

# **AASLD Position Paper: The Management of Acute Liver Failure: Update 2011**

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## **Preamble**

These recommendations provide a data-supported approach. They are based on the following: 1) Formal review and analysis of recently-published world literature on the topic [Medline search]; 2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines;<sup>1</sup> 3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the AGA Policy Statement on Guidelines;<sup>2</sup> and 4) the experience of the authors in the specified topic.

Intended for use by physicians, the recommendations in this document suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. This document has been designated as a Position Paper, since the topic contains more data based on expert opinion than on randomized controlled trials and is thus not considered to have the emphasis and certainty of a Practice Guideline. Nevertheless, it serves an important

purpose of facilitating proper and high level patient care and we have characterized the quality of evidence supporting each recommendation, in accordance with the Practice Guidelines Committee of the AASLD recommendations used for full Practice Guidelines (Table 1)<sup>3</sup> These recommendations are fully endorsed by the AASLD.

## **Introduction**

Acute liver failure (ALF) is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in individuals without known pre-existing liver disease. U.S. estimates are placed at approximately 2,000 cases per year.<sup>4,5</sup> A recent estimate from the United Kingdom was 1-8 per million population.<sup>6</sup> The most prominent causes include drug-induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion; many cases (~15%) have no discernible cause.<sup>7</sup> Acute liver failure often affects young persons and carries a high morbidity and mortality. Prior to transplantation, most series suggested less than 15% survival. Currently, overall short-term survival (one year) including those undergoing transplantation is greater than 65%.<sup>7</sup> Because of its rarity, ALF has been difficult to study in depth and very few controlled therapy trials have been performed. As a result, standards of intensive care for this condition have not been established although a recent guideline provides some general directions.<sup>8</sup>

## **Definition**

The most widely accepted definition of ALF includes evidence of coagulation abnormality, usually an International Normalized Ratio (INR)  $\geq 1.5$ , and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of <26 weeks' duration.<sup>9</sup> Patients with Wilson disease, vertically-acquired hepatitis B virus (HBV), or autoimmune hepatitis may be included in spite of the possibility of cirrhosis if their disease has only been recognized for <26 weeks. A number of other terms have

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*Abbreviations: ALF, acute liver failure; NAC, N-acetylcysteine; HELLP, Hemolysis, Elevated Liver Enzymes, Low Platelets syndrome; gm/day, grams per day; gm/kg, grams per kilogram; ICH, intracranial hypertension; ICP, intracranial pressure; INR, international normalized ratio; CT, computerized tomography; US ALFSG, United States Acute Liver Failure Study Group; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; mg/dL, milligrams per deciliter; SIRS, systemic inflammatory response syndrome; FFP, fresh frozen plasma; rFVIIa, recombinant activated factor; GI, gastrointestinal; H<sub>2</sub>, histamine-2; PPI, proton pump inhibitors; CVVHD, continuous venovenous hemodialysis; AFP, alpha fetoprotein; MELD, Model for End-stage Liver Disease; mg/kg, milligrams per kilogram; IU/L, international units per liter;*

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**Table 1. Quality of Evidence on Which a Recommendation Is Based<sup>3</sup>**

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

been used for this condition, including fulminant hepatic failure and fulminant hepatitis or necrosis. "Acute liver failure" is a better overall term that should encompass all durations up to 26 weeks. Terms used signifying length of illness, such as "hyperacute" (<7 days), "acute" (7-21 days) and "subacute" (>21 days and <26 weeks), are popular but not particularly helpful since they do not have prognostic significance distinct from the cause of the illness. For example, hyperacute diseases tend to have a better prognosis, but this is because most are due to acetaminophen toxicity or ischemic hepatopathy, both of which have good initial recovery rates.<sup>7</sup>

## Diagnosis and Initial Evaluation

All patients with clinical or laboratory evidence of acute hepatitis should have immediate measurement of prothrombin time and careful evaluation for subtle alterations in mentation. If the prothrombin time is prolonged by ~4-6 seconds or more (INR  $\geq$ 1.5) and there is any evidence of altered sensorium, the diagnosis of ALF is established and hospital admission is mandatory. Since the condition may progress rapidly, patients determined to have any degree of encephalopathy should be transferred to the intensive care unit (ICU) and contact with a transplant center made to determine if transfer is appropriate. Transfer to a transplant center should take place for patients with grade I or II encephalopathy (Table 5) because they may worsen rapidly. Early transfer is important as the risks involved with patient transport may increase or even preclude transfer once stage III or IV encephalopathy develops.

History taking should include careful review of possible exposures to viral infection and drugs or other toxins. If severe encephalopathy is present, the history may be provided entirely by the family or may be unavailable. Limited historical information, particularly regarding possible toxin/drug ingestions, complicates the initial assessment and may be responsible for many indeterminate diagnoses.<sup>10</sup> Physical examination should include a mental status examination and a

search for stigmata of chronic liver disease. Jaundice is often but not always seen at presentation and may be absent in acetaminophen cases early on. Right upper quadrant tenderness is variably present. Inability to palpate the liver or even to percuss a significant area of dullness over the liver may indicate decreased liver volume. An enlarged liver may be seen early in viral hepatitis but is particularly noteworthy for malignant infiltration, congestive heart failure, or acute Budd-Chiari syndrome. History or signs suggesting underlying chronic liver disease should have different management implications. Furthermore, the prognostic criteria mentioned below are not applicable to patients with acute-on-chronic liver disease.

Initial laboratory examination must be extensive in order to evaluate both the etiology and severity of ALF (Table 2). Early testing should include routine chemistries (especially glucose, as hypoglycemia may be present and require correction), arterial blood gas measurements, complete blood counts, blood typing, acetaminophen level and screens for other drugs and toxins, viral serologies (Table 2), tests for Wilson disease, autoantibodies, and a pregnancy test in females. Plasma ammonia, preferably arterial, may also be helpful.<sup>11,12</sup> Liver biopsy, most often done via the transjugular route because of coagulopathy, is indicated when certain conditions such as autoimmune hepatitis,

**Table 2. Initial Laboratory Analysis**

Prothrombin time/INR
Chemistries
sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate
glucose
AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin creatinine, blood urea nitrogen
Arterial blood gas
Arterial lactate
Complete blood count
Blood type and screen
Acetaminophen level
Toxicology screen
Viral hepatitis serologies
anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HEV $\delta$ , anti-HCV, HCV RNA*, HSV1 IgM, VZV
Ceruloplasmin level <sup>#</sup>
Pregnancy test (females)
Ammonia (arterial if possible)
Autoimmune Markers
ANA, ASMA, Immunoglobulin levels
HIV-1, HIV-2 $\ddagger$
Amylase and lipase

\*Done to recognize potential underlying infection.

<sup>#</sup>Done only if Wilson disease is a consideration (e.g., in patients less than 40 years without another obvious explanation for ALF); in this case uric acid level and bilirubin to alkaline phosphatase ratio may be helpful as well.

$\ddagger$ Implications for potential liver transplantation.

$\S$ If clinically indicated.

metastatic liver disease, lymphoma, or herpes simplex hepatitis are suspected, but is not required to determine prognosis. Imaging may disclose cancer or Budd Chiari syndrome but is seldom definitive. The presence of a nodular contour can be seen in ALF and should not be interpreted as indicating cirrhosis in this setting.

Once at the transplant facility, the patient's suitability for transplantation should be assessed.<sup>13</sup> Evaluation for transplantation should begin as early as possible, even before the onset of encephalopathy if possible. Social and financial considerations are unavoidably tied to the overall clinical assessment where transplantation is contemplated. It is also important to inform the patient's family or other next of kin of the potentially poor prognosis and to include them in the decision-making process.

#### **Recommendations**

1. *Patients with ALF should be hospitalized and monitored frequently, preferably in an ICU (III).*
2. *Contact with a transplant center and plans to transfer appropriate patients with ALF should be initiated early in the evaluation process (III).*
3. *The precise etiology of ALF should be sought to guide further management decisions (III).*

### **Determining Etiologies and Specific Therapies**

Etiology of ALF provides one of the best indicators of prognosis, and also dictates specific management options.<sup>6,7</sup>

#### **Acetaminophen Hepatotoxicity**

Acetaminophen hepatotoxicity is suggested by historic evidence for excessive ingestion either as an intended suicidal overdose or the inadvertent use of supra-therapeutic quantities of pain medications. Acetaminophen is a dose-related toxin; most ingestions leading to ALF exceed 10 gm/day (~150 mg/kg). However, severe liver injury can occur rarely when doses as low as 3-4 gm/day are taken.<sup>14</sup> Very high aminotransferase levels are typically seen; serum levels exceeding 3,500 IU/L are highly correlated with acetaminophen poisoning and should prompt consideration of this etiology even when historic evidence is lacking.<sup>15</sup> Because acetaminophen is the leading cause of ALF (at least in the United States and Europe) and there is an available antidote, acetaminophen levels should be drawn in all patients presenting with ALF.<sup>7</sup> However, low or absent levels of the parent com-

pound, acetaminophen, do not rule out hepatotoxicity since the time of ingestion may be relatively remote or unknown, especially when overdose may have been unintentional or occurred over several days.<sup>10</sup>

If acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation, activated charcoal may be useful for gastrointestinal decontamination. While it is most effective if given within one hour of ingestion,<sup>16</sup> it may be of benefit as long as 3 to 4 hours after ingestion.<sup>17</sup> Administration of activated charcoal (standard dose 1 gm/kg orally, in a slurry) just prior to administration of N-acetylcysteine does not reduce the effect of N-acetylcysteine.<sup>17</sup> N-acetylcysteine (NAC), the antidote for acetaminophen poisoning, has been shown to be effective and safe for this purpose in numerous controlled trials.<sup>18,19</sup> The standard acetaminophen toxicity nomogram<sup>20</sup> may aid in determining the likelihood of serious liver damage, but cannot be used to exclude possible toxicity due to multiple doses over time, when the time of ingestion is unknown, or when altered metabolism occurs such as in the alcoholic or fasting patient.<sup>21</sup> Given these considerations, administration of NAC is recommended in any case of ALF in which acetaminophen overdose is a suspected or possible cause; specific indications that acetaminophen may be the culprit include very high aminotransferases and low bilirubin levels, in the absence of apparent hypotension or cardiovascular collapse.<sup>10</sup> NAC should be given as early as possible, but may still be of value 48 hours or more after ingestion.<sup>22</sup> NAC may be given orally (140 mg/kg by mouth or nasogastric tube diluted to 5% solution, followed by 70 mg/kg by mouth q 4 h x 17 doses) and has few side effects (nausea and vomiting particularly with rapid infusion or oral NAC,<sup>23</sup> rare urticaria or bronchospasm). Allergic reactions are infrequent and are successfully treated with discontinuation, antihistamines and epinephrine if bronchospasm is present.<sup>24</sup> Oral administration has largely been replaced by intravenous administration (loading dose is 150 mg/kg in 5% dextrose over 15 minutes; maintenance dose is 50 mg/kg given over 4 hours followed by 100 mg/kg administered over 16 hours or 6 mg/kg/hr). Controversy exists over when to stop use of NAC, whether a standard 72-hour period is optimal or continuation until liver chemistry values have improved.

#### **Recommendations**

4. *For patients with known or suspected acetaminophen overdose within 4 hours of presentation, give activated charcoal just prior to starting NAC dosing (I).*

**5. Begin NAC promptly in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferases indicate impending or evolving liver injury (II-1).**

**6. NAC may be used in cases of acute liver failure in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate but aminotransferases suggest acetaminophen poisoning (III).**

#### **Non-acetaminophen Acute Liver Failure**

For patients whose disease appears to be caused by etiologies other than acetaminophen, *N*-acetylcysteine may improve outcomes. In a randomized, controlled trial, NAC appeared to improve spontaneous survival when given during early coma stages (grades I and II) in the setting of non-acetaminophen acute liver failure including, for example, drug-induced liver injury and hepatitis B.<sup>23</sup>

#### **Mushroom Poisoning**

Mushroom Poisoning (usually *Amanita phalloides*) may cause ALF, and the initial history should always include inquiry concerning recent mushroom ingestion. There is no available blood test to confirm the presence of these toxins, but this diagnosis should be suspected in patients with a history of severe gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramping), which occur within hours to a day of ingestion. If these effects are present, it may be early enough to treat patients with gastric lavage and activated charcoal via nasogastric tube. Fluid resuscitation is also important. Traditionally, very low rates of survival have been reported without transplantation,<sup>25</sup> but more recently complete recovery has been described with supportive care and medical treatment.<sup>26</sup> Penicillin G and silybinin (silymarin or milk thistle) are the accepted antidotes despite a lack of controlled trials proving their efficacy.<sup>27-30</sup> While some reports have not found penicillin G to be helpful,<sup>29</sup> enough efficacy has been reported to warrant consideration of the drug (given intravenously in doses of 300,000 to 1 million units/kg/day) in patients with known or suspected mushroom poisoning.<sup>30</sup> Silybinin has generally been reported to be more successful than penicillin G, although penicillin G has been used more frequently in the United States.<sup>31,32</sup> *Silybinin is not available as a licensed drug in the United States*, although it is widely available in Europe and South America. Emergency application can be made to receive the medication rapidly in the United States. When used for treatment of mushroom poisoning, silybinin has been given in aver-

age doses of 30-40 mg/kg/day (either intravenously or orally) for an average duration of 3 to 4 days.<sup>28</sup> NAC is often combined with these other therapies, but has not been shown to be effective in animal studies;<sup>30</sup> nevertheless, case reports have described its use as a part of overall management.

#### **Recommendation**

**7. In ALF patients with known or suspected mushroom poisoning, consider administration of penicillin G and *N*-acetylcysteine (III).**

**8. Patients with acute liver failure secondary to mushroom poisoning should be listed for transplantation, as this procedure is often the only lifesaving option (III).**

#### **Drug Induced Liver Injury (DILI)**

Many prescription and over-the-counter medications have been associated with acute liver injury and liver failure. A careful drug history should include listing of all agents taken, the time period involved, and the quantity or dose ingested. Determination of a particular medication as the cause of ALF is a diagnosis of exclusion; guidelines for assessment of causality have recently been proposed by the Drug-Induced Liver Injury Network.<sup>33</sup> Drugs other than acetaminophen rarely cause dose-related toxicity. Most examples of idiosyncratic drug hepatotoxicity occur within the first 6 months after drug initiation. A potentially hepatotoxic medication that has been used continually for more than 1 to 2 years is unlikely to cause *de novo* liver damage. Certain herbal preparations, weight loss agents and other nutritional supplements have been found to cause liver injury, so inquiry about such substances should be included in a complete medication history.<sup>34-35</sup> There are no specific antidotes for idiosyncratic drug reactions; corticosteroids are not indicated unless a drug hypersensitivity such as the 'drug rash with eosinophilia and systemic symptoms' (DRESS) syndrome or an autoimmune reaction is suspected.<sup>36</sup> Other causes of ALF should still be ruled out even if a drug is suspected. Any presumed or possible offending agent should be stopped immediately where possible. Classes of drugs commonly implicated include antibiotics, non-steroidal anti-inflammatory agents and anti-convulsants (Table 3).

#### **Recommendations**

**9. Obtain details (including onset of ingestion, amount and timing of last dose) concerning all prescription and non-prescription drugs, herbs and dietary supplements taken over the past year (III).**

**Table 3. Some Drugs Which May Cause Idiosyncratic Liver Injury Leading to ALF**

Isoniazid	Pyrazinamide
Sulfasalazine	Isoflurane
Phenytoin	Itraconazole
Statins	Nicotinic acid
Propylthiouracil	Imipramine
Ciprofloxacin	Gemtuzumab
Nitrofurantoin	Terbinafine
Disulfiram	Methyl dopa
Cocaine	MDMA (Ecstasy)
Valproic acid	Labetalol
Amiodarone	Tolcapone
Dapsone	Allopurinol
Etodolac	Methyl dopa
Didanosine	Ketoconazole
Efavirenz	Abacavir
Carbamazepine	Doxycycline
Valproic Acid	Diclofenac

Combination agents with enhanced toxicity:

- Trimethoprim-sulfamethoxazole
- Rifampin-Isoniazid
- Amoxicillin-clavulanate

Some herbal products/dietary supplements that have been associated with hepatotoxicity include:

- Kava Kava
- Herbalife
- Hydroxycut
- Comfrey
- Senecio
- Greater celandine
- He Shon Wu
- LipoKinetix
- Ma Huang

**10. Determine ingredients of non-prescription medications whenever possible (III).**

**11. In the setting of acute liver failure due to possible drug hepatotoxicity, discontinue all but essential medications (III)**

**12. N-acetylcysteine may be beneficial for acute liver failure due to drug-induced liver injury (I).**

### Viral Hepatitis

Hepatitis serological testing should be done for identification of acute viral infection (Table 2) even when another putative etiology has been identified. Viral hepatitis has become a relatively infrequent cause of ALF (United States: 12%; hepatitis B – 8%, hepatitis A – 4%).<sup>6,7</sup> Acute hepatitis D may occasionally be diagnosed in a hepatitis B positive individual. Although controversial, hepatitis C alone does not appear to cause ALF.<sup>7,37</sup> Hepatitis E is a significant cause of liver failure in countries where it is endemic, and tends to be more severe in pregnant women.<sup>38</sup> This virus should be considered in anyone with recent travel to an endemic area such as Russia, Pakistan,

Mexico, or India, but cases in the US without associated travel are beginning to be reported.<sup>39</sup> With acute viral hepatitis, as with many other etiologies of ALF, care is mainly supportive. Of note, the nucleoside analog lamivudine (and possibly other nucleos(t)ide analogues), used widely in the treatment of chronic hepatitis B, may be considered in patients with acute hepatitis B, although evidence of efficacy is equivocal.<sup>40,41</sup> Acute liver failure due to reactivation of chronic or inactive hepatitis B may occur in the setting of chemotherapy or immunosuppression. Patients found to be positive for HBsAg who are to begin such therapy should be treated prophylactically with a nucleos(t)ide analog, and that treatment should be continued for 6 months after completion of immunosuppressive therapy.<sup>42</sup> Herpes virus infection rarely causes ALF.<sup>43</sup> Immunosuppressed patients or pregnant women (usually in the third trimester) are at increased risk, but occurrences of herpes virus ALF have been reported in healthy individuals.<sup>43-45</sup> Skin lesions are present in only about 50% of cases, and frequently patients are anicteric and appear septic. Liver biopsy is helpful in making the diagnosis.<sup>42</sup> Treatment should be initiated with acyclovir (5-10 mg/kg every 8 hours for at least 7 days) for suspected or documented cases.<sup>44,45</sup> Other viruses such as varicella zoster have occasionally been implicated in causing hepatic failure.<sup>46</sup> (diagnostic tests in Table 2). Results after liver transplantation for herpes are unclear but this group should not be excluded from transplantation consideration.

### Recommendations

**13. Viral hepatitis A- (and E-) related acute liver failure must be treated with supportive care as no virus-specific treatment has proven to be effective (III).**

**14. Nucleos(t)ide analogues should be considered for hepatitis B-associated acute liver failure and for prevention of post-transplant recurrence. (III)**

**15. Patients with known or suspected herpes virus or varicella zoster as the cause of acute liver failure should be treated with acyclovir (5-10 mg/kg IV every 8 hours) and may be considered for transplantation (III).**

### Wilson disease

Wilson disease is an uncommon cause of ALF (2% to 3% of cases in the U.S. ALFSG).<sup>47</sup> Early identification is critical because the fulminant presentation of Wilson disease is considered to be uniformly fatal without transplantation.<sup>48</sup> The disease typically occurs

in young patients, accompanied by the abrupt onset of Coombs negative hemolytic anemia with serum bilirubin levels >20 mg/dL. Due to the presence of hemolysis, the indirect-reacting bilirubin is often markedly elevated along with the total bilirubin. Kayser-Fleischer rings are present in about 50% of patients presenting with ALF due to Wilson disease.<sup>49</sup> Serum ceruloplasmin is typically low, but may be normal in up to 15% of cases and is reduced in ~50% of other forms of ALF;<sup>50</sup> high nonceruloplasmin-bound plasma and urinary copper levels as well as hepatic copper measurement will confirm the diagnosis.<sup>49</sup> Very low serum alkaline phosphatase or uric acid levels suggest Wilson disease in the absence of other indicators. A high bilirubin (mg/dL) to alkaline phosphatase (IU/L) ratio (>2.0) is a rapid, reliable (albeit indirect) indicator of Wilson disease that can be obtained much more rapidly than urinary or serum copper.<sup>48-50</sup> Renal function is often impaired as the released copper can cause renal tubular damage. Treatment to acutely lower serum copper and to limit further hemolysis should include albumin dialysis, continuous hemofiltration, plasmapheresis, or plasma exchange.<sup>51</sup> Initiation of treatment with penicillamine is not recommended in ALF as there is a risk of hypersensitivity to this agent.<sup>49</sup> Although such copper lowering measures should be considered, recovery is very rare absent transplantation.<sup>48,50</sup> Wilson disease represents a special circumstance in which patients typically have unrecognized cirrhosis but can still be considered to have a diagnosis of ALF when rapid deterioration occurs. Please refer to the AASLD Practice Guideline on Wilson Disease for more detailed information regarding the diagnosis and management of patients with this condition.<sup>50</sup>

#### **Recommendations**

**16. To exclude Wilson disease one should obtain ceruloplasmin, serum and urinary copper levels, slit lamp examination for Kayser-Fleischer rings, hepatic copper levels when liver biopsy is feasible, and total bilirubin/alkaline phosphatase ratio (III).**

**17. Patients in whom Wilson disease is the likely cause of acute liver failure must be promptly considered for liver transplantation (III).**

#### **Autoimmune Hepatitis**

With autoimmune hepatitis, as with Wilson disease, patients may have unrecognized preexisting chronic disease and yet still be considered as having ALF. AIH patients that develop ALF represent the most severe form of the disease; they are generally recommended to receive corticosteroid therapy as outlined by the

AASLD Practice Guidelines for the Diagnosis and Treatment of Autoimmune Hepatitis (although ALF is not specifically discussed in that document).<sup>52</sup> Initiation of steroid therapy may be considered for some patients with early stage acute liver failure without multi-organ failure (prednisone starting at 40-60 mg/day). However, in some patients this may be deleterious, and consideration for liver transplantation should not be delayed while awaiting a response to corticosteroid treatment.<sup>53,54</sup> Patients are often considered to have indeterminate ALF when autoantibodies are absent (up to 30% of cases); liver biopsy should be considered if autoimmune hepatitis is suspected and autoantibodies are negative.<sup>55</sup>

#### **Recommendations**

**18. Liver biopsy is recommended when autoimmune hepatitis is suspected as the cause of acute liver failure, and autoantibodies are negative (III).**

**19. Patients with coagulopathy and mild hepatic encephalopathy due to autoimmune hepatitis may be considered for corticosteroid treatment (prednisone, 40-60 mg/day) (III).**

**20. Patients with autoimmune hepatitis should be considered for transplantation even while corticosteroids are being administered (III).**

#### **Acute Fatty Liver of Pregnancy/HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) Syndrome**

A small number of women near the end of pregnancy will develop rapidly progressive hepatocyte failure that has been well characterized and associated with increased fetal or maternal mortality.<sup>56-59</sup> A variety of presentations may be seen, generally confined to the last trimester. The triad of jaundice, coagulopathy, and low platelets may occasionally be associated with hypoglycemia. Features of pre-eclampsia such as hypertension and proteinuria are common. Steatosis documented by imaging studies supports the diagnosis. The Oil-red O staining technique best demonstrates hepatic steatosis on biopsy. Intrahepatic hemorrhage and/or hepatic rupture constitute rare emergent situations requiring rapid resuscitation and intervention. Early recognition of these syndromes and prompt delivery are critical in achieving good outcomes. Recovery is typically rapid after delivery, and supportive care is the only other treatment required. However, postpartum deterioration with need for transplantation has been recognized. The presence of long chain fatty acid deficiency represents an underlying abnormality in fat metabolism with implications for the unborn child.<sup>60</sup> It is

important to keep in mind that ALF in pregnant women may also be caused by entities not necessarily related to the pregnant state.

#### **Recommendation**

**21. For acute fatty liver of pregnancy or the HELLP syndrome, expeditious delivery of the infant is recommended. Transplantation may need to be considered if hepatic failure does not resolve quickly following delivery (III).**

#### **Acute Ischemic Injury**

A syndrome often referred to as “shock liver” may occur after cardiac arrest, any period of significant hypovolemia/hypotension, or in the setting of severe congestive heart failure.<sup>61</sup> Documented hypotension is not always found. Drug-induced hypotension or hypoperfusion may be observed with long-acting niacin,<sup>62</sup> or with cocaine,<sup>63</sup> or methamphetamine.<sup>64</sup> Other physical findings may be lacking, but evidence of cardiac dysfunction may be elicited via echocardiogram.<sup>65</sup> Amino-transferase levels will be markedly elevated as will lactic dehydrogenase enzyme levels (indicative of cell necrosis, not apoptosis) and improve rapidly with stabilization of the circulatory problem. Simultaneous onset of renal dysfunction and muscle necrosis may be noted. Successful management of the heart failure or other cause of ischemia determines the outcome for these patients, and transplantation is seldom indicated. Approximately two-thirds suffer from cardiac disease. Early recovery of hepatic function is frequent but the long-term outcome depends on the underlying cardiac process and poor one and two-year outcomes are expected.<sup>61</sup>

#### **Recommendation**

**22. In ALF patients with evidence of ischemic injury, cardiovascular support is the treatment of choice (III).**

#### **Budd-Chiari Syndrome**

The Budd-Chiari syndrome (acute hepatic vein thrombosis) can also present as ALF. Abdominal pain, ascites and striking hepatomegaly are often present. The diagnosis should be confirmed with hepatic imaging studies (computed tomography, Doppler ultrasonography, venography, magnetic resonance venography) and testing to identify hypercoagulable conditions (polycythemia, malignancies) is indicated. Overall, the prognosis in this condition is poor if hepatic failure is present, and transplantation may be required as opposed to venous decompression.<sup>66</sup> It is

important to rule out underlying cancer or other thrombotic disorders prior to transplantation. For an overview of vascular disorders and their evaluation, refer to AASLD Practice Guidelines on this topic.<sup>67</sup>

#### **Recommendation**

**23. Hepatic vein thrombosis with acute hepatic failure is an indication for liver transplantation, provided underlying malignancy is excluded (II-3).**

#### **Malignant Infiltration**

Malignant infiltration of the liver may cause ALF. Massive hepatic enlargement may be seen. Diagnosis should be made by imaging and biopsy, and treatment appropriate for the underlying malignant condition is indicated. Transplantation is not an option for such patients.<sup>68</sup> Acute severe hepatic infiltration occurs with breast cancer,<sup>69,70</sup> small cell lung cancers,<sup>70</sup> lymphoma,<sup>71</sup> melanoma,<sup>72</sup> and myeloma.<sup>73</sup>

#### **Recommendations**

**24. In patients with acute liver failure who have a previous cancer history or massive hepatomegaly, consider underlying malignancy and obtain imaging and liver biopsy to confirm or exclude the diagnosis (III).**

#### **Indeterminate Etiology**

When the etiology of ALF cannot be determined after routine evaluation, biopsy using a transjugular approach may be helpful in diagnosing malignant infiltration, autoimmune hepatitis, certain viral infections and Wilson disease. Lack of a clear diagnosis suggests that the history may have been inadequate regarding toxin or drug exposures. Causes of cases believed to represent indeterminate acute liver failure, and subsequently recognized include acetaminophen, autoimmune hepatitis and malignancies.<sup>10,55</sup>

#### **Recommendation**

**25. If the etiological diagnosis remains elusive after extensive initial evaluation, liver biopsy may be appropriate to attempt to identify a specific etiology that might influence treatment strategy (III).**

## **Therapy: General Considerations**

#### **Background**

While patients with ALF represent a heterogeneous group, they have consistent clinical features: acute loss of hepatocellular function, the systemic inflammatory response, and multi-organ system failure. Despite

**Table 4. Intensive Care of Acute Liver Failure**

<b>Cerebral Edema/Intracranial Hypertension</b>	
<b>Grade I/II Encephalopathy</b>	
Consider transfer to liver transplant facility and listing for transplantation	
Brain CT: rule out other causes of decreased mental status; little utility to identify cerebral edema	
Avoid stimulation; avoid sedation if possible	
Antibiotics: surveillance and treatment of infection required; prophylaxis possibly helpful	
Lactulose, possibly helpful	
<b>Grade III/IV Encephalopathy</b>	
Continue management strategies listed above	
Intubate trachea (may require sedation)	
Elevate head of bed	
Consider placement of ICP monitoring device	
Immediate treatment of seizures required; prophylaxis of unclear value	
Mannitol: use for severe elevation of ICP or first clinical signs of herniation	
Hypertonic saline to raise serum sodium to 145-155 mmol/L	
Hyperventilation: effects short-lived; may use for impending herniation	
<b>Infection</b>	
Surveillance for and prompt antimicrobial treatment of infection required	
Antibiotic prophylaxis possibly helpful but not proven	
<b>Coagulopathy</b>	
Vitamin K: give at least one dose	
FFP: give only for invasive procedures or active bleeding	
Platelets: give only for invasive procedures or active bleeding	
Recombinant activated factor VII: possibly effective for invasive procedures	
Prophylaxis for stress ulceration: give H <sub>2</sub> blocker or PPI	
<b>Hemodynamics/Renal Failure</b>	
Volume replacement	
Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure	
Avoid nephrotoxic agents	
Continuous modes of hemodialysis if needed	
Vasopressin recommended in hypotension refractory to volume resuscitation and no repinephrine	
<b>Metabolic Concerns</b>	
Follow closely: glucose, potassium, magnesium, phosphate	
Consider nutrition: enteral feedings if possible or total parenteral nutrition	

decades of research, however, no single therapy has been found to improve the outcome of all patients with ALF, with the possible exception of NAC. Systemic corticosteroids are ineffective and may be detrimental.<sup>74-76</sup>

Since most patients with ALF tend to develop some degree of circulatory dysfunction, agents that may improve hemodynamics have been of particular interest. While prostacyclin and other prostaglandins have appeared promising in some reports,<sup>77,78</sup> others have not supported their efficacy in ALF.<sup>79</sup> NAC may improve systemic circulation parameters in patients with ALF,<sup>80</sup> but this was not observed in all studies.<sup>81</sup> NAC has been shown to improve liver blood flow and function in patients with septic shock.<sup>82</sup> As noted above, a large, multi-center, randomized, double-blind controlled trial of intravenous NAC versus placebo for non-acetaminophen ALF has recently shown improvement for early coma grade patient in transplant-free survival.<sup>23</sup>

Since there is no proven therapy for ALF in general, management consists of intensive care support after treatments for specific etiologies have been initiated. While some patients with evidence of acute liver injury without significant encephalopathy may be monitored on a medicine ward, any patient with altered mental status warrants admission to an intensive care unit (ICU) since the condition may deteriorate quickly. Careful attention must be paid to fluid management, hemodynamics and metabolic parameters as well as surveillance for, and treatment of, infection. Coagulation parameters, complete blood counts, metabolic panels (including glucose) and arterial blood gas should be checked frequently. Serum aminotransferases and bilirubin are generally measured daily to follow the course of the condition; however, changes in aminotransferase levels correlate poorly with prognosis, and a decline should not be interpreted as a sign of improvement.

#### *Specific Issues* (Table 4)

## Central Nervous System

Cerebral edema and intracranial hypertension (ICH) have long been recognized as the most serious complications of acute liver failure.<sup>83</sup> Uncal herniation may result and is uniformly fatal. Cerebral edema may also contribute to ischemic and hypoxic brain injury, which may result in long-term neurological deficits in survivors.<sup>84</sup> The pathogenic mechanisms leading to the development of cerebral edema and intracranial hypertension in ALF are not entirely understood. It is likely that multiple factors are involved, including osmotic disturbances in the brain and heightened cerebral blood flow due to loss of cerebrovascular autoregulation. Inflammation and/or infection, as well as factors yet unidentified, may also contribute to the phenomenon.<sup>85</sup> Several measures have been proposed and used with varying success to tackle the problem of cerebral

**Table 5. Grades of Encephalopathy**

<b>Grade</b>	<b>Definition</b>
I	Changes in behavior with minimal change in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion; incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

Note: some patients will overlap grades; clinical judgment is required. Adapted from Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology* 1977;72:573-583.



edema and intracranial hypertension in patients with ALF. Interventions are generally supported by scant evidence; no uniform treatment protocol has been established.

### ***Prevention/Management of elevated intracranial pressure (ICP)***

The occurrence of cerebral edema and ICH in ALF is related to the severity of hepatic encephalopathy (Table 5). Cerebral edema is seldom observed in patients with grade I-II encephalopathy, but increases to 25% to 35% with progression to grade III, and 65% to 75% or more in patients reaching grade IV coma.<sup>86</sup> A stepwise approach to management is therefore advised.<sup>87</sup>

### ***Grades I-II Hepatic Encephalopathy***

Depending on the overall clinical picture, patients with grade I encephalopathy may be safely managed on a medicine ward with skilled nursing in a quiet environment to minimize agitation. Frequent neurological assessments should be performed, and transfer to an ICU should occur promptly if the level of consciousness declines. With progression to grade II encephalopathy, an ICU setting is indicated. Head imaging with computerized tomography (CT) may be used to exclude other causes of decline in mental status such as intracranial hemorrhage. Sedation is to be avoided, if possible; unmanageable agitation may be treated with short-acting benzodiazepines in small doses.

### ***Lactulose***

There is increasing evidence that ammonia plays an important role in the pathogenesis of cerebral edema/ICH. Ammonia infusion causes brain edema in animal models,<sup>88</sup> and an arterial ammonia level >200 ug/dL in humans is strongly associated with cerebral herniation;<sup>11</sup> conversely, serum ammonia <75 ug/dL is rarely associated with the development of hepatic encephalopathy.<sup>89</sup> Based on this evidence and on experience with treatment of hepatic encephalopathy in cirrhotic patients, it has been suggested that reducing elevated ammonia levels with enteral administration of lactulose might help prevent or treat cerebral edema in ALF. A preliminary report from the United States Acute Liver Failure Study Group (US ALFSG), retrospectively compared patients who received lactulose to a well-matched group of patients who did not, and found a small increase in survival time in those who received lactulose, but no difference in the severity of encephalopathy or in overall outcome.<sup>90</sup> One concern regarding the use of lactulose in this setting is the

potential for gaseous distension of the bowel that could present technical difficulties during liver transplantation.

### ***Grades III-IV Hepatic Encephalopathy***

As patients progress to grade III/IV encephalopathy, intubation and mechanical ventilation are mandatory. The choice of sedation and paralysis for purposes of mechanical ventilation have not been specifically studied, but non-depolarizing neuro-muscular blocking agents such as *cis*-atracurium may be preferable since they do not cause muscle contraction, and therefore do not increase ICP.<sup>91</sup> After intubation, propofol is often chosen for sedation because it may reduce cerebral blood flow.<sup>92</sup> Small doses of propofol may be adequate, given its long half-life in patients with liver failure. Patients in advanced stages of encephalopathy require intensive follow-up. Monitoring and management of hemodynamic and renal parameters as well as glucose, electrolytes and acid/base status becomes critical. Frequent neurological evaluation for signs of ICH, such as pupillary size and reactivity, posturing, and changes in peripheral reflexes, should be conducted. As prophylactic measures to reduce the incidence of ICH, patients should be positioned with the head elevated at 30 degrees,<sup>93</sup> and stimulation and pain should be minimized, sometimes requiring the administration of short-acting analgesics. Maneuvers that increase intrathoracic pressure by a Valsalva mechanism such as endotracheal suctioning may also increase ICP, and endotracheal lidocaine administration has been advocated.

### ***Seizures***

Seizures increase ICP,<sup>94</sup> and must be promptly controlled with phenytoin. Short-acting benzodiazepines should be administered in phenytoin-refractory cases. Seizure activity may also cause cerebral hypoxia and thus contribute to cerebral edema. Some experts have advocated prophylactic use of phenytoin, since seizure activity in patients with ALF may be sub-clinical. One randomized, controlled trial of prophylactic phenytoin in patients with ALF showed no difference in overall survival, but a striking diminution in cerebral edema at autopsy in the treated group.<sup>95</sup> However, a subsequent trial did not show improvement in the prevention of seizures, brain edema or survival;<sup>96</sup> therefore, prophylactic phenytoin cannot be recommended at this time.

### ***Intracranial Pressure Monitoring***

The use of intracranial pressure (ICP) monitoring devices in patients with ALF remains contentious, and

practices vary widely among US centers. A survey of the initial 14 transplant centers in the US ALFSG found ICP monitoring devices were used in 13 of these sites from 1998-2000;<sup>97</sup> a more recent review of more than 20 US sites found ICP monitors used in a little more than half.<sup>98</sup>

The rationale for the insertion of an ICP monitor is to improve the early recognition of ICH so that corrective therapy can be initiated. Clinical signs of elevated ICP (systemic hypertension, bradycardia and irregular respirations—Cushing's triad) are not uniformly present, and other neurologic changes such as pupillary dilatation or signs of decerebration are typically evident only late in the course. Furthermore, CT of the brain does not reliably demonstrate evidence of edema especially at early stages.<sup>99</sup> Other methods of monitoring ICP (such as transcranial doppler ultrasonography, near-infrared spectrophotometry, and measurement of serum S-100 beta and neuronal specific enolase) are in various stages of evaluation, but have thus far not been proven reliable in estimating ICP, and are not widely available.<sup>100-104</sup>

Monitoring ICP also allows assessment of the cerebral perfusion pressure (CPP; calculated as mean arterial pressure [MAP] minus ICP), in order to avoid hypoperfusion of the brain, which can result in hypoxic injury. The goal in management of ICH is therefore to lower ICP (generally to <20 mmHg) while preserving CPP (generally to >60 mmHg) either by administering osmotically-active agents and/or vasopressors. Monitoring is particularly important during orthotopic liver transplantation, when shifts in electrolytes and hemodynamics can cause large fluctuations in ICP.<sup>104</sup> Additionally, refractory ICH and/or decreased CPP are considered relative contraindications to liver transplantation in many centers because of concern about poor neurological recovery.<sup>105,106</sup> Although case reports of full neurological recovery after prolonged ICH and decreased CPP may call this practice into question,<sup>106</sup> there is no way of determining whether these patients would have survived the rigors of transplantation surgery. Non-randomized reports indicate that ICP monitoring devices can be inserted safely, provide information to guide management of ICH,<sup>88,105,108</sup> and may even lengthen survival time, but do not demonstrate overall survival benefit compared to patients who were managed without ICP monitoring.

Reluctance to place ICP monitors has been primarily spawned by concern over the risks (mainly infection and bleeding) in critically ill, coagulopathic patients. An early report based on the experience with ICU monitors in 262 patients with ALF at US transplant

centers observed a complication rate of 3.8% (1% fatal hemorrhage) with epidural catheters.<sup>109</sup> The unreliability of pressure monitoring in the epidural space was improved by placement in subdural or intraparenchymal locations, but complications also increased. It is not known whether newer, smaller monitoring devices have decreased the risk of complications. More aggressive correction of coagulation parameters such as with recombinant activated factor VII may further reduce the bleeding risk while avoiding the volume overload and transfusion-associated lung injury associated with plasma infusion, allowing wider use of ICP monitoring devices.<sup>110</sup> Indeed, a more recent report has suggested a considerable reduction in the prevalence of bleeding complications (2 out of 58 cases, with the majority being subdural monitors).<sup>98</sup> The same series, however, failed to demonstrate improved outcomes in patients managed with ICP monitors compared to those who were not.

### ***Specific Treatment of Elevated Intracranial Pressure***

Immediate interventions beyond the preventative strategies outlined above are indicated after the development of cerebral edema. If an ICP monitor is placed, key parameters to follow are both ICP and CPP. ICP should be maintained below 20-25 mm Hg if possible, with CPP maintained above 50-60 mm Hg.<sup>4,111</sup> Evidence from trauma patients with cerebral edema suggests that maintaining CPP above 70 mm Hg may further improve neurologic outcomes, if this level can be achieved.<sup>112</sup> Support of systemic blood pressure, first with a volume challenge and then with vasopressors,<sup>91</sup> may be required to maintain adequate CPP. Conversely, fluid-overloaded patients in renal failure should undergo continuous renal replacement therapy to remove ~500 ml plasma volume.<sup>91</sup>

### ***Mannitol***

If ICH develops, either as seen on ICP monitoring or by obvious neurological signs (decerebrate posturing, pupillary abnormalities), osmotic agents such as mannitol are often transiently effective in decreasing cerebral edema.<sup>113</sup> Mannitol has been shown in very small series to correct episodes of elevated ICP in ALF patients, and also to improve survival. However, the effect is transient, and mannitol does not reduce ICP to acceptable levels (<25 mmHg) in patients with severe ICH (ICP >60 mmHg).<sup>114</sup> Administration of intravenous mannitol (in a bolus dose of 0.5-1.0 g/kg) is therefore recommended as first-line therapy of ICH in patients with ALF. The dose may be repeated once

or twice as needed as long as the serum osmolality is <320 mOsm/L. Volume overload is a risk with mannitol use in patients with renal impairment, and may necessitate use of dialysis to remove excess fluid. Hyperosmolality or hypernatremia also may result from overzealous use. The prophylactic administration of mannitol in patients at high risk of ICH has not been studied.

### ***Hyperventilation***

Hyperventilation to PaCO<sub>2</sub> of 25-30 mmHg restores cerebrovascular autoregulation, resulting in vasoconstriction and reduction of ICP.<sup>115</sup> Patients with ALF routinely hyperventilate spontaneously, which should not be inhibited. Unfortunately, the effect of hyperventilation on cerebral blood flow is short-lived.<sup>116</sup> A randomized, controlled trial of prophylactic continuous hyperventilation in ALF patients showed no reduction in incidence of cerebral edema/ICH and no survival benefit, though onset of cerebral herniation appeared to be delayed in the hyperventilated group.<sup>117</sup> There has been some concern that cerebral vasoconstriction with hyperventilation could potentially worsen cerebral edema by causing cerebral hypoxia.<sup>118</sup> Based on available evidence, there is no role for prophylactic hyperventilation in patients with ALF. If life-threatening ICH is not controlled with mannitol infusion and other general management outlined above, hyperventilation may be instituted acutely to delay impending herniation; beyond this acute situation, forced hyperventilation cannot be recommended as routine management.

### ***Hypertonic Sodium Chloride***

In patients with ALF and severe hepatic encephalopathy, a controlled trial of the prophylactic induction of hypernatremia with hypertonic saline (to a serum sodium 145-155 mEq/L) suggested a lower incidence of ICH compared to management under "normonatremic" conditions.<sup>119</sup> Although survival benefit of induced hypernatremia was not demonstrated, this trial presents the most compelling data favoring the use of osmotic agents in ALF, and therefore hypertonic saline as a prophylactic measure is recommended in patients at highest risk of developing cerebral edema (high serum ammonia, high grade hepatic encephalopathy, acute renal failure, and/or requirement for vasopressors). Studies of hypertonic saline as treatment for established ICH have not been performed.

### ***Barbiturates***

Barbiturate agents (thiopental or pentobarbital) may also be considered when severe ICH does not respond to other measures; administration has been shown to effectively decrease ICP. Significant systemic hypotension frequently limits its use, and may necessitate additional measures to maintain adequate mean arterial pressure (MAP).<sup>120</sup> It should be recognized that barbiturate clearance is markedly reduced in patients with ALF, precluding neurological assessment for prolonged periods of time.

### ***Corticosteroids***

Corticosteroids are often used in the prevention and management of ICH caused by brain tumors and some infections of the central nervous system. In a controlled trial in patients with ALF, however, corticosteroids failed to improve cerebral edema or survival, and cannot be advocated.<sup>76</sup>

### ***Hypothermia***

Hypothermia may prevent or control ICH in patients with ALF.<sup>121,122</sup> It has been shown in experimental animal models to prevent development of brain edema,<sup>123,124</sup> possibly by preventing hyperemia, altering brain ammonia or glucose metabolism, or by a combined effect. Limited experience in humans with ALF supports the use of hypothermia (cooling to core temperature of 33-34°C) as a bridge to liver transplantation or to control ICP during transplant surgery.<sup>125,126</sup> However, hypothermia has not been compared to normothermia in a controlled trial, and has not been shown to improve transplant-free survival. Potential deleterious effects of hypothermia include increased risk of infection, coagulation disturbance, and cardiac arrhythmias;<sup>127</sup> concern about the effect of hypothermia on hepatic regeneration has also been raised.<sup>128</sup>

### ***Pharmacologic Treatment of Hyperammonemia***

In theory, compounds that facilitate the detoxification and elimination of ammonia may be useful in the prevention and treatment of cerebral edema. Unfortunately, a randomized, placebo-controlled trial of L-ornithine L-aspartate (LOLA) failed to demonstrate a decline in arterial ammonia levels or improvement in survival in a large study population.<sup>129</sup>

### **Recommendations**

**26. In early stages of encephalopathy, lactulose may be used either orally or rectally to effect a bowel purge, but should not be administered to the point of diarrhea, and may interfere with the surgical field**

*by increasing bowel distention during liver transplantation (III).*

*27. Patients who progress to high-grade hepatic encephalopathy (grade III or IV) should undergo endotracheal intubation (III).*

*28. Seizure activity should be treated with phenytoin and benzodiazepines with short half-lives. Prophylactic phenytoin is not recommended (III).*

*29. Intracranial pressure monitoring is recommended in ALF patients with high grade hepatic encephalopathy, in centers with expertise in ICP monitoring, in patients awaiting and undergoing liver transplantation (III).*

*30. In the absence of ICP monitoring, frequent (hourly) neurological evaluation is recommended to identify early evidence of intracranial hypertension (III).*

*31. In the event of intracranial hypertension, a mannitol bolus (0.5-1.0 gm/kg body weight) is recommended as first-line therapy; however, the prophylactic administration of mannitol is not recommended (II-2).*

*32. In ALF patients at highest risk for cerebral edema (serum ammonia > 150  $\mu$ M, grade 3/4 hepatic encephalopathy, acute renal failure, requiring vasopressors to maintain MAP), the prophylactic induction of hyponatremia with hypertonic saline to a sodium level of 145-155 mEq/L is recommended (I).*

*33. Short-acting barbiturates and the induction of hypothermia to a core body temperature of 34-35°C may be considered for intracranial hypertension refractory to osmotic agents as a bridge to liver transplantation (II-3).*

*34. Corticosteroids should not be used to control elevated ICP in patients with ALF (I).*

## Infection

All ALF patients are at risk for bacterial<sup>130,131</sup> or fungal<sup>132</sup> infection or sepsis, which may preclude liver transplantation or complicate the post-operative course. Although prophylactic parenteral antimicrobial therapy reduces the incidence of infection in certain groups of patients with ALF, survival benefit has not been shown,<sup>133,134</sup> making it difficult to recommend the practice uniformly. Similarly, poorly absorbable antibiotics for selective bowel decontamination have not been shown to impact survival.<sup>134</sup> If antibiotics are not given prophylactically, surveillance for infection (including chest radiography and periodic cultures of sputum, urine and blood for fungal and bacterial

organisms) should be undertaken, while maintaining a low threshold for starting appropriate anti-bacterial or anti-fungal therapy.

Deterioration of mental status in hospital, particularly in patients with acetaminophen toxicity, may represent the onset of infection. There are no controlled trials available to confirm whether the use of prophylactic antimicrobials decreases the likelihood of progression of encephalopathy and/or development of cerebral edema in ALF. However, studies have suggested an association between infection and/or the systemic inflammatory response syndrome (SIRS) and progression to deeper stages of encephalopathy.<sup>133,134</sup> Given that prophylactic antibiotics have been shown to reduce the risk of infection, that later stages of encephalopathy are associated with increased incidence of cerebral edema, and that fever may worsen intracranial hypertension,<sup>135</sup> it is possible that antibiotic and anti-fungal prophylaxis may decrease the risk of cerebral edema and ICH. This hypothesis is yet to be proven, however.

## Recommendations

*35. Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens as early as possible. Antibiotic treatment should be initiated promptly according to surveillance culture results at the earliest sign of active infection or deterioration (progression to high grade hepatic encephalopathy or elements of the SIRS) (III).*

*36. Prophylactic antibiotics and antifungals have not been shown to improve overall outcomes in ALF and therefore cannot be advocated in all patients, particularly those with mild hepatic encephalopathy (III).*

## Coagulopathy

Although an elevated INR constitutes part of the definition of ALF, the magnitude of the bleeding diathesis remains undefined. The synthesis of coagulation factors is universally decreased, while consumption of clotting factors and platelets also may occur, so that platelet counts frequently drop to  $\leq 150,000/\text{mm}^3$  (50-70%).<sup>136</sup> However, a recent study has suggested that overall hemostasis as measured by thromboelastography is normal by several compensatory mechanisms, even in patients with markedly elevated INR.<sup>137</sup> In the absence of bleeding, it is not advisable to correct the INR with plasma,<sup>137</sup> since clinically significant blood loss is rare and correction obscures trends in the INR, an important marker of prognosis.

Plasma transfusion has other drawbacks, including the risk of transfusion-related acute lung injury and volume overload. Although plasma is frequently administered prior to invasive procedures such as ICP monitor insertion, guidelines and goals of repletion have not been studied, and recommendations remain driven by consensus.<sup>8</sup> Vitamin K (5-10 mg subcutaneously) should be administered routinely, since vitamin K deficiency has been reported in patients with ALF.<sup>138</sup>

The occurrence of clinically significant bleeding, or in anticipation of a high-risk procedure, warrants treatment of clotting factor deficiency. Plasma infusion alone frequently does not adequately correct severely elevated INR and risks volume overload, in which case plasmapheresis<sup>139</sup> or recombinant activated factor VII (rFVIIa) may be considered. A nonrandomized trial of fifteen patients with ALF found that administration of rFVIIa in combination with FFP produced effective temporary correction of coagulopathy without volume overload;<sup>110</sup> a second report of 11 patients supported these findings, and reported no bleeding or thrombotic complications.<sup>140</sup> Important barriers to the routine use of rFVIIa remain, however, including its very high cost, and reports of serious thromboembolism in patients with ALF (myocardial infarction and portal vein thrombosis).<sup>141</sup>

Experts differ regarding prophylactic use of platelets in thrombocytopenic patients with ALF. Similar to the case with plasma, platelet transfusions are not generally recommended in the absence of spontaneous bleeding or prior to invasive procedures. In the absence of bleeding, a threshold platelet count of 10,000/mm<sup>3</sup>, has been recommended to initiate platelet transfusion in non-ALF patients, although some experts recommend more conservative levels of 15-20,000/mm<sup>3</sup>, especially in patients with infection or sepsis.<sup>142</sup> Experience in patients without ALF suggests that platelet counts of  $\geq 10,000/\text{mm}^3$  are generally well tolerated.<sup>143</sup> When invasive procedures must be performed in patients with ALF, platelet counts of 50-70,000/mm<sup>3</sup> have been considered adequate,<sup>144</sup> although thromboelastography suggests that a platelet count of 100,000/mm<sup>3</sup> may be more appropriate.<sup>137</sup> Patients who develop significant bleeding with platelet levels below approximately 50,000/mm<sup>3</sup> should generally be transfused with platelets provided no contraindication (such as thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia) exists. It should be emphasized, however, that threshold platelet counts for transfusion have not been studied in patients with ALF, in whom many other coagulation defects coexist.

## Recommendation

**37. Replacement therapy for thrombocytopenia and/or prolonged prothrombin time is recommended only in the setting of hemorrhage or prior to invasive procedures (III).**

## Bleeding

As noted above, spontaneous bleeding in patients with ALF is uncommon, and clinically significant bleeding (requiring blood transfusion) is rare.<sup>145</sup> Spontaneous bleeding in ALF is capillary-type, usually from mucosal sites of the stomach, lungs, or genitourinary system. Although portal hypertension occurs in acute liver injury due to architectural collapse of the liver,<sup>146</sup> bleeding from esophageal varices almost never occurs. Similarly, despite intracranial hypertension, spontaneous intracranial bleeding in the absence of ICP monitors has been reported in <1% of patients. The incidence of spontaneous bleeding in patients with ALF appears to have decreased in the last 30 years, probably as the result of improvements in ICU care. Histamine-2 receptor (H<sub>2</sub>) blocking agents have long been used in the prophylaxis of gastrointestinal (GI) bleeding in critically ill patients; their efficacy has been supported in several trials.<sup>147-150</sup> Similarly, acid suppression with cimetidine, and by inference, proton pump inhibitors, are likely to have contributed to the decreased incidence of significant upper GI bleeding in patients with ALF.<sup>150</sup> Sucralfate has also been found to be effective in non-ALF ICU populations, and there have been smaller randomized trials and a meta-analysis which suggested that sucralfate may be as effective in preventing gastrointestinal bleeding and might be associated with lower risk of nosocomial pneumonia than H<sub>2</sub> blocker.<sup>151,152</sup>

## Recommendation

**38. Patients with ALF in the ICU should receive prophylaxis with H<sub>2</sub> blocking agents or proton pump inhibitors (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress (I).**

## Hemodynamics and Renal Failure

Hemodynamic derangements occur frequently in patients with ALF and contribute peripheral tissue oxygenation and multi-organ system failure. The fundamental hemodynamic abnormality in ALF, similar to cirrhosis or sepsis, is low systemic vascular resistance; in contrast to cirrhosis, however, splanchnic pooling of blood is less pronounced. Maintaining adequate

hemodynamics becomes increasingly important in cases of intracranial hypertension and/or compromised renal function, as preservation of renal and brain perfusion is imperative. Depletion of intravascular volume may be present on admission due to decreased oral intake resulting from altered mental status and transudation of fluid into the extra-vascular space; most patients with ALF will require fluid resuscitation initially. Hypotensive patients with ALF should be resuscitated with normal saline first, and changed to half-normal saline containing 75 mEq/L sodium bicarbonate if acidotic, before consideration of the use of vasopressors.<sup>153</sup> Crystalloid solutions should contain dextrose to prevent hypoglycemia, if necessary.

While adequate fluid replacement and treatment of potential infection and sepsis may help to correct hypotension, inotropic or pressor support may be required in order to maintain a MAP of at least 75 mmHg or a CPP of 60-80 mmHg.<sup>153</sup> There are no studies that define the optimal vasopressor regimen for use in hypotensive patients with ALF. The general consensus in the US and UK appears to be that norepinephrine may best augment peripheral organ perfusion while minimizing tachycardia and preserving splanchnic (thereby hepatic) blood flow.<sup>153</sup>

In patients who do not respond to a volume challenge and norepinephrine, vasopressin and its analogues may potentiate the effects of norepinephrine and allow a decrease in its infusion rate, which in turn may avoid intense vasoconstriction in peripheral tissues which can lead to ischemia.

Acute renal failure is a frequent complication in patients with acute liver failure<sup>154</sup> and may be due to hemodynamic alterations (functional renal failure similar to the hepatorenal syndrome in patients with cirrhosis) or acute tubular necrosis.<sup>155</sup> The frequency of renal failure may be even greater with acetaminophen overdose or other hepatotoxins with direct nephrotoxicity (for example, *Amanita* poisoning, trimethoprim-sulfamethoxazole).<sup>156</sup> Though few patients die of renal failure alone, it often contributes to mortality and may portend a poorer prognosis.<sup>13,157</sup> Every effort should be made to protect renal function by maintaining adequate hemodynamics, avoiding nephrotoxic agents such as aminoglycosides and non-steroidal anti-inflammatory drugs, and by the prompt identification and treatment of infection. When dialysis is needed, continuous modes of renal replacement therapy should be used, as they have been shown in randomized trials to result in improved stability in cardiovascular and intracranial parameters compared with intermittent modes of hemodialysis.<sup>158</sup> Intravenous contrast agents are

associated with nephrotoxicity in the setting of compromised hepatic function, and should be used with caution.

The potential utility of prostaglandins and NAC in improving hemodynamics and renal function was discussed previously; neither has sufficient evidence to be recommended as part of the management of hemodynamic derangements in ALF at this time, although NAC may have other benefits as discussed above.<sup>159,160</sup> The observation that hemodynamic status as well as ICH tends to improve after removal of the native liver during transplantation for ALF led to a recommendation of hepatectomy to stabilize severe circulatory dysfunction and uncontrollable ICH. Hepatectomy, which presumably removes the source of vasoactive cytokines, has been shown in uncontrolled studies and case reports to bridge patients to successful liver transplantation even after 48 hours.<sup>161-163</sup> Despite these reports, hepatectomy to control hemodynamics can only be advocated as a last resort with a suitable liver graft *en route*.

### Recommendations

**39. Fluid resuscitation and maintenance of adequate intravascular volume are recommended on presentation in patients with ALF. The initial treatment of hypotension should be with intravenous normal saline (III).**

**40. If dialysis support is needed for acute renal failure, it is recommended that a continuous mode rather than an intermittent mode be used (I).**

**41. Pulmonary artery catheterization is rarely necessary in patients with ALF and is associated with significant morbidity. Instead, appropriate volume status should be ensured with a volume challenge (III).**

**42. Systemic vasopressor support with agents such as norepinephrine should be administered in volume-refractory hypotension or to ensure adequate CPP. Vasopressin or terlipressin can be added to norepinephrine in norepinephrine-refractory cases, but should be used cautiously in severely encephalopathic patients with intracranial hypertension (II-1).**

**43. Goals of circulatory support in patients with ALF are a MAP  $\geq$  75 mmHg and CPP 60-80 mmHg (II).**

### Metabolic Concerns

A number of metabolic derangements are common in ALF. Alkalosis and acidosis may both occur and are

best managed by identifying and treating the underlying cause. Hypoglycemia should be managed with continuous glucose infusions, since symptoms may be obscured in the presence of encephalopathy. Phosphate, magnesium, and potassium levels are frequently low and may require repeated supplementation throughout the hospital course. Nutrition is also important. Enteral feedings should be initiated early. Severe restrictions of protein should be avoided; 60 grams per day of protein is reasonable in most cases. Branched-chain amino acids have not been shown to be superior to other enteral preparations.<sup>164</sup> If enteral feedings are contraindicated, parenteral nutrition should be considered. Enteral and parenteral nutrition may reduce the risk of gastrointestinal bleeding due to stress ulceration in critically ill patients.<sup>165</sup>

### Recommendation

**44. Metabolic homeostasis must be carefully maintained in ALF patients. Overall nutritional status as well as glucose, phosphate, potassium and magnesium levels should be monitored frequently, with expeditious correction of derangements (III).**

## Prognosis and Transplantation

### Prognosis (See Table 6.)

It is critical to quickly and accurately identify those patients most likely to benefit from emergent OLT. It is, therefore, crucial that reliable predictive models of survival and need for liver transplantation be developed. Successfully predicting outcome would allow more judicious use of scarce organs and spare those who will ultimately recover the necessity of transplantation and life-long immunosuppression. The wide variety of etiologies that lead to ALF, the variability in patient survival, and the unpredictability of subsequent complications makes it very difficult to determine who will survive without transplantation. Prognostic scoring systems, although derived from data on relatively large numbers of patients, still fail to achieve success.

**Clinical Predictors.** Clinical predictors of death may help determine which patients are more likely to die, however, these are generally unreliable. In the largest US multi-center study of ALF to date, the etiology of ALF was one of the more important predictors of outcome.<sup>7</sup> With the epidemiologic shift to more benign causes of ALF (i.e., acetaminophen), the advent of improved clinical management, and selected utilization of liver transplantation, the overall mortality has improved to between 30-40%. Transplant free-survival was  $\geq 50\%$  in the setting of ALF due to acetaminophen,

**Table 6. Potentially Helpful Indicators\* of Poor Prognosis in Patients With ALF**

Etiology
Idiosyncratic drug injury
Acute hepatitis B (and other non-hepatitis A viral infections)
Autoimmune hepatitis
Mushroom poisoning
Wilson disease
Budd-Chiari syndrome
Indeterminate cause
Coma Grade on Admission
III or IV
King's College Criteria
<i>Acetaminophen-Induced ALF</i>
• Strongly consider OLT listing if:
• arterial lactate $>3.5$ mmol/L after early fluid resuscitation
• List for OLT if:
• pH $<7.3$ - or -
• arterial lactate $>3.0$ mmol/L after adequate fluid resuscitation
• List for OLT if all 3 occur within a 24-hour period:
• presence of grade 3 or 4 hepatic encephalopathy
• INR $>6.5$
• Creatinine $>3.4$ mg/dL
<i>Non-Acetaminophen-Induced ALF</i>
• List for OLT if:
• INR $>6.5$ and encephalopathy present (irrespective of grade) or any three of the following (encephalopathy present; irrespective of grade):
• Age $<10$ or $>40$ years $\ddagger$
• Jaundice for $>7$ days before development of encephalopathy $\ddagger$
• INR $\geq 3.5$
• serum bilirubin $\geq 17$ mg/dL
• Unfavorable etiology, such as Wilson Disease idiosyncratic drug reaction seronegative hepatitis

\*Please note: None of these factors, with the exception of Wilson Disease and possibly mushroom poisoning, are either necessary or sufficient to indicate the need for immediate liver transplantation.

$\ddagger$ These criteria, in particular, have not been found to be predictive of outcome in recent analyses.<sup>7</sup>

hepatitis A, shock liver, or pregnancy-related disease; while all other etiologies showed  $<25\%$  transplant-free survival. Other predictors of a worse spontaneous survival include the presence of renal dysfunction in non-acetaminophen ALF and the degree of hepatic encephalopathy. Patients presenting in grade III or IV encephalopathy are less likely than those patients presenting in grade I or II encephalopathy to survive without receiving a liver graft.<sup>7</sup> Factors such as age and the length of time between onset of illness and onset of encephalopathy have previously been proposed as important prognostic indicators in ALF; however, these parameters did not affect outcome in the US study.<sup>7,13,166</sup>

**Prognostic Models.** Multiple prognostic models have been proposed to help determine the likelihood of spontaneous survival.<sup>167-172</sup> Many of these models; however, are methodologically flawed and subject to bias.<sup>173</sup> In addition, many equate transplantation with

death, which falsely elevates the positive predictive value of the particular system.<sup>174,175</sup> Factors implicated have included serum phosphate levels, Factor V levels, alpha-fetoprotein, ammonia, Gc globulin, and finally MELD scores. None has proven fully satisfactory. It appears that survival after acute liver failure is multifactorial and depends on etiology, grade of coma on admission, ability to regenerate a healthy liver, and the absence of significant and often unpredictable complications.

The most widely applied prognostic system is the King's College Hospital criteria (KCH Criteria), developed from a retrospective cohort of nearly 600 patients (Kings Criteria; Table 6).<sup>13</sup> These criteria incorporate both the etiology of ALF and clinical parameters of disease. Several studies have shown positive predictive values ranging from 70% to nearly 100% and negative predictive values ranging from 25% to 94%.<sup>176-178</sup> In a meta-analysis of studies using the KCH Criteria, the pooled sensitivity and specificity was 68% to 69% and 82% to 92%, respectively.<sup>174,179</sup> The Clichy criteria were developed in a cohort of French patients with acute hepatitis B virus infection.<sup>180</sup> A serum factor V level of <20% in patients younger than 30 years or <30% in any patient with grade 3-4 HE predicted mortality with a positive predictive value of 82% and a negative predictive value of 98%. Factor V level measurements are less readily available than the measures in the KCH Criteria, and subsequent studies have shown these criteria to be less accurate than the KCH Criteria in predicting outcome.<sup>177,178</sup>

### Recommendation

***45. Currently available prognostic scoring systems do not adequately predict outcome and determine candidacy for liver transplantation. Reliance entirely upon these guidelines is thus not recommended.(III)***

### Transplantation

Advances in critical care medicine and changing trends toward more benign etiologies such as acetaminophen (having a better overall outcome) have improved the spontaneous survival in ALF patients from 10% to 20% to about 40%.<sup>7</sup> However, orthotopic liver transplantation remains the only definitive therapy for patients who are unable to achieve regeneration of sufficient hepatocyte mass to sustain life. The advance of transplantation has coincided with further improvement in overall survival rates to over 60% currently.<sup>7</sup> Overall, the 1-year survival following liver transplant is less than that seen in patients who have been transplanted for chronic liver failure; however, following the first year this trend has reversed and

ALF patients have a better long-term survival.<sup>7,181-183</sup> The majority of deaths occur within the first one to three months following transplantation, and are usually secondary to neurologic complications or sepsis.

In addition to whole-organ deceased donor liver transplantation, other types of transplantation have been attempted in this setting. Living donor liver transplantation (LDLT) accounted for approximately 2% of transplants for ALF between January 1, 1988 and March 31, 2010 (Based on Organ Procurement and Transplantation Network [OPTN] data as of May, 2011). The use of LDLT remains controversial.<sup>184-187</sup> Unique ethical issues exist. The donor evaluation must be compressed which carries the risk of an incomplete evaluation and the possibility of donor coercion. The team and the donor must consider the associated donor complications, including death in 0.2%.<sup>188-192</sup> Nevertheless, right-lobe LDLT improves survival of patients with acute liver failure, and the 1-year survival following LDLT is approximately 75%.<sup>187</sup> The use of ABO-incompatible grafts (e.g., A graft, B recipient) show less favorable outcome (30% to 60% 1-year graft survival).<sup>193,194</sup> Auxiliary liver transplant leaves the recipient's liver in place, using a partial left or right lobe from the donor which acts as temporary liver support. Ideally, immunosuppression could ultimately be withdrawn following native liver recovery.<sup>195</sup> Overall survival rate for auxiliary transplantation is reported to be approximately 60-65%, and immunosuppression has successfully been withdrawn in 65% to 85% of these patients by 1-year post-transplant.<sup>187,195,196</sup>

Candidacy for transplantation must be determined very quickly, given the rapid pace of the clinical syndrome. Acute liver failure is one of few conditions for which a patient can be listed as a UNOS status 1A (urgent) in the US and "super urgent" in the UK. Although about half of ALF patients undergo liver transplantation, ALF accounts for less than 10% of US transplants and approximately 11% in Europe.<sup>183</sup> Of patients listed for transplantation, approximately 35% will recover spontaneously without the need for grafting; thus, as many as 20% of ALF patients may be transplanted needlessly.<sup>197</sup> In the largest US study, 44% of patients were listed, yet only 29% of patients received a liver graft, and 10% of the overall group (25% of patients listed for transplantation) died on the waiting list.<sup>7</sup> Other series have reported death rates for those listed for transplant as high as 40%.<sup>190,198</sup> In addition, many patients have medical or psychosocial contraindications to transplantation, including irreversible brain injury, underlying cardiovascular disease, infection/sepsis, alcohol or drug abuse, poorly



controlled psychiatric disease, or inadequate family support.<sup>199</sup> Therefore, it is vital to identify and even delist patients who are too ill to benefit from OLT.

Developing effective methods of liver support or other alternatives to transplantation and better prognostic scoring systems remain key goals to further improve overall survival rates for the condition.

### **Recommendation**

**46. Urgent hepatic transplantation is indicated in acute liver failure where prognostic indicators suggest a high likelihood of death (II-3).**

**47. Living donor or auxiliary liver transplantation may be considered in the setting of limited organ supply, but its use remains controversial (II-3).**

### **Liver Support Systems**

A support device to replace the acutely failing liver seems a reasonable but elusive goal. The objective of liver assist therapies has been to either support the patient until the native liver has had time to recover, or to bridge the patient to liver transplantation. Artificial support therapies provide detoxification support without the use of cellular material. Bioartificial systems utilize cellular material and, in theory, provide not only detoxification, but also assume many of the liver's synthetic functions. A variety of systems have been tested to date, all in nonrandomized trials.

**Artificial Support.** These sorbent-based systems, which detoxify only, employ charcoal or other adherent particles, such as albumin, in a capsule or column device placed in an extracorporeal circuit.<sup>200,201</sup> Plasmapheresis has been shown to improve hepatic encephalopathy and some systemic hemodynamic parameters, but its survival benefit is questionable.<sup>202-204</sup> The molecular absorbents recirculation system (MARS) is a two-circuit system, which allows albumin-bound toxins to be removed.<sup>205</sup> A meta-analysis of studies using MARS failed to show a significant survival benefit in ALF patients.<sup>206</sup> The Prometheus albumin dialysis system functions similarly to MARS, however there exists even less data on its survival benefit.<sup>207,208</sup> Thus, there has been no good evidence that any artificial support system reliably reduces mortality in the setting of ALF.<sup>200,201,209</sup>

**Bioartificial Support.** Hepatocytes, whether of human or other mammalian origin, have been used in cartridges in extracorporeal circuits, either with or without sorbent columns. Five systems have been tested clinically: HepatAssist<sup>TM</sup> (Arbios, formerly Circe, Waltham MA), extracorporeal liver support device (ELAD<sup>TM</sup>; Vital Therapies, San Diego, CA), modular extracorporeal liver support system (MELS<sup>TM</sup>; Charité,

Berlin, Germany), bioartificial liver support system (BLSS<sup>TM</sup>; Excorp Medical, Minneapolis MN), and the Amsterdam Medical Center bioartificial liver (AMC-BAL<sup>TM</sup>; AMC, Amsterdam, The Netherlands).<sup>210-214</sup> Few controlled trials have been published, and preliminary reports suggest no benefit to outcome, with or without transplantation.<sup>215</sup> HepatAssist<sup>TM</sup>, a porcine hepatocyte based bioartificial liver, in a small randomized trial showed a survival advantage in patients with ALF and subacute liver failure.<sup>210</sup> Despite this, the device was not approved by the FDA, and further testing in patients with ALF was recommended.

All such trials are difficult to perform and to control properly due to the rarity of well-characterized patients, the heterogeneity of etiologies, varying levels of disease severity, and varying access to liver transplantation. A recent meta-analysis, considering all forms of devices together, demonstrated no efficacy for bioartificial liver devices for the treatment of ALF.<sup>209</sup> A variety of other strategies have been employed, including exchange transfusion, charcoal hemoperfusion, extracorporeal liver perfusions, and intra-portal hepatocyte infusions.<sup>216-218</sup> To date, none can be recommended, and their use remains experimental. Efforts to improve hepatocyte regeneration remains in its infancy.<sup>219,220</sup>

### **Recommendation**

**48. Currently available liver support systems are not recommended outside of clinical trials; their future in the management of acute liver failure remains unclear (II-1).**

## **Summary**

Management of ALF challenges our best skills as physicians and intensivists. Treatments for specific etiologies and consideration of transplantation should be under-taken urgently in all patients that demonstrate evidence of encephalopathy. Because patients may deteriorate rapidly, arranging care in a center with experience and expertise in managing patients with ALF will secure the best possible outcomes for these patients.

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