy is thought to be related to cerebral edema. Any signs of worsening neurologic status warrant prompt attention. Computed tomography of the brain should be performed early in the course to assess for evidence of cerebral edema. The recommended medical approach to hepatic encephalopathy corresponds to the degree of cerebral edema (**Table 7**). Treatment for stage I hepatic encephalopathy is largely supportive with frequent neurologic assessments to monitor for worsening mental status.<sup>35</sup> Patients with stage II hepatic encephalopathy should be monitored in an ICU. Lactulose is an osmotic agent commonly used to reduce elevated levels of ammonia. The routine use of lactulose is not recommended and should be administered with caution due to the potential for increased gaseous distention, aspiration, and hypovolemia.<sup>44</sup> Patients with stages III and IV encephalopathy should be closely monitored and require endotracheal intubation for airway protection. Sedation should be initiated prior to intubation. A recent review suggests that propofol and IV opiates can be used for sedation purposes.<sup>35</sup> Other supportive measures, including head elevation to 30 degrees, administration of IV mannitol, and hypertonic saline infusions, should be performed to prevent or reduce the occurrence of ICP (**Table 6**). The use of an ICP monitoring device may be indicated, although evidence to support survival associated with this device is lacking.<sup>45</sup> There are benefits and disadvantages to ICP monitoring. One study found that

**Table 6.** Management of Complications of Acute Liver Failure

Complications	Management
Hepatic encephalopathy	Admit to ICU, brain CT, frequent neurologic examinations, lactulose, endotracheal intubation for airway protection
Cerebral edema	ICP monitoring, head elevation, IV mannitol, hypertonic saline
Coagulopathy	Vitamin K, fresh frozen plasma, platelet transfusion if clinically indicated
Renal failure	Avoid nephrotoxic agents, continuous venovenous hemodialysis
Infection	Surveillance cultures, low threshold for empiric antimicrobials
Metabolic abnormalities	Continuous glucose infusion, replete potassium, magnesium, phosphate

CT = computed tomography; ICP = intracranial pressure; ICU = intensive care unit; IV = intravenous.

Data from references 1, 4, 35, and 44.

ICP monitoring offered early detection and improved management of ICP and also helped determine which patients would be good candidates for liver transplantation.<sup>45</sup> Placement of a monitoring device may cause intracranial hemorrhage, although clinically significant bleeding was reported in only 10% of cases in this study.<sup>45</sup> Correcting coagulopathy prior to placement of the device is critical and can be achieved with fresh frozen plasma and other measures such as administration of recombinant factor VIIa.<sup>44,45</sup>

### Renal Failure

Appropriate measures should be taken to ensure adequate intravascular volume and hemodynamic stability, as these efforts have the potential to prevent renal failure and ameliorate any existing renal insufficiency. Volume depletion should be corrected cautiously to avoid excessive administration of free water, which can exacerbate cerebral edema.<sup>46</sup> In the setting of severe renal failure, renal replacement therapy is usually indicated. Continuous venovenous hemodialysis has been shown to be more effective than intermittent hemodialysis in achieving precise control of renal parameters.<sup>47,48</sup> Additional efforts to avoid nephrotoxic agents and limit use of IV contrast are prudent.

### Coagulopathy

Fresh frozen plasma should be reserved for invasive procedures or signs of active bleeding. Thrombocytopenia should be managed conservatively. In the setting of profound thrombocytopenia (platelet count

**Table 7.** Stages of Hepatic Encephalopathy

Stage I	Minimal change in sensorium, alterations in sleeping pattern
Stage II	Disorientation, drowsy, decreased alertness, asterixis
Stage III	Increased somnolence, confusion, asterixis, hyperreflexia
Stage IV	Unresponsive to verbal or painful stimuli, coma

≤ 10,000 cells/ $\mu$ L), platelet transfusion may be indicated. Histamine-2 ( $H_2$ ) receptor blockers have been shown to reduce gastrointestinal bleeding.<sup>1</sup> There is also growing evidence that proton pump inhibitors may be efficacious in managing patients with gastrointestinal bleeding.<sup>1,4</sup> One study found that proton pump inhibitors are as effective as  $H_2$  receptor blockers in preventing stress-related mucosal bleeding.<sup>49</sup>

### Infection

The use of prophylactic antibiotics in ALF remains controversial, with little data to support a mortality benefit. It is recommended that early surveillance cultures be drawn.<sup>1,32</sup> Early signs of infection should prompt immediate administration of antibiotics and/or antifungal agents.

### Metabolic Abnormalities

Early recognition of hypoglycemia is paramount. Rapid correction of hypoglycemia can be achieved with continuous glucose infusion. Serum glucose monitoring should be performed hourly.<sup>4</sup> Frequent monitoring and correction of other metabolic derangements commonly seen in ALF (hypokalemia, hypophosphatemia, and hypomagnesemia) are critical.

### Liver Transplantation

Orthotopic liver transplantation is the only definitive therapy for patients who do not recover from ALF with the aforementioned management strategies. ALF-associated orthotopic liver transplantation accounted for approximately 7% of all orthotopic liver transplantations in 2005.<sup>3</sup> One-year survival rates are estimated at 60% to 80%.<sup>7</sup> Ostapowicz et al<sup>6</sup> reported similar survival rates, with an 84% posttransplant survival rate at 3 weeks. Success in this area has been largely due to appropriate timing of liver transplantation, selection of candidates of liver transplantation, advanced surgical techniques, and improved immunosuppressive therapy and posttransplant management. The United Networks of Organ Sharing listing criteria for liver transplantation for ALF are shown in **Table 8**.

**Table 8.** United Networks of Organ Sharing Criteria for Acute Liver Failure–Related Liver Transplant Listing

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Aged $\geq$ 18 yr without preexisting liver disease except for Wilson's disease
Life expectancy $\leq$ 7 days
Development of hepatic encephalopathy within a timeframe of 8 wk of onset of acute liver failure
The patient must also meet 1 of the following criteria:
Admission to intensive care unit on mechanical ventilator
Renal failure requiring renal replacement therapy
Coagulopathy (international normalized ratio $>$ 2.0)

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**CURRENT TRENDS AND FUTURE APPROACHES**

Emerging data suggest that NAC, traditionally used to treat acetaminophen-induced ALF, may also have a role in nonacetaminophen-related causes of ALF.<sup>4</sup> A recent study found that administration of IV NAC in children with nonacetaminophen-related ALF was safe and resulted in increased recovery of native liver without transplantation as well as improved survival rates following transplantation.<sup>50</sup> A large randomized study is currently underway evaluating the efficacy of IV NAC in the adult population with nonacetaminophen-related ALF, and recent data have been published in abstract form.<sup>51</sup> Data showed a significant improvement in spontaneous survival for coma grade I–II in NAC versus placebo groups ( $P = 0.02$ ), and fewer patients required transplantation in the NAC group as compared with the placebo group (32% versus 45%;  $P < 0.09$ ). Plasmapheresis and the use of hypothermia have also demonstrated promise in the management of ALF.<sup>52</sup>

Artificial and bioartificial liver support systems are used largely as temporizing measures for patients awaiting liver transplantation. The artificial liver support system functions to remove toxins from the blood by hemofiltration.<sup>53,54</sup> Several studies have evaluated the Molecular Adsorbents Recirculating System, which utilizes an albumin adsorbent column to detoxify the circulation. To date, this model has demonstrated the most potential.<sup>53,54</sup> Bioartificial support systems utilize hepatocytes with the aim of restoring lost hepatic function caused by ALF.<sup>53,54</sup> The clinical efficacy of this technique has not been proven.<sup>53,54</sup> These liver support systems pose a number of challenges (eg, cost, feasibility) that have restricted their use to clinical research.<sup>54</sup>

Hepatocyte transplantation is currently under investigation as an alternative to traditional liver transplantation. This technique uses cryopreserved human hepatocytes, which are injected into specific sites that allow for optimal hepatocyte engraftment. Earlier studies

have demonstrated improvement in several clinical parameters using hepatocyte transplantation, including hepatic encephalopathy.<sup>55</sup> Other advances are being made in the areas of embryonic stem cell research and liver tissue engineering.<sup>55</sup>

**SUMMARY**

ALF is a potentially life-threatening condition that can develop from various etiologies. Morbidity and mortality remain high. Management is focused on identifying the cause(s) of the liver insult and supportive management in the ICU, including liver transplantation when clinically indicated. Early recognition of the ALF-associated complications is paramount. Prognostic models may be helpful in identifying patients suitable for liver transplantation. More evidence is needed to determine if liver support systems have a definitive role in the management of ALF. **HP**

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