Critical Management Decisions in Patients With Acute Liver Failure

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Critical Management Decisions in Patients With Acute Liver Failure*

R. Todd Stravitz, MD

Few admissions to the ICU present a greater clinical challenge than the patient with acute liver failure (ALF), the syndrome of abrupt loss of liver function in a previously unaffected individual. Although advances in the intensive care management of patients with ALF have improved survival, the prognosis of ALF remains poor, with a 33% mortality rate and a 25% liver transplant rate in the United States. ALF adversely affects nearly every organ system, with most deaths occurring from sepsis and subsequent multiorgan system failure, and cerebral edema, resulting in intracranial hypertension (ICH) and brainstem herniation. Unfortunately, the optimal management of ALF remains poorly defined, and practices are often based on local experience and case reports rather than on randomized, controlled clinical trials. The paramount question in any patient presenting with ALF remains defining an etiology, since specific antidotes can save lives and spare the liver. This article will consider recent advances in the assignment of an etiology, the administration of etiology-specific treatment to abate the liver injury, and the management of complications (eg, infection, cerebral edema, and the bleeding diathesis) in patients with ALF. New data on the administration of N-acetylcysteine to patients with non-acetaminophen ALF, the treatment of ICH, and assessment of the need for liver transplantation will also be presented.

Key words: hepatitis; liver; liver failure

Abbreviations: ALF = acute liver failure; APACHE = acute physiology and chronic health evaluation; APAP = acetaminophen; CPP = cerebral perfusion pressure; FFP = fresh-frozen plasma; HTS = hypertonic saline; ICH = intracranial hypertension; ICP = intracranial pressure; INR = international normalized ratio; MELD = model for end-stage liver disease; MOSF = multiorgan system failure; NAC = N-acetylcysteine; OLT = orthotopic liver transplantation; PT = prothrombin time; rFVIIa = activated recombinant factor VIIa; SIRS = systemic inflammatory response syndrome

A
cute liver failure (ALF) may be defined as the abrupt loss of liver function, characterized by hepatic encephalopathy and coagulopathy, within 26 weeks of the onset of symptoms (classically jaundice) in a patient without previous liver disease.1 Many author-

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ogy, and more frequently exhibit symptoms and signs of chronic liver failure, such as ascites and azotemia (Table 1).2,3

An attempt at defining the “optimal” management of ALF must begin with the following disclaimer: the management of ALF has largely defied systematic study. As alluded to above, ALF is a syndrome, not a disease, and may be precipitated by many insults to the liver (Fig 1), resulting in very different clinical courses and complications. Thus, studying a specific treatment in a homogeneous population of patients with ALF has been very difficult. Furthermore, the syndrome is rare, with an estimated incidence of 2,000 cases per year in the United States4; indeed, few of even the largest liver transplant centers care for > 10 cases a year. The need for multicenter trials spawned the founding of the US Acute Liver Failure Study Group in 1998, which was composed of 23 centers in an ongoing effort to study all aspects of ALF.4 Finally, ALF generally has a poor prognosis without OLT (spontaneous survival rate, < 50%), the application of which interrupts its natural history, rendering the efficacy of a therapeutic maneuver difficult to interpret.

The current synopsis will highlight important practical developments in the management of patients with ALF including the accurate identification of etiology, the administration of agents to treat the liver injury, and the management of the three major complications of ALF (ie, infection, cerebral edema, and the bleeding diathesis). Specific details of all aspects of the management of patients with ALF are also available in a recent ALF Study Group consensus report.5 The reader is also referred to two recent state-of-the-art treatises on artificial and bioartificial liver support devices,6,7 which will not be discussed.

Table 1—Characteristics of ALF According to the Tempo of Evolution (Jaundice-to-Encephalopathy Interval)*

<table>
<thead>
<tr>
<th>Liver Failure Subcategory</th>
<th>Jaundice-to-Encephalopathy Interval</th>
<th>Common Etiologies</th>
<th>Spontaneous Survival, %</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>0–7 d</td>
<td>APAP, Hep A, ischemia (<em>shock liver</em>)</td>
<td>80–90</td>
<td>Cerebral edema most common</td>
</tr>
<tr>
<td>Acute</td>
<td>8–28 d</td>
<td>Hep B, drugs</td>
<td>50–60</td>
<td>Cerebral edema less common</td>
</tr>
<tr>
<td>Subacute</td>
<td>5–26 wk</td>
<td>Drugs, indeterminate</td>
<td>15–20</td>
<td>Ascites, peripheral edema, renal failure</td>
</tr>
</tbody>
</table>

*Hep A = acute hepatitis A; Hep B = acute hepatitis B; drugs = idiosyncratic drug reactions; indeterminate = no etiology identifiable; spontaneous survival = survival without liver transplantation. It should be noted that these observations are generalizations based upon large population studies and do not apply to individual patients.2–4,77

Figure 1. Etiologies of acute liver failure in the United States: data from the Acute Liver Failure Study Group Registry, from 1998 to 2007. Percentages of the total number of patients enrolled are shown above each etiology (unpublished data courtesy of W.M. Lee, Principal Investigator, the Acute Liver Failure Study Group). See Table 1 footnote for expansion of abbreviations.
here due to their experimental nature, unavailability, and disappointing preliminary results.8

ADVANCES IN DIAGNOSIS AND MANAGEMENT OF THE LIVER INJURY

The first steps in managing a patient with ALF must include an attempt to identify an etiology so that specific treatment of the liver injury may be initiated. No question is more important than whether an APAP overdose is either the sole etiology or a significant contributor to the liver injury. APAP overdose constitutes nearly 50% of the cases of ALF in the United States (Fig 1) and in many western European nations.4,9 The prompt recognition of APAP-induced ALF is critical, since a specific antidote, N-acetylcysteine (NAC), effectively limits hepatocellular injury by replenishing glutathione, the putative scavenger of the reactive APAP metabolite [N-acetylp-benzoquinoneimine)], thereby preventing its binding to hepatocellular proteins.10 While studies11 have documented the efficacy of NAC in ameliorating APAP-induced liver injury, the recognition of APAP as the etiology of the liver injury remains challenging. While an estimate of the risk of liver injury has been made by using a nomogram of serum concentration of APAP vs time after ingestion,12 estimates of time from ingestion often cannot be reliably determined, and up to 50% of ingestions occur as “therapeutic misadventures” after repeated ingestions of APAP-containing drugs.13 It should be obvious that the nomogram applies to patients with normal transaminase levels. Moreover, in circumstances of uncertain timing or dose of APAP ingestion, NAC therapy should not be withheld regardless of whether a low likelihood of injury has been estimated by the nomogram.

In order to improve the detection of an APAP overdose, an assay of APAP-protein adducts has been tested in a large group of patients with ALF.14 Such APAP-protein adducts represent the irreversible step in the development of liver toxicity and have relatively long half-lives in serum compared to APAP concentrations. APAP-protein adducts were detected in 100% of sera samples from patients with known APAP overdose, and in none of those patients with other well-defined etiologies.14 Moreover, APAP-protein adducts were also observed in nearly 20% of those patients with indeterminate ALF, indicating that these patients had surreptitiously ingested APAP and may have benefited from NAC therapy had the ingestion been recognized. Other preliminary studies15 in children have reported similar rates of APAP-protein adducts in patients with ALF of indeterminate etiology and in nearly 10% of patients with ALF attributed to other causes (eg, acute viral hepatitis). The APAP-protein adduct assay may also improve the specificity of serum APAP tests in ALF patients with total bilirubin concentrations of > 10 mg/dL, in whom false-positive test results occur frequently using standard colorimetric assays.16 Once the APAP-protein adduct assay has been refined for rapid turnaround, it will likely become an important tool for the evaluation of all patients presenting with ALF.

The US Acute Liver Failure Study Group has also recently completed a randomized, controlled trial17 of NAC therapy in patients with ALF not due to APAP overdose (available in abstract form only). The hypothesis that NAC therapy would improve outcomes in patients with non-APAP ALF extends from observations that NAC therapy improves microcirculatory abnormalities and systemic inflammatory response syndrome (SIRS) in addition to its effects on glutathione repletion.18 One hundred seventy-three patients were randomized to receive IV NAC or placebo, and patients were stratified a priori for the degree of hepatic encephalopathy (mild-to-moderate [grade 1–2] vs severe [grade 3–4]) on admission to the trial. Spontaneous survival in subjects with grade 1 or 2 hepatic encephalopathy at randomization was significantly better in subjects who received NAC compared to those who received placebo (52% vs 30%, respectively; p = 0.02) [Table 2]. However, the primary end point of the study, overall survival at 3 weeks, was not significantly better in patients who received NAC than in those who received placebo (70% vs 67%, respectively; p = 0.57). Furthermore, spontaneous survival was not improved in NAC recipients with grade 3–4 hepatic encephalopathy

<table>
<thead>
<tr>
<th>Encephalopathy Grade at Admission</th>
<th>Spontaneous Survival</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>NAC</td>
</tr>
<tr>
<td>1–2</td>
<td>17/56 (30%)</td>
<td>30/58 (52%)</td>
</tr>
<tr>
<td>3–4</td>
<td>8/36 (22%)</td>
<td>2/23 (9%)</td>
</tr>
<tr>
<td>Total</td>
<td>25/92 (27%)</td>
<td>32/81 (45%)</td>
</tr>
</tbody>
</table>

*Secondary outcome: spontaneous survival. Patients who were randomized to receive NAC received a loading dose of 150 mg/kg IV in 250 mL of 5% dextrose in water (D5W) over 1 h, followed by 50 mg/kg in 500 mL of D5W over 4 h, 125 mg/kg in 1,000 mL of D5W over 19 h, and 150 mg/kg in 1,000 mL of D5W over 24 h for an additional 48 h (72 h total). Patients who were randomized to receive placebo received the same volume of D5W. The primary outcome of the trial, overall survival rate (ie, spontaneous survival + survival after OLT), was 61 of 92 patients (67%) in the placebo group, and 57 of 81 patients (70%) in the NAC group (p = 0.57).17
compared to those who received placebo (9% vs 22%, respectively; p = 0.18), although the number of patients with high-grade encephalopathy was relatively small (Table 2). The significance of the apparent benefit of NAC therapy in patients with early-stage encephalopathy, therefore, remains somewhat uncertain, since the data were gleaned from a subgroup analysis. A nonrandomized, retrospective review of children with non-APAP ALF has also recently suggested that NAC administration improved spontaneous survival over children treated with standard care without NAC. However, these results must also be interpreted cautiously, since the two groups were noncontemporaneous, with the NAC group seen in a more recent era undoubtedly benefiting from advances in critical care management of ALF. It is doubtful that more definitive studies of NAC in non-APAP ALF will be performed in the United States. Consequently, and considering its relative safety, the administration of NAC may become the standard of care for ALF patients with mild-to-moderate hepatic encephalopathy without a more conclusive demonstration of efficacy.

In the last few years, the administration of compounds to treat other specific etiologies of ALF has also been examined for acute hepatitis B and autoimmune hepatitis. Although one retrospective study of lamivudine in patients with severe and fulminant acute hepatitis B suggested an improvement in spontaneous survival compared to historical control subjects, a larger, randomized, placebo-controlled study found no benefit, although it may have been underpowered. Similarly, a small retrospective series of patients with autoimmune hepatitis presenting as ALF found no improvement in outcomes with the administration of corticosteroids, and suggested an increase in septic complications.

**Advances in Management of the Complications of ALF**

**Management of Infection**

Infection remains one of the most common causes of death in patients with ALF and commonly precipitates multiorgan system failure (MOSF), the most common cause of death. Furthermore, sepsis with SIRS is a major risk factor for developing cerebral edema and intracranial hypertension (ICH). Therefore, the prevention and rapid recognition of infection in the patient with ALF is a problem of paramount importance, especially considering that signs of infection are often absent.

Rolando and colleagues have best described the incidence of infections in ALF patients. Pneumonia (50%), urosepsis (22%), IV catheter-induced bacteremia (12%), and spontaneous bacteremia (16%) account for the majority of infections in patients with ALF, as they do in non-ALF ICU patients; however, their high incidence (up to 90% of patients) emphasizes the fact that ALF patients are immunocompromised. The most common offending organisms include Gram-negative enteric bacilli, Gram-positive cocci, and Candida species. These observations have led to randomized trials of prophylactic antibiotics in patients with ALF. The spontaneous seeding of blood by enteric organisms has been suggested in the pathogenesis of sepsis in patients with ALF, consequently, these studies have included the administration of both nonabsorbable, orally administered agents as well as IV antibiotics. Unfortunately, the primary end point of the first study, improved survival, was not achieved (possibly due to type 2 error) by prophylactic administration of antibiotics, although the incidence of infections was decreased. The second study concluded that enteral decontamination provided no additional benefit over prophylactic therapy with parenteral antibiotics.

Based on these limited data, prophylactic therapy with antibiotics cannot be advocated for all patients with ALF. Several guidelines, however, should be observed. As with all critically ill patients, IV lines should be minimized, and their placement and maintenance performed with the strictest aseptic technique. In severely ill patients (ie, those with high-grade encephalopathy, mechanical ventilation, renal failure, and severe coagulopathy), chest radiographs and surveillance cultures of blood, urine, and sputum should be performed daily. Indeed, the study referenced above reported earlier recognition and treatment of infection in patients receiving surveillance cultures. Finally, patients with ALF should be empirically administered broad-spectrum antibiotics without culture results in the following situations where infection has been reported frequently in the following patients: those with progression to high-grade encephalopathy; those with renal failure; and/or those with any of the components of the SIRS. Most programs would also administer prophylactic antibacterial and antifungal agents to patients with ALF awaiting OLT, since posttransplant infection after immunosuppression has dire consequences.

**Cerebral Edema and ICH**

Cerebral edema remains a dramatic and numerically important cause of death in patients with ALF (22% of deaths at the King’s College Liver Unit), although its incidence may be decreasing. The pathogenesis of cerebral edema in ALF patients is
multifactorial and incompletely understood, but the primary mechanism includes the uptake of ammonia by astrocytes, resulting in an accumulation of osmotically active glutamine, followed by the passive influx of water. In patients with cirrhosis and hyperammonemia, a slower rate of glutamine accumulation may be offset by the export of organic osmolytes from astrocytes to maintain osmotic balance, accounting for the fact that ICH occurs rarely in such patients. However, the rapid development of hyperammonemia in ALF patients does not allow the time for this compensation to occur, and likely explains the observation that the incidence of cerebral edema in patients with ALF is proportional to the rapidity of its clinical evolution as estimated by the jaundice-to-encephalopathy interval.

Basic maneuvers to minimize the risk of ICH in patients with ALF should be applied universally in patients with high-grade hepatic encephalopathy. These maneuvers include elevation of the head of the bed to 30°, maintenance of a neutral neck position, avoidance or minimization of painful stimuli (including suctioning), and facilitation of a state of mild respiratory alkalosis (eg, to a PCO₂ of 30 to 35 mm Hg), which usually occurs spontaneously. The decision to place an intracranial pressure (ICP) monitor remains one of the most contentious issues in the management of the patient with ALF. Some authorities routinely place ICP monitors in patients who are at the highest risk of cerebral edema, including those with grade 3–4 hepatic encephalopathy, elevated arterial ammonia levels (ie, > 150 μmol/L), and hyperacute liver failure (eg, APAP etiology), or in those receiving therapy with vasoressors. Some centers place ICP monitors only in patients who are deemed to be OLT candidates, while other centers never use the device, citing an absence of data showing improved outcome, the risk of intracranial bleeding, and a lack of consensus regarding goal pressures. Based on limited data, however, the US Acute Liver Failure Study Group recently endorsed the use of ICP monitors in patients with ALF who are at high risk of ICH, including nontransplant candidates with relatively high rates of spontaneous survival (ie, those who have experienced an APAP overdose or have acute hepatitis A). Despite the lack of consensus, many experts believe that ICP monitors improve the management of ICH in ALF patients and that they may also provide information regarding the likelihood of poor neurologic recovery after OLT. Specifically, it has been suggested that a cerebral perfusion pressure (CPP) [CPP = ICP − mean arterial pressure] of < 40 mm Hg for > 2 h was associated with poor neurologic prognosis, although four case reports refute this observation. Most literature cites an ICP of > 20 to 25 mm Hg as an indication for treatment. Although the goals for CPP are less well defined, most authorities treat hypotension with vasoressors (usually norepinephrine) to maintain a CPP of > 50 to 60 mm Hg.

The simplified pathogenesis of cerebral edema outlined above forms the rationale for administering osmotically active agents to patients with ALF and ICH (Table 3). IV mannitol osmotically draws water from astrocytes into the intravascular space. Surprisingly few published data are available to support the...
efficacy of mannitol, although the following original observations are impressive: mannitol (1 g/kg IV bolus) resolved ICH in >80% of patients and increased spontaneous survival compared to no treatment.  

Unfortunately, patients with a very high ICP (>60 mm Hg) do not usually achieve normal ICP after receiving mannitol boluses, and other therapies are needed to delay herniation. The administration of hypertonic saline (HTS) solution, which acts similarly to mannitol, has only been tested as a prophylactic agent to prevent ICH, but not in patients with established ICH. Patients with ALF and high-grade hepatic encephalopathy but normal ICP were randomized to receive HTS solution (30%) to achieve a serum sodium concentration of 145 to 155 mEq/L or to “normonatremia” (ie, 135 to 145 mEq/L). ICH was effectively prevented from developing in patients who were rendered hyponatremic compared to the control group (p = 0.04). Although the administration of HTS solution as a treatment for established ICH has not been tested, it would seem reasonable to raise serum sodium levels to 145 to 155 mEq/L in patients with persistent ICH despite therapy with mannitol, which is similar to the practice in patients with other causes of cerebral edema. 

Patients with ALF and ICH despite the use of osmotic agents present an urgent clinical problem, for most progress to herniation and brain death. Other salvage maneuvers (Table 3) include the induction of barbiturate coma, the use of paralytic agents and deep sedation, and therapy with IV indomethacin (25-mg boluses), which is not available in the United States. Intractable ICH also portends herniation during OLT, as ICP frequently increases with dissection of the native liver and following reperfusion of the transplanted liver. Spikes of ICP may even occur during OLT in patients without ICH prior to transplant.

Therapeutic hypothermia has become a commonly employed method to improve neurologic recovery after cardiac arrest, anoxia, and head trauma, other conditions in which cerebral edema contributes to brain injury. In experimental models of ALF, the induction of hypothermia has been shown to be neuroprotective, with beneficial effects on numerous physiologic targets and may also attenuate APAP-induced liver injury. Based on these observations, 38 patients with ALF and uncontrolled ICH (defined as an ICP of >25 mm Hg despite two boluses of mannitol [1 g/kg body weight over 20 min] and ultrafiltration [500 mL fluid removed]) were cooled to 32 to 33°C. The mean ICP decreased from 37 to 45 mm Hg to 16 mm Hg after the institution of hypothermia, cerebral hyperperfusion decreased, and CPP increased. Furthermore, hypothermia prevented relapses of ICH, stabilized ICP to bridge patients to OLT, and prevented spikes in ICP during the dissection of the native liver and reperfusion of the implanted liver during OLT. These promising preliminary results require validation in a randomized, controlled trial of hypothermia before widespread adoption of the practice, especially considering that the safety of hypothermia in ALF patients remains poorly defined.

Management of the Bleeding Diathesis

Despite the fact that an abnormal prothrombin time (PT)/international normalized ratio (INR) comprises part of the definition of the ALF syndrome, spontaneous, clinically significant bleeding occurs rarely (approximately 5% of cases). Patients with ALF typically have near-normal portal pressure, in contrast to patients with cirrhosis, and bleeding generally occurs from superficial mucosal lesions, rather than varices. The most common site of bleeding in patients with ALF is from gastric erosions, but may occur from nasopharyngeal and genitourinary sources. The suppression of gastric acid secretion with the administration of histamine-2 receptor antagonists (cimetidine) has been shown to decrease the risk of gastric mucosal bleeding and thereby decrease the transfusion requirements in patients with ALF; by inference, prophylaxis with proton pump inhibitors has been advocated. Despite the frequency of ICH, spontaneous intracranial bleeding in ALF patients is exceedingly rare (<1%) in the absence of the insertion of an ICP monitor.

More frequently, concern about coagulopathy in patients with ALF arises before invasive procedures. There are few data regarding the risk of significant bleeding after invasive procedures in patients with ALF, such as transjugular liver biopsy, or the placement of a central venous catheter or ICP monitor. Furthermore, evidence-based guidelines regarding the goals of INR do not exist, although a general consensus has arisen that the INR should be corrected to ≤1.5. It must be emphasized, however, that PT/INR poorly reflects the bleeding risk in ALF patients since levels of liver-derived anticoagulants (eg, protein C/S or antithrombin III) decrease in concert with procoagulant factors. In a large survey of ALF patients who underwent ICP monitor placement, the risk of bleeding was proportional to the depth of insertion of the device (epidural location, 4%; subdural location, 20%; intraparenchymal locations, 22%). In the same series, fatal hemorrhage occurred in only 1%, 5%, and 4%, respectively. A more recent series documented intracranial hemorrhage in 10% of subjects, but half were inci-
concentrations of less than approximately 100 mg/dL). Strategies for the management of coagulopathy in ALF patients have also not been well defined (Table 4). In the absence of clinically significant bleeding, the prophylactic administration of fresh-frozen plasma (FFP) has not been shown to decrease the risk of bleeding or to improve outcome, and most authorities recognize the importance of the spontaneous trend in PT/INR and factor V in assessing prognosis and the need for OLT. Although significant bleeding provides a clinical rationale for treating coagulopathy with FFP, normalization of PT/INR without causing volume overload is usually an unattainable goal. In ALF patients with severe coagulopathy, isovolumetric plasmapheresis has been shown to be very effective and well tolerated.

Although there are no data to support the prophylactic correction of coagulopathy before invasive procedures in patients with ALF, the practice is nearly universal. Activated recombinant factor VII (rFVIIa) has been administered before invasive procedures such as ICP monitor placement. Modest doses of rFVIIa dramatically improve PT/INR and decrease the risk of volume overload compared to the administration of FFP alone in patients undergoing ICP monitor placement; however, FFP should also be given prior to rFVIIa to replenish other deficient factors. Cryoprecipitate should also be administered before rFVIIa and FFP when patients are significantly hypofibrinogenemic (ie, fibrinogen concentrations of less than approximately 100 mg/dL). Despite promising preliminary observations regarding the use of rFVIIa, several concerns remain undefined, such as the risk for thrombotic complications, the optimal dosing of rFVIIa, and the follow-up of PT/INR after its administration.

Fewer data exist regarding the treatment of thrombocytopenia in patients with ALF. As with FFP, platelet replacement therapy is not indicated in the absence of active bleeding; the goals of platelet transfusion have not been defined, although a concentration of 50,000 platelets/µL has been suggested as an acceptable threshold before an invasive procedure. Whether to issue platelet transfusions for patients with platelet counts of 10,000 to 30,000 cells/µL remains controversial, particularly in those with indwelling ICP monitors. As above, hypofibrinogenemia (fibrinogen concentration of <100 mg/dL) should be corrected with cryoprecipitate administration before the patient undergoes invasive procedures; but, again, no data exist to support its prophylactic use. Severe hypofibrinogenemia may reflect disseminated intravascular coagulation and hyperfibrinolysis, which is a relatively common complication of ALF that adversely affects outcome. Although heparin has not been shown to improve outcome in such circumstances and may increase bleeding complications, the administration of epsilon aminocaproic acid is reasonable. Finally, vitamin K (10 mg administered parenterally) should be considered in all patients with ALF, as >25% of patients may have vitamin K deficiency as a contributing factor.

**ADVANCES IN ASSESSING PROGNOSIS**

There may be no more weighty a management decision than whether a patient with ALF should be listed for OLT, since the US organ allocation system prioritizes ALF patients above all with cirrhosis, often resulting in a rapid offer of an organ and precluding the option of watchful waiting. Although long-term survival after OLT for the treatment of ALF is comparable to OLT for cirrhosis, perioperative mortality is definitively higher, reflecting the acuity of the clinical situation. Furthermore, OLT introduces the need for lifelong immunosuppression therapy and the inevitability of long-term metabolic complications. These considerations emphasize the

<table>
<thead>
<tr>
<th>Blood Product/Maneuver</th>
<th>Indication</th>
<th>Adverse Effects</th>
<th>Study/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>Overt bleeding; prophylaxis for procedure; before rFVIIa</td>
<td>Volume overload; TRALI</td>
<td>Rana et al(^6) 2006; Munoz et al(^6) 2008</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Volume overload or insufficient correction of coagulopathy with FFP</td>
<td>TRALI?</td>
<td>Munoz et al(^9) 1989</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Volume overload or insufficient correction of coagulopathy with FFP</td>
<td>Thrombosis</td>
<td>Shami et al(^6) 2003; Pavese et al(^7) 2005</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Fibrinogen &lt; 100 mg/dL</td>
<td></td>
<td>Munoz et al(^8) 2008; Straitz et al(^7) 2007</td>
</tr>
<tr>
<td>ε-Aminocaproate</td>
<td>Mucosal/puncture site oozing, evidence of hyperfibrinolytic state</td>
<td></td>
<td>Munoz et al(^8) 2008; Lissman et al(^2) 2002</td>
</tr>
<tr>
<td>Platelets</td>
<td>Overt bleeding; prophylaxis for procedure</td>
<td>Transfusion reactions</td>
<td>Straitz et al(^7) 2007</td>
</tr>
</tbody>
</table>

*TRALI = transfusion-related acute lung injury.*
undesirability of performing OLT in a patient who will recover with medical management, especially considering that successful liver regeneration after ALF generally connotes an excellent long-term prognosis.

The following two types of approaches have been developed to assess prognosis in patients with ALF: those that estimate the severity of liver injury and MOSF (Table 5); and those that attempt to quantify liver regeneration (Table 6). Since the extent of liver injury contributes to the vigor of liver regeneration, the two are not mutually exclusive. The most time-tested prognostic assessments for estimating the former are the King’s College Criteria,77 but other systems such as acute physiology and chronic health evaluation (APACHE) II score and the model for end-stage liver disease (MELD) have also been evaluated (Table 5).78,79 Unfortunately, none of these schemes is adequately sensitive to predict death.80 Similarly, assays which can be determined serially to predict hepatic regeneration may improve identification of spontaneous recovery, but generally lack specificity (Table 6).

Table 5—Systems Used To Assess the Severity of Liver and MOSF in ALF Patients

<table>
<thead>
<tr>
<th>Systems</th>
<th>Etiology of ALF</th>
<th>Criteria Predicting Death</th>
<th>Study/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>King’s College criteria</td>
<td>APAP overdose</td>
<td>Arterial pH &lt; 7.30 Or All of the following: PT &gt; 100 s (INR &gt; 6.5), creatinine level of &gt; 3.4 mg/dL, and grade 3–4 encephalopathy</td>
<td>O’Grady et al77/1989</td>
</tr>
<tr>
<td></td>
<td>Non-APAP overdose</td>
<td>PT &gt; 100 s (INR &gt; 6.5) Or Any three of the following: NANB/drug/halothane etiology; jaundice to encephalopathy time &gt; 7 d; age &lt; 10 yr or &gt; 40 y; PT &gt; 50 s (INR &gt; 3.5); and bilirubin level of &gt; 17.4 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Clichy criteria</td>
<td>Viral</td>
<td>Age &lt; 30 yr and factor V &lt; 20% Or Any age, factor V &lt; 30%, and grade 3–4 encephalopathy</td>
<td>Berman et al84/1991; Berman et al85/1986</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>APAP overdose</td>
<td>Score &gt; 15</td>
<td>Mitchell et al78/1998</td>
</tr>
<tr>
<td>MELD/AMELD score</td>
<td>APAP overdose</td>
<td>&gt; 33/−0.4</td>
<td>Schmidt and Larsen79/2007</td>
</tr>
</tbody>
</table>

Table 6—In Vivo Assays Used To Estimate Hepatic Regeneration and Predict Death or Spontaneous Recovery in ALF Patients*

<table>
<thead>
<tr>
<th>Assays</th>
<th>Method/Sample</th>
<th>Criteria Predicting Death</th>
<th>Criteria Predicting Survival/Regeneration</th>
<th>Study/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT/INR ratio</td>
<td>Plasma</td>
<td>Rising 3 d after APAP OD</td>
<td>Declining within 3 d of APAP OD</td>
<td>Harrison et al87/1990</td>
</tr>
<tr>
<td>α-Fetoprotein</td>
<td>Serum</td>
<td>&lt; 3.9 ng/dL 1 d after peak ALT level</td>
<td>Increasing within 3 d of APAP OD</td>
<td>Schmidt and Dalhoff86/2005</td>
</tr>
<tr>
<td>Lactate</td>
<td>Serum (arterial)</td>
<td>&gt; 3.5 mmol/L</td>
<td>Declining within 12 h of hospital admission</td>
<td>Bernal et al87/2002; Macquillan et al88/2005</td>
</tr>
<tr>
<td>Phosphate</td>
<td>Serum (arterial)</td>
<td>&gt; 1.2 mmol/L</td>
<td>Declining within 1 d of hospital admission</td>
<td>Schmidt and Dalhoff89/2002</td>
</tr>
<tr>
<td>Factor V</td>
<td>Plasma</td>
<td>≤ 10% of normal on hospital admission; absence of increase within 3 d</td>
<td>Increasing within 3 d of hospital admission</td>
<td>Pereira et al89/1992</td>
</tr>
<tr>
<td>Galactose elimination capacity</td>
<td>Plasma ELISA</td>
<td>&lt; 16.5 μmol/kg/min (normal, 25–55 μmol/kg/min)</td>
<td>Increasing elimination within 4 d of APAP OD</td>
<td>Schmidt et al89/2004</td>
</tr>
<tr>
<td>¹³C-Methacetin breath test</td>
<td>Breath ¹³CO₂</td>
<td>Absence of increase within 3 d</td>
<td>Increasing within 3 d of hospital admission</td>
<td>Ilan87/2007</td>
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*CK-18 = cytokeratin-18; NANB = non-A, non-B viral hepatitis; ELISA = enzyme-linked immunosorbent assay; OD = overdose.
CONCLUSIONS

The optimal management of ALF remains poorly defined and specific to the particular medical center. Nevertheless, the rates of overall and spontaneous survival have increased over the last 20 years because of improved intensive care management and advances in OLT techniques. The relative frequency of complications of ALF leading to death may be evolving, with a decrease in the number of cerebral deaths, and an increase in the number of patients with sepsis and MOSF. Unfortunately, patients with ALF continue to have a dismal prognosis, with an overall mortality rate of 33% and a transplant rate of 25% in the United States. The importance of the recognition of APAP as the sole or contributing etiology to a liver injury cannot be overstated, for the timely administration of NAC can be lifesaving and organ-saving; the APAP-protein adduct assay should improve our diagnostic accuracy. Recent studies in patients with non-APAP ALF have suggested that the administration of NAC should be considered in patients with early-stage hepatic encephalopathy regardless of etiology. Multicenter studies to better define the optimal management of ALF, as well as the prediction of outcome, are urgently needed.

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## Critical Management Decisions in Patients With Acute Liver Failure

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