

ICU Management of Acute Liver Failure

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- Coagulopathy • Liver assist devices • Hypothermia

Acute liver failure (ALF) is defined as the development of impaired hepatic synthetic function with coagulopathy and the development of hepatic encephalopathy in the absence of underlying liver disease in less than 2 to 3 months time.¹ In the setting of ALF, hepatic encephalopathy may be associated with life-threatening cerebral edema, whereas by contrast this association is absent in patients who have chronic liver failure with encephalopathy. The recovery from the loss of functional liver mass in acute liver injury occurs more readily than in the chronic setting because of the lack of long-standing fibrosis and portal hypertension, and the host's overall better nutritional status. Therefore, if the individual can be supported properly throughout the acute event, and the inciting injury is removed or ameliorated, recovery will follow the rapid regeneration of liver cells. For those in whom spontaneous recovery is not possible, liver transplant may be life-saving.

PATHOGENESIS OF ACUTE LIVER FAILURE

The specific pathogenesis of the liver injury is dependent to a large degree on the etiology. There are features of injury common to most etiologies of ALF, however. Injury to hepatocytes causes cell damage or cell death by necrosis or apoptosis;

however, these processes may coexist.² Triggering of the mitochondrial permeability transition by injury typically is associated with apoptosis if ATP stores are preserved, and necrosis if there is ATP depletion.² Examples of mitochondrial injury associated with apoptosis include acute Wilson disease³ and Reye's syndrome.⁴ In the early phase of injury from warm and cold ischemia, hepatocytes and endothelial cells activate the mitochondrial permeability transition, and mitochondrial injury results in ATP depletion and ensuing necrosis.

Necrotic injury of liver cells leads to a loss of cell membrane integrity and eventual rupture and cell death with the release of cytosolic proteins including lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and ferritin. Cellular glutathione is diminished, especially following ALF with acetaminophen.⁵ This increases cellular susceptibility to oxidative injury and impairs the ability to conjugate and detoxify some toxic substances. Other detoxification mechanisms are impaired, including the transport systems for bilirubin, leading cholestasis and conjugated hyperbilirubinemia.

An important feature of acute and chronic liver injury is the general loss of Kupffer cell function that results in reduced clearance of endotoxin and other substrates regularly presented to

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hepatocytes by means of the portal system, increasing the risk of infection.⁶

The site of injury within the liver plays an important role in determining the ability of the liver to regenerate. Arterial blood and portal blood rich in oxygen and nutrients are supplied in the portal tract where the liver progenitor cells, ductal hepatocytes, or oval cells are present.⁷ Injury to the portal zone inhibits the regenerative response, while injury to the central zone with sparing of the portal zone permits more frequent spontaneous recovery. The central zone is more susceptible to ischemic injury. Other toxic injuries may differ in their site of action because of differences in the metabolism of central hepatocytes compared with portal hepatocytes.

ETIOLOGIES OF ACUTE LIVER FAILURE AND SPECIFIC THERAPIES

The specific etiology of ALF is the most important determinant of outcome.⁸ The frequency of specific types of liver injury varies in different geographic locations.^{8,9} The following section focuses on specific etiologies and therapies for ALF.

Toxins

Acetaminophen remains by far the most common cause of toxic liver injury.⁸ Liver failure caused by acetaminophen typically is associated with ingestion of at least 4 mg and more frequently greater than 10 g of the drug. Lesser amounts of acetaminophen may cause liver failure in the setting of alcohol use or underlying liver disease, presumably because of activation of the microsomal enzymes that metabolize acetaminophen, although the degree of increased susceptibility has been questioned by some.¹⁰ In theory, this increased susceptibility should be worse in women who have a reduced threshold for alcohol-related liver injury because of reduced alcohol dehydrogenase activity relative to males.¹¹ Interestingly, in patients who have muscular dystrophy, there appears to be an increased susceptibility to severe liver injury with therapeutic dosages of acetaminophen for as yet uncertain reasons.¹² Acetaminophen is metabolized in hepatocytes by cytochrome enzymes to the toxic metabolite N-acetyl P-benzoquinoneimine (NAPQI) that normally is detoxified by conjugation with glutathione. Depletion of glutathione leads to accelerated liver injury by virtue of reduced detoxification of NAPQI. N-acetylcysteine (NAC) is administered to patients with toxic acetaminophen ingestion to replenish glutathione stores.¹³ Acetaminophen-induced injury is concentrated in the

central zones of the liver, and portal tracts are mostly spared excepting in extreme injury, permitting spontaneous recovery in as many as 80% with timely NAC therapy.⁸ Serum levels of acetaminophen in the blood are typically proportional to the amount of acetaminophen ingested and permit stratification of the risk for liver failure if the time of ingestion is known. Recently, acetaminophen adducts were measured in some patients in whom acetaminophen ingestion was uncertain.¹⁴ Whether the acetaminophen alone was causative in these individuals and whether these levels can be used to prognosticate injury in a similar fashion to acetaminophen alone remain to be determined. NAC previously had been administered to patients as an oral solution that was as efficacious as the intravenous preparation.¹⁵ Intravenous preparations, however, are now available and are preferable in the setting of ALF, because they eliminate problems related to absorption, especially in patients who have been given charcoal or other adsorbents.¹⁶ Reactions to the medication, allergic or cardiac dysrhythmia that can be related to the rate of infusion, are rare and typically reversible with the use of antihistamines and discontinuation of the NAC.

Amanita poisoning from the heat-stable toxin contained in the mushroom *Amanita phalloides* and *Amanita virosa* may lead to acute liver injury. Initially, these patients suffer gastrointestinal symptoms of vomiting and diarrhea.¹⁷ This is followed by liver injury and then development of secondary injury to other organ systems. Mortality approaches 10% to 30%. Treatment with silibinin or with penicillin G early on in high dosages may ameliorate the hepatic injury.¹⁸

Other drugs and herbal compounds may cause severe acute liver injury, and the site within the liver that is affected, central versus portal, in part may determine the ability to spontaneously recover from the injury. Many of these injuries are idiosyncratic. There may be some predisposition to developing severe drug-induced liver injury due to individual differences in drug metabolism, however.¹⁹ Examples for which this is suspected include isoniazid, ketoconazole, disulfuram, valproate, and amiodarone, among others. Other toxic injuries, one excellent example being halothane, may trigger severe immune-mediated liver injury upon re-exposure.²⁰

Viral Hepatitis

Viral infection with hepatotropic viruses such as hepatitis A, B, and E is associated more often with acute liver injury with recovery; however, a small percent of patients who have each of these

infections will develop acute liver failure.^{8,9} There are no specific therapies for hepatitis A or E, but there are antiviral agents that inhibit the replication of hepatitis B. Although use of antiviral agents in patients who have acute hepatitis B virus (HBV) seems logical, studies from India and the United States experience from the Acute Liver Failure Study Group (ALFSG) fail to demonstrate that treatment reduces the risk for ALF.^{21,22} For patients who have acute HBV with liver failure, however, use of antiviral agents may be warranted if for no other reason than to suppress the virus in a patient destined for liver transplant to reduce the risk of recurrence in the graft. Acute HBV may be even more severe if there is coinfection or superinfection with hepatitis D virus (HDV). Acute outbreaks of HBV and HDV infection have been reported in association with injection drug use.²³ Hepatitis E is rarely fatal; however, in pregnant patients in India who had acute hepatitis E virus (HEV) infection, liver failure and death without transplantation were reported to be as high as 20% of affected individuals.²⁴ Another recent report suggests that this high mortality with HEV during pregnancy is not seen in other geographic regions, and the reason for these differences are as yet unknown.²⁵

Other viral infections that are associated with ALF include herpes simplex virus, varicella zoster virus, and cytomegalovirus.⁸ Rarely, ALF may be caused by Epstein-Barr virus (EBV) infection.²⁶

Metabolic

ALF may result from underlying metabolic liver disease. Liver failure caused by copper toxicosis in Wilson disease is unusual in that underlying liver disease is present, often previously unrecognized, and ALF occurs on the background of advanced fibrosis or cirrhosis of the liver.²⁷ This accounts for the almost uniform mortality of these patients without transplantation, because there is little hepatic reserve.²⁸ ALF caused by Wilson disease typically is accompanied by a nonimmune hemolytic anemia, and may be recognized by a low alkaline phosphatase to bilirubin ratio (less than four) and ALT to AST ratio of less than 2, markedly elevated serum copper greater than 200 µg/dL, and 24-hour urine copper often greater than 200 µg.^{27,29} Although Kayser-Fleischer rings are pathognomonic, they are present only in approximately 30% to 50% of patients diagnosed with Wilson disease in the setting of ALF;²⁷ thus, the absence of rings does not exclude the diagnosis. Ceruloplasmin levels, useful for the diagnosis of most other patients who have Wilson disease, are poorly predictive in the setting of ALF.²⁹ Renal

insufficiency is often present because of tubular damage caused by acute copper exposure. Treatments that acutely lower circulating copper levels of the patient by some form of plasma exchange or other treatment such as albumin dialysis may help in acutely stabilizing the patient by breaking the cycle of liver and renal tubular injury and hemolysis. These therapies delay but do not stay the need for transplant in these patients, however. Treatment with copper chelation and zinc, mainstays of medical treatment for Wilson disease, may be best used for those who have chronic liver failure and has little influence on the outcome of patients who have this acute presentation.²⁷

Acute fatty liver of pregnancy (AFLP) is an unusual disorder where the metabolic disruption in the fetus causes maternal-fetal distress.³⁰ This disorder typically presents in the third trimester with marked elevation of liver tests and may progress rapidly to jaundice and liver failure. Fifty percent of the patients have preeclampsia. Fatty liver may be suspected on noninvasive imaging, but the type and percent of the fat content cannot be estimated. Liver biopsy is the standard for diagnosis, with fatty change concentrated in the centrilobular hepatocytes. Delivery of the fetus is necessary for maternal and fetal survival. Underlying defects in fetal fatty acid metabolism have been demonstrated.³¹ More recently, use of plasma exchange was studied in six patients who had AFLP 2 to 8 days after delivery, and may have improved outcomes with reduced hospital stays and prevention of multiorgan failure syndrome.³² Although this needs further study, the relatively low risk of performing this procedure suggests it could be tried as adjunctive therapy for these individuals.

Preeclampsia during pregnancy can be associated with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets).³³ This disorder also occurs most commonly in patients in the last stage of pregnancy, but may develop after delivery. Delivery of the fetus is the only known treatment that may arrest the progression of the disease.

Vascular

Acute obstruction of hepatic venous outflow or Budd Chiari syndrome may result in ALF. This often is recognized by the presence of hepatomegaly, new and rapid onset of ascites, and imaging studies showing hepatic venous thrombosis. Acute decompression of the obstruction with transhepatic intrahepatic portosystemic shunt (TIPS)³⁴ or surgical portosystemic shunt procedure³⁵ may prevent further hepatic injury. If there

is underlying cirrhosis or continued decompensation, transplantation may become necessary.^{34–36} This disorder frequently is associated with hypercoagulable states or disorders causing hypercoagulability.^{36,37} If the patient survives the acute injury, remodeling of the liver and efforts for vascular decompression and anticoagulation may improve or stabilize hepatic function with time.

Ischemic hepatitis or shock liver is associated with acute liver injury mainly in the central zone. Typically there is a history of significant hypotension that precedes the development of the injury. Treatment of the underlying condition that led to the hepatic injury is critical for recovery.³⁸

Other vascular causes of acute liver injury includes sinusoidal obstruction syndrome that occurs with smaller vessel veno-occlusive disease³⁹ and infiltrative disease associated with malignancy, more commonly with lymphoma but also from other tumors.⁴⁰

Autoimmune

Autoimmune hepatitis rarely may present with ALF. Some patients may have acute or chronic disease if the earlier injury was unrecognized. Up to 30% of patients who have acute presentation of autoimmune hepatitis will not have the typical serum markers for autoimmune hepatitis.⁴¹ Some patients may respond to high-dose steroid treatment following the exclusion of viral hepatitis. Liver biopsy may help to identify these individuals, and transjugular liver biopsy may be warranted in selected patients despite coagulopathy.

EVALUATION OF THE PATIENT WITH ACUTE LIVER FAILURE

The most critical element to patient survival with ALF is its early recognition. This permits rapid identification of the etiology of the liver failure, initiation of etiology-specific treatments when appropriate, and importantly the proper mobilization of personnel involved in various aspects of patient care.

The first phase of the evaluation includes obtaining a detailed history from the patient if possible or from others who may know the patient's medical history. Physical examination should assess the patient's mental status and evaluate liver and spleen size and presence or absence of ascites. Lack of stigmata of chronic liver disease such as spider angiomas, splenomegaly, or gynecomastia is typical in ALF. Neurologic evaluation should note pupil size and reactivity and reflexes, presence or absence of clonus, and the presence or absence of hepatic encephalopathy.

Encephalopathy should be graded using a standard scale such as the Glasgow coma scale or West Haven Criteria. It is important to recognize that patients with the earliest phase of encephalopathy may demonstrate only very subtle signs, and the use of standard testing such as the trails test⁴² can help establish the presence of early impairment even in the absence of lethargy or demonstrated tremor or asterixis. The neurologic evaluation needs to be monitored frequently in patients who have rapidly accelerating disease, as changes may occur in hours.

Initial laboratory testing and imaging that should be performed on patients who have ALF are outlined in **Box 1**. Many of the tests will help assess the degree of impairment of the liver and other organs such as the kidney. Other tests should be obtained to determine the etiology of the injury, identify any other toxic ingestion, exclude active infection, and provide a basis for comparison with future or historical laboratory determinations. Blood typing is necessary for any factor replacement by the blood bank, and for matching of organs for potential transplant candidates. Two separate blood types are needed for patient listing for liver transplant with the United Network for Organ Sharing (UNOS). The frequency of the full panel for blood testing (complete blood cell count [CBC], international normalized ratio [INR], electrolytes, liver tests) is typically twice daily in more stable patients, but specific testing such as blood glucose levels should be obtained more frequently.

Imaging of the liver should focus on liver size, spleen size, and demonstration of a patent portal and hepatic veins and hepatic artery. Presence of a smaller size liver with splenomegaly suggests the presence of underlying chronic liver disease, while hepatomegaly may accompany the acute vascular obstruction of venous outflow associated with Budd Chiari. The absence of detectable liver lesions is also important, especially in patients who have a suspected history of malignancy. If renal dysfunction is present, imaging should include the kidneys and exclude any obstruction and look for changes in size or texture that could suggest chronic kidney disease.

Very detailed social work and psychiatric evaluations are important in patients where there is suspected history of substance use or underlying psychiatric disorder. Information from these consultants may be helpful for managing the patient with respect to the use of careful sedation and cognizance of substance use and risk for withdrawal. If the patient has a history of suicidal drug ingestion, a careful evaluation may help determine eligibility for liver transplant.

Box 1**Initial laboratory testing for patients with acute liver failure**

Blood testing

Complete blood cell count with platelets
 Electrolytes and renal function – Na, K, Cl, CO₂, BUN, Cr
 International normalized ratio
 Factors 5, 7

Liver panel

Alanine aminotransferase
 Aspartate aminotransferase
 Alkaline phosphatase
 Total bilirubin
 Direct bilirubin
 Albumin
 Gamma glutamyl transpeptidase

Blood lactate

Ammonia

Blood gas with pH

HIV testing (rapid)

Viral markers

Hepatitis A virus IgM
 HBcAb IgM
 HBsAg
 HBsAb
 HBcAb total
 Hepatitis C virus Ab
 Hepatitis B virus DNA
 Hepatitis C virus RNA
 Hepatitis E virus Ab
 Hepatitis E virus polymerase chain reaction (PCR) (in appropriate patients with travel history)
 Cytomegalovirus (CMV) PCR
 CMV Ab
 Herpes simplex virus (HSV) PCR
 HSV Ab
 Epstein-Barr virus Ab

Autoimmune markers

Antinuclear antibody
 Antismooth muscle antibody
 Anti-liver kidney microsomal

Metabolic markers

Uric acid
 Serum copper and urine copper

Hypercoagulable markers

Lupus anticoagulant
 Factor 5 Leiden

Toxicology screen and drug panel

Acetaminophen
 Opiates
 Barbiturates
 Cocaine
 Alcohol

Pregnancy testing (females)

beta human chorionic gonadotropin
 Urinalysis and microscopic analysis
 Urine electrolytes and osmolarity
 Blood cultures
 Urine cultures

Imaging and other testing

Chest radiograph
 Abdominal ultrasound with Doppler study of the liver
 ECG
 Echocardiogram with estimation of pulmonary artery pressures

Logistical considerations should permit daily multidisciplinary team meetings with transplant surgeons, hepatologists, and intensivists, and may include consultants from other disciplines (**Table 1**). This last group may include nephrologists, infectious disease specialists, cardiologists, radiologists, anesthesiologists, neurologists, hematologists, and others. The purpose of these meetings is to discuss changes in patient management and help determine whether any new interventions or consultations are needed. Daily communication between the care team and the patient's family is very important given the rapidly changing clinical picture.

ASSESSING THE PATIENT FOR LIVER TRANSPLANTATION

Although liver transplantation is not required for many patients who have ALF, in appropriate

Table 1 Consultations for patients with acute liver failure		
Consultant	Role	Testing
Intensivist	Evaluate patient status and need for ventilatory, hemodynamic, or renal support Establish vascular access Coordinate contact with consultants	Physical examination Laboratory testing Oxygen saturation monitoring Chest radiograph ECG
Hepatology	Help assess etiology of the liver disease and the use of specific therapies, begin evaluation and education for liver transplant	Physical examination Laboratory testing Liver imaging
Transplant surgery	Assess patient as a surgical candidate, educate patient and family about options for transplantation and their outcomes	Physical examination Laboratory testing Liver imaging
Social work	Assess patients social supports, identify any pattern of substance use or underlying psychiatric disturbance, help identify resources to assist patient and family	Interview of patient Interview of family or other patient support
Psychiatry	Assess status of patient's mental health, determine if there is untreated psychiatric illness, assess ability of the patient and family to cooperate with medical treatments	Interview of patient Interview of family or other patient support Contact mental health providers for the patient
Neurology	Assess neurologic changes, help with monitoring of any intervention for cerebral edema	Physical examination Laboratory testing Brain imaging
Neurosurgery	Placement of cerebral pressure monitor and helping assess neurologic status of treated patient	Physical examination Laboratory testing Brain imaging Cerebral pressure tracings
Cardiology	Evaluate for evidence of any underlying cardiac illness and make recommendations for hemodynamic management	Physical examination Laboratory testing ECG Echocardiogram
Nephrology	Assess renal function and provide assistance with renal replacement therapy and electrolyte management	Laboratory testing Monitoring of hemodynamics and urine excretion Renal imaging
Nutrition	Assess ability to eat and nutritional support needs	Examination and interview of the patient and caregivers
Transplant coordinator	Assess eligibility for transplant Review information needed for listing for liver transplant Educate patient and family about transplantation	Interview with patient and family Coordinate information about patient transplant listing status with transplant surgery and hepatology

candidates, liver transplant will be lifesaving. The decision as to whether a patient will recover with conservative management or require transplantation has been the subject of many different reports and case series; however, the Kings College Criteria remain the current standard for clinicians.⁴³ These criteria are used to predict death in patients presenting with ALF in the setting of

acetaminophen and other causes of ALF (**Box 2**). Patients who had a high probability of death were considered to be candidates for liver transplantation. Other studies have attempted to look at etiology-specific indices (ie, Dhawan and colleagues⁴⁴ and Korman and colleagues for Wilson disease)²⁹ or have tried to use other additional serum-based tests to help predict survival (Schiodt

Box 2**Kings Criteria for increased mortality in acute liver failure**

Acetaminophen-induced acute liver failure (ALF)

Hepatic encephalopathy coma grades 3 to 4

Arterial pH <7.3

Prothrombin time (PT) greater than 100 seconds

Serum creatinine greater than 300 $\mu\text{g/mL}$ (3.4 mg/dL)

Nonacetaminophen-induced ALF

PT of greater than 100 seconds or three of the following five criteria:

1. Age less than 10 years or greater than 40 years
2. ALF caused by non-A, non-B, non-C hepatitis, halothane hepatitis, or idiosyncratic drug reactions
3. Jaundice present more than 1 week before onset of encephalopathy
4. PT greater than 50 seconds
5. Serum bilirubin greater than 300 mmol/L (17.5 mg/dL)

and colleagues;⁴⁵ Gc protein, phosphate for acetaminophen),⁴⁶ and these may be used adjunctively along with the Kings Criteria to help with the clinical decision as to whether to move toward transplant. Decision making with respect to the timing of transplantation is difficult for transplant surgeons and hepatologists. Although established criteria such as Kings College Criteria have been used to predict poor outcomes without transplantation, the right decision can be made only by the transplant team after following the patient's clinical course and disease progression.

Once transplantation is considered, the patient must undergo a rapid multidisciplinary evaluation to determine candidacy. Unlike standard transplant evaluations, where there is time to obtain very detailed medical records from other treating physicians or to evaluate difficult social or psychiatric issues that could be barriers to candidacy for transplantation, in the setting of ALF, a rapid judgment must be made. The first step in this process is a conscious decision to engage the transplant team in the care of the patient. In units that are run by liver teams or where the liver team initiates the admission or transfer of the patient to the ICU, this is automatic. In other ICUs, however, the liver transplant team must be consulted. Either way,

a cooperative effort to rapidly complete the evaluation and meetings to discuss important care decisions should take place. It is useful to have very clear protocols for the evaluation, along with predetermined lines of communication in place, so that time is not lost following the decision to move forward with the evaluation.

The job of the transplant hepatologist working in concert with the transplant surgeon is to critically assess the patient with respect to appropriate indications for transplantation, and assure that no contraindications to transplantation exist. Along with the transplant coordinator, he or she also must be able to educate the patient and family about the timing for transplantation and potential outcomes. To be actively listed for liver transplantation, patients must meet the minimal listing criteria for transplant at the center where they are being evaluated, and to be considered for the highest status for transplant, must have ALF with encephalopathy, coagulopathy with INR greater than 2, and be in an intensive care setting.⁴⁷ Whether the patient is intubated and requires other system support such as renal replacement therapy also is taken into consideration. A rapid social work and possible psychiatric evaluation may require the participation of family members or other patient supports if the patient cannot conduct an interview. This is especially important if there is a prior history of substance use or a history of suicide or serious mental health issue. Active substance use or multiple suicide attempts are contraindications for candidacy for liver transplantation. Other issues where family and friends and the patient's prior treating physicians play an important role is in obtaining a history of any recent malignancies or infectious disease that may preclude or delay listing for transplantation.

Other medical evaluation for transplantation includes imaging of the liver to exclude liver masses and establish the patency of the hepatic vasculature, cardiac evaluation, neurologic evaluation, interventions if there is advancing encephalopathy, and help from other consultants such as nephrologists if there is concurrent renal insufficiency or renal failure. Cardiac evaluation is especially important for patients older than 45 years or those who have a prior cardiac history or history of multiple risk factors for cardiac disease. For critically ill patients, the ECG, bedside echocardiography, and chest radiograph typically are obtained. If necessary, central lines can be converted to pulmonary artery catheters for direct monitoring while the patient is in the ICU.

The transplant coordinator, financial counselors, and social worker are important team members who should be engaged immediately in the

transplant process. Often they must rapidly educate and work with a family that was not prepared for the acute illness and incapacitation of the patient. It is important that these family members receive information regarding the transplant process, have the resources to care for the patient, obtain the necessary post-transplant medications, and obtain emergent assistance for care of any dependents of the patient.

Once the initial evaluation is complete, the transplant team often will hold an emergent meeting to discuss patient candidacy that will include representatives from all members of the care team for the patient. If a patient is found to meet listing criteria and has no contraindications to transplant, emergent listing as status 1A will be made with UNOS, the federally contracted agency that controls organ distribution. If a patient has contraindications to listing that are correctable, then listing can be delayed until the appropriate issues are resolved. If, however, the decision is made not to list the patient for transplantation, this information must be shared with the patient and family members and with the care team in a timely fashion to help with care decisions.

ICU-BASED INTERVENTIONS

Advances in critical care medicine and in management strategies have reduced mortality for ALF to approximately 33% according to the USALF Study Group Registry.⁸ This mortality is attributed to three complications in particular: cerebral edema, multiorgan dysfunction syndrome (MODS), and sepsis. The following section will review ICU-based management strategies and interventions that have evolved to address the various organ dysfunctions associated with ALF.

NEUROLOGIC FAILURE: CEREBRAL EDEMA AND INTRACRANIAL HYPERTENSION

Management of intracranial hypertension (ICH) remains challenging. Left untreated, mortality can exceed 90%, and some estimate that up to a third of patients succumb to brainstem herniation while awaiting an organ. Clinically recognizable risk factors associated with cerebral edema include: high-grade encephalopathy (grades 3 to 4), elevated serum ammonia (greater than 150 to 200 μm),^{48,49} rapid/hyperacute progression of liver injury to hepatic encephalopathy, infection or systemic inflammatory syndrome (SIRS), and requirement for vasopressor support or renal replacement therapy.⁵⁰ Neuroimaging is not reliable in diagnosing early ICH⁵¹ but may help exclude other problems such as intracranial

bleeding or stroke. Invasive intracranial pressure (ICP) monitoring remains the only objective gold standard for measuring and monitoring ICH.

INTRACRANIAL PRESSURE MONITORING: GENERAL CONSIDERATIONS

In clinical practice, ICP monitoring for patients who have ALF remains controversial, in part because randomized controlled trials are lacking to guide clinicians through nuanced scenarios in which invasive monitoring may or may not be helpful. The lack of an accepted consensus protocol for managing cerebral edema hampers attempts at rigorous multicenter research studies. To fuel the controversy further, in nonrandomized studies, such devices have not been shown to improve survival.⁵² Despite lack of consensus, many centers place ICP monitors to actively manage cerebral edema in patients who have advanced (stage 3 or 4) encephalopathy. Such devices have the additional benefit of providing important prognostic information regarding neurologic recovery after orthotopic liver transplant (OLT), and may serve as one additional data point used in the complex decision making that occurs in identifying the ideal transplantation candidate. For example, severe sustained ICP greater than 40 mm Hg (or cerebral perfusion pressure less than 40 mm Hg) for over 2 hours is associated with brainstem herniation or poor neurologic recovery post-OLT.

Furthermore, because early edema can be clinically silent, placement of a device may allow for early detection and intervention. Some have argued that ICP monitoring also may be helpful in patients who have a good prognosis (ie, unlikely to require liver transplant), but with severe encephalopathy. Aggressive treatment in this subset may reduce mortality and morbidity by stabilizing neurologic function and allowing a longer time for hepatic recovery. On the other hand, because of the uniformly high mortality of ALF in patients who have extremely poor prognosis without the option for liver transplant, this subset of patients is unlikely to benefit from invasive monitoring.

Intracranial bleeding, an often-cited complication of ICP monitoring, is encountered in 10% to 20% of patients. Most intracranial bleeding is mild and of little clinical significance.⁵² Among patients who have severe coagulopathy, reduction of INR has been managed successfully with the use of recombinant factor 7a, although whether this translates into a reduced risk for bleeding complications is uncertain.⁵³ Correction of coagulopathy should be continued for approximately 48 hours after the insertion of probes/catheters to

prevent bleeding. Undoubtedly, the experience of the team in placing ICP monitors is important in keeping this complication rate low.

INTRACRANIAL PRESSURE MONITORING: PRACTICAL CONSIDERATIONS

Even after a decision is made to proceed with invasive ICP monitoring, the ideal location of placement remains unclear. In general, intraventricular placement carries the highest risk of bleeding (although with the added therapeutic potential), and epidural placement the lowest risk. The latter approach however, suffers from less accuracy in ICP measurement. The subdural position is the most commonly used location in the United States, according to a recent survey.⁵² Ultimately, until definitive evidence accumulates, local expertise and comfort level will define where and how the monitors are placed.

INTRACRANIAL HYPERTENSION: GENERAL MANAGEMENT PRINCIPLES

In general, patients should be kept in a quiet room with minimal stimulus, including infrequent endotracheal suctioning. The head of the bed should be elevated to 30° (to improve CSF drainage), and neck rotation or flexion should be limited (to avoid compromise of jugular venous drainage). Fevers should be controlled by cooling, because acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, and rigoring or shivering also avoided, as these may exacerbate ICP.⁵⁴ When invasive monitoring is available, the ICP should be maintained below 25 mm Hg. The mean arterial pressure (MAP) should be adequate to maintain cerebral perfusion pressure (CPP) between 50–80 mm Hg. Care should be taken to avoid an overly robust CPP (some have argued a range between 50 and 65 mm Hg as ideal in this fragile population), as this may exacerbate cerebral hyperemia.

Meticulous attention needs to be paid to metabolic and acid–base abnormalities including hyper- and hypoglycemia, hyponatremia, hyperlactatemia, and hypercapnia, as these have been shown to contribute to higher ICP. Mannitol can be used as first-line therapy and given as repeated boluses, provided serial serum osmolality remains below 320 mOsm/L. Its use is limited once patients develop significant renal injury. In patients requiring renal support, continuous venovenous hemofiltration is preferred over traditional hemodialysis to prevent rapid fluid shifts and swings in blood pressure.⁵⁵ In contrast to mannitol, hypertonic saline can be used as a prophylactic measure with few adverse effects, with a goal of achieving sodium

of 145 to 155 mEq/L.⁵⁶ Evidence, however, is limited to a single randomized controlled trial, and hypertonic saline never has been tested formally as a treatment of established ICH in patients who have ALF.

If osmotic therapies fail to adequately control ICP, other adjunctive measures to reduce ICP include:

- Barbiturate coma (to reduce brain metabolism, although incremental benefit is unclear if the patient is already in stage 4 encephalopathy with coma)
- Indomethacin
- Paralytic agents
- Phenytoin (may reduce cerebral edema regardless of seizure activity)

There are no good data that show lactulose or other nonabsorbable oral antibiotics, such as rifaximin, improve ICP; however, these may help lower ammonia and are of theoretic benefit. There is no role for corticosteroids given cerebral edema is of cytotoxic, as opposed to vasogenic origin in the patient who has ALF. In the midst of relative therapeutic disappointments, one modality that is garnering increasing attention is therapeutic hypothermia.

KEEPING IT COOL: THERAPEUTIC HYPOTHERMIA

Moderate hypothermia (32°C to 33°C) so far appears to be a formidable tool for managing refractory ICP elevations.^{57,58} Therapeutic hypothermia simultaneously alters multiple pathways important in the pathogenesis of cerebral edema and ICH and leads to:

- Reductions in brain energy metabolism (both metabolic and electrophysiologic components)
- Possible suppression of subclinical seizure activity
- Normalization of cerebral blood flow and autoregulation
- Reduced delivery of ammonia to the brain
- Amelioration in anaerobic glycolysis and oxidative stress in astrocytes
- Decrement in brain extracellular glutamate and normalization of brain osmolality
- Reversal of SIRS
- Nitric oxide metabolism⁵⁹

In some patients, cooling also may restore vascular responsiveness and has the added benefit of less vasopressor requirement.⁵⁷

On a practical level, the markedly vasodilated state typical of patients who have ALF allows for efficient heat exchange from external cooling

devices. Although endovascular devices have been used in cardiac arrest and traumatic brain injury (TBI), such invasive devices are probably not necessary to achieve modest hypothermia, and are not ideal given bleeding and infection risks in this patient population. For example, in preliminary studies, goal temperatures have been reached within 1 hour of initiating cooling blankets.^{57,59} Therapeutic hypothermia consistently reduces ICP and cerebral blood flow (CBF). It additionally improves CPP and has been used for the treatment of refractory ICH and as a bridge for OLT. Intraoperative surges in ICP (during the reperfusion and dissection phases of the procedure in particular) also may be averted with maintenance of moderate hypothermia in the operating room.⁵⁹ Finally, its role as a prophylactic measure also has been explored in a small pilot study (see **Box 2**).⁶⁰

Potential adverse effects of cooling include arrhythmia, infection (which increases with degree and duration of hypothermia), bleeding, electrolyte imbalance, hyperglycemia, and alteration in drug metabolism. Many of these abnormalities are difficult to distinguish from physiologic changes that commonly accompany ALF itself, making recognition difficult. Theoretic concerns exist regarding the negative effect of hypothermia upon liver regeneration, but there may be beneficial effects in limiting progression of liver injury.

Regardless, there remain many unanswered questions regarding therapeutic hypothermia, including optimal target population, timing, degree and duration of treatment, hypothermia, and rewarming techniques. Although one patient in Jalan's series was cooled for up to 5 days, duration of safety is unknown, and the markers that can be used to indicate adequate hepatic recovery (and therefore safe discontinuation of therapy) are unclear. Rapid rewarming can exacerbate electrolyte abnormalities and lead to hemodynamic instability and worsening CPP. In the TBI literature, safe rewarming has been documented at a range of rates from 1°C/h to 1°C/d. Given the special hemodynamic issues inherent in this population, some have suggested a conservative rate, perhaps at 1°C per 12 hours.⁴⁹

NEUROLOGIC MANIFESTATIONS: SEIZURES

Seizures can aggravate cerebral edema and ICH, but they also can be a manifestation of ICP surges. There is at least one study that has shown a benefit of phenytoin infusion in preventing subclinical seizure activity,⁶¹ although a recent clinical trial noted no benefit.⁶² Hypothermia reduces seizure activity in experimental models of epilepsy, and may be an

additional important mechanism of action of hypothermia in ALF.^{63,64} Presently the authors do not recommend prophylaxis for seizures, but continuous EEG monitoring has become available and may be useful for patients at high risk for seizures.

RESPIRATORY FAILURE: MECHANICAL VENTILATION

The ideal timing for endotracheal intubation is not always clear. When considering interhospital patient transfer to a liver transplant center, one of the discussions commonly includes whether the patient should be intubated before transfer, as neurologic deterioration can be very rapid. Intubation should be considered strongly once advanced encephalopathy becomes evident at grade 3 or more. In addition to preventing gross aspiration events, mechanical ventilation and judicious sedation may help manage extreme agitation, which can contribute to dangerous surges in ICP.

Development of acute lung injury/acute respiratory distress syndrome (ARDS) is not uncommon among patients who have ALF and cerebral edema. Attention should be paid to pCO₂ once a low tidal volume ARDS protocol is instituted, to counter the detrimental effects of severe hypercarbia on ICP. Prophylactic hyperventilation, on the other hand, has not been shown to modify the ultimate development of cerebral edema.⁶⁵ For patients suspected of having brainstem herniation, acute hyperventilation can be used emergently.

Higher positive-end expiratory pressure (PEEP) theoretically also can increase ICP, but the level in which this becomes clinically significant in a particular patient is unclear. In general, using the lowest level of PEEP that can maintain adequate oxygenation is recommended.

SEDATION AND ANALGESIA

Because agitation (including excessive coughing and straining) and pain can exacerbate ICP elevations, adequate analgesia and judicious sedation are required, particularly before and after placement of invasive devices such as endotracheal tubes and ICP monitors.

In reality, there are not enough data to suggest a standard agent or dosing regimen in this scenario. In general, short-acting agents are preferred, although it is important to note that all sedative drugs are subject to delayed metabolism. Recovery time from propofol tends to be shorter than from benzodiazepines and may allow for more reliable serial neurologic testing when this agent is withdrawn. Despite adverse effects on hemodynamics, prohibitive cost, and infusion

syndromes that can be seen with prolonged use, propofol has the added benefit of decreasing CBF and lowering ICP.⁶⁶ Both propofol and benzodiazepines can increase γ -aminobutyric acid (GABA) neurotransmission and theoretically exacerbate hepatic encephalopathy. For treatment of pain, bolus doses of fentanyl are preferred as the first-line agent. Morphine and meperidine are not recommended because of active metabolites. In the case of meperidine, seizure thresholds may be lowered.

HEMODYNAMIC FAILURE: SHOCK MANAGEMENT

Hypotension is common in patients who have ALF and is marked by a state of high cardiac output and reduced systemic vascular resistance. This hemodynamic picture closely mimics septic shock, and differentiating between the two can be challenging. Concurrent infectious workup is mandatory. Relative adrenal insufficiency occurs frequently, but treatment with moderate-dose corticosteroids is reserved for those unresponsive to pressors. In one series, 62% of patients who had ALF were found to have an abnormal response to high-dose corticotrophin stimulation.^{67,68} As in other states of shock, assessment of volume status and adequate resuscitation, if appropriate, is a crucial first step. Vasopressors can be used adjunctively to maintain a MAP above 50 mm Hg, with a goal CPP of 50 to 80. Surges in MAPs also should be avoided as this may lead to cerebral hyperemia.

The risks and benefits of individual vasopressor agents have not been evaluated carefully, but extrapolation of data from TBI suggests that norepinephrine should be preferred, as it is associated with consistent and predictable increases in CPP. There are conflicting data on the use of newer agents, such as vasopressin or terlipressin. In one study, terlipressin caused cerebral vasodilation and increased ICP at low doses that did not alter systemic hemodynamics.⁶⁷ In a rat model, vasopressin appears to accelerate development of cerebral edema.⁶⁹ More recently however, in another small study, terlipressin appeared to increase CPP and CBP in patients who had ALF without detrimental effects on ICP or increase in cerebral metabolic rate.⁷⁰

VENOUS ACCESS DEVICES

Catheter-related infections are a major source of avoidable complications in patients who have ALF.^{71,72} As such, when placing venous access devices, meticulous attention to catheter care is paramount. Routine placement of multiple catheters is unnecessary, and placement of venous access devices probably should occur only as the need arises.

IMPORTANCE OF CARDIAC DYSFUNCTION

Recent data suggest myocardial injury may occur in ALF. Although classically felt to spare the heart, nearly 75% of patients in the US Acute Liver Failure Study Group cohort demonstrated an elevation of troponin 1 of 0.1 ng/mL or more. Importantly, patients who had elevated troponins experienced arrhythmias and higher coma grades (stage 3 or 4) at a rate two and four times respectively compared with those patients who had normal troponins.⁷³ Mortality rates (before and after transplant) were significantly higher in patients who had elevated troponins in a level-dependent manner, such that patients in the highest quintile (troponin 1 greater than 3.0 ng/mL) ultimately died at a rate of 33.3%. Advanced coma occurred in 71.4% of these patients. The corresponding rate for patients who had normal troponin was 10.2% and 22.4%. Troponin levels may be an important biomarker with prognostic implications in ALF.

HEMATOLOGIC FAILURE: DEALING WITH COAGULOPATHY

Despite severe derangements in coagulation profile, clinically significant spontaneous bleeding remains relatively uncommon. Because subclinical vitamin K deficiency contributes to coagulopathy in up to 25% of patients, empiric administration of vitamin K 10 mg intravenously given as a single dose is recommended.⁷⁴ Prophylactic transfusions to normalize coagulation profile in all patients who have ALF is unnecessary, as it has not been shown to alter the risk of significant bleeding or future transfusion requirement. Additionally, it carries a risk of volume overload and pulmonary edema (particularly in patients facing deteriorating renal function), and it obscures the trend of prothrombin time, which is useful as a prognostic marker.

For patients who have clinically significant bleeding or before placement of invasive devices, an attempt at improving coagulopathy should be made. Although strict guidelines do not exist, a rough target would be to correct the INR to approximately 1.5 and platelet count to approximately 50,000/mm³ before procedures with the use of fresh frozen plasma (FFP) and platelets. Concomitant administration of cryoprecipitate is recommended for patients who have significant hypofibrinogenemia (less than 100 mg/dL). When FFP fails to adequately normalize PT/INR, the use of recombinant factor 7a (rF7) can be considered and has been used successfully to facilitate placement of ICP monitors.⁵³ FFP or cryoprecipitate should be administered before rF7 (40 μ g/kg) if fibrinogen

levels are less than 100 mg/dL to replete factors involved in the clotting cascade. The procedure generally should be performed within 30 to 60 minutes of infusion of rF7. Repeat prophylactic doses of rF7 are probably not necessary after successful device placement, unless there is clinical evidence of oozing or bleeding (duration of action greater than 2 hours).

RENAL FAILURE MANAGEMENT

Renal insufficiency that progresses to renal failure may accompany liver failure. The causes may be multifactorial, including ischemia from hypotension that may cause acute tubular necrosis, hepatorenal syndrome, and other direct toxic injuries such as copper induced tubular injury in Wilson disease,²⁷ and contrast-induced nephropathy if contrast studies were recently performed. Urine sodium may be low in hypovolemic states, hepatorenal syndrome, and with contrast nephropathy. It is important to establish as best as possible whether the patient is euvoletic to avoid excess fluid administration that can exacerbate cerebral edema and cause pulmonary congestion and accelerate ascites formation. This may necessitate central pressure monitoring or indirect estimates of volume by measurement of end diastolic volume in the heart by echocardiography. In patients who have worsening renal function or acidemia, renal replacement therapy should be started early to avoid volume overload and to help with control of acid-base status and electrolyte balance. Continuous veno-venous hemofiltration with dialysis as opposed to standard hemodialysis is the preferred method for achieving renal replacement therapy because of the reduced shifts in blood pressure associated with its use. If the patient moves forward to transplantation, the continuous veno-venous hemofiltration may be continued intra- and perioperatively as necessary.

INFECTIOUS DISEASE CONSIDERATIONS

Infections are the most common cause of death and morbidity in patients who have ALF. With severe injury to the liver, Kupffer cell function is impaired, and clearance of normal gut bacteria that translocate is less efficient. This increases the risk of patients who have ALF to infection. The most common site of bacterial infection is the lung, then urinary tract and blood.^{71,72,75-77} The most frequently identified organisms are *Staphylococcus*, *Streptococcus* and enteric gram-negative bacilli. Fungal infections, in particular *Candida*, may be present in up to one third of patients who have ALF. Catheter-related sepsis is a serious concern,

and avoidance of unnecessary intravenous lines and careful attention to proper hygiene and changing of access are important.

Although it is not universally accepted that all patients who have ALF should be treated with prophylactic antibiotics, there is justification for careful surveillance for infection in all of these patients and a low threshold for treatment. Survival has not been shown to be altered by the use of prophylactic antibiotics; however, the numbers of patients studied may not have been large enough to definitively preclude benefits of prophylactic treatment.^{71,72,75-77}

On admission, a chest radiograph is performed, and urinalysis and urine and blood cultures should be obtained routinely. For any patient on a ventilator, sputum smear and cultures also should be obtained. These cultures and radiograph surveillance should continue every 48 to 72 hours or if the clinical status worsens.

Empiric use of antibiotics is recommended when surveillance cultures are positive, when encephalopathy is rapidly progressive, when there is hemodynamic instability with refractory hypotension or systemic signs of infection such as elevated temperature, tachycardia, and leukocytosis. Leukocytosis, however, may occur merely as a result of the liver injury, and the differential of the CBC should be watched for changes from baseline values. Antifungal therapy may be particularly warranted in patients who have had prior antibiotic treatment and for those who have renal failure.

The choice of an antimicrobial agent must take into account the need to cover a broad spectrum of gram-positive and -negative organisms. In general, third-generation cephalosporin drugs are recommended. Once speciation from any culture is possible, antimicrobial therapy may be narrowed accordingly. When line infection is suspected, vancomycin should be started pending results of cultures. All dosages must be adjusted based on renal function, and levels obtained when appropriate to help guide therapy further. Aminoglycosides are to be avoided if possible, owing to their potential for nephrotoxicity. Antifungal therapy should be given empirically and in the setting of prolonged use of antibacterial agents or the lack of a prompt response to institution of antibacterial therapy.

NUTRITION FOR THE PATIENT WITH ACUTE LIVER FAILURE

Patients are prone to hypoglycemia in acute liver injury because of loss of glycogen stores, impairment of gluconeogenesis, and increased circulating insulin. Intravenous supplementation with

glucose solutions is recommended if the patient is not being fed. Marked hyperglycemia should be avoided, because this may impair control of intracranial pressure;⁷⁸ however the benefits of attempting tight control must be weighed against the risk of hypoglycemia.

There is a need for nutritional supplementation in ALF, because these patients are catabolic.⁷⁹ The means of supplementation will vary with the ability of the patient to eat. In patients who have minimal hepatic encephalopathy, oral feeding is possible, but with advancing encephalopathy, oral feeding may need to be discontinued if there is a risk of aspiration. This clearly holds for patients transitioning from grade 2 to grade 3 hepatic coma. If oral feeding is discontinued, then enteral supplementation by means of feeding tube is recommended, at a minimum to provide the gut with some trophic feeds to reduce the risk of bacterial translocation.

Caloric goals for patients who have ALF should be approximately 25 to 30 kcal/kg/d. Parenteral or enteral nutrition may be used if oral feeding is not possible. The fear of parenteral nutrition-induced liver failure does not appear to be founded in the setting of ALF;⁸⁰ however careful attention to prevent line sepsis must be taken. Protein intake of approximately 1 g/kg/d does not appear to worsen hyperammonemia. Excess glutamine supplementation should be avoided given glutamine's role in the production of ammonia and development of cerebral edema in ALF.

LIVER SUPPORT DEVICES

Liver support devices may benefit patients who have liver failure by being used as a bridge to liver transplantation or liver recovery; however their utility only has been tested in nonrandomized studies to date.⁸¹ The results of ongoing multicenter trials are awaited. There are two main types of liver support devices that have been developed:

- Artificial (cell-free systems) such as those based on plasma filtration and removal of substances by use of dialysis or charcoal or other ion exchange columns

- Bioartificial systems that rely upon the use of liver cells (human or nonhuman) to perform detoxification and secretion of hepatocytes derived factors⁸²

Both of these aim to remove known and unknown toxins that are released or are not cleared in the setting of liver failure. Some treatments such as hemofiltration and hemodialysis have difficulty with removal of toxins bound to larger molecules such as albumin, and newer

techniques have evolved that also can deal with these substances. Specific units for which clinical data are emerging include the molecular adsorbents recirculating system, and fractionated plasma separation and adsorption (SEPAD- Prometheus).⁸³ Although neither of these units has been shown to change survival in the setting of ALF, other endpoints such as changes in degree of hepatic encephalopathy and lowering of serum bilirubin have been achieved. Interestingly, there are reports of the use of molecular absorption recirculation system for acute Wilson disease where copper was lowered and patients stabilized before transplantation.⁸⁴ This also has been achieved using hemofiltration and plasma exchange.⁸⁵

Fewer data are available for bioartificial support devices that use human hepatocytes, such as the extracorporeal liver assist device, and some limited data are available regarding the HepatAssist device (Arbios Systems, inc., HepaLife Technologies, Boston, Massachusetts), which uses porcine hepatocytes. The difficulty with these systems is the need to have viable cells available on demand for use for patients who have liver failure. Another concern is the development of antibodies to foreign proteins that can occur with nonhuman devices.

At present, the use of these devices remains experimental; however, results of new studies that are ongoing and technological advances suggests that one should remain optimistic about the development of a useful device for liver support in the near future. For those in whom the devices are being tried, one must pay careful attention to blood coagulation, glucose levels, and levels of antibiotics and antifungals that can be altered by these potential treatments.

LIVER TRANSPLANTATION

Patients who have ALF not recovering despite medical/supportive treatment are candidates for liver transplantation. It is the authors' policy to list patients who have ALF meeting the minimal listing criteria as UNOS status 1A immediately after completing medical and UNOS-required evaluations. When a suitable liver offer becomes available, transplantation will be performed. The availability of deceased donor liver allograft is unpredictable, however, because of a shortage of organ donors and the current organ allocation system. As a result, patients who have ALF may die because of brain herniation while waiting for transplant or become nontransplantable secondary to sepsis and multiorgan system failure.

Types of transplants offered for patient who have ALF are deceased donor liver

transplantation, living donor liver transplantation (LDLT) and auxiliary orthotopic liver transplantation (APOLT). Although there have been case reports, LDLT in the adult ALF setting has not been accepted uniformly as a result of the short time period for living donor evaluation, leading to possible mishaps that can cause adverse living donor outcomes. APOLT is an appealing concept, in which usually the right lobe of the native liver is removed, and right lobe of the donor liver is transplanted in an orthotopic fashion. The native liver part left in place will regenerate within 6 to 8 months following the operation, at which point immunosuppressive therapy is tapered gradually, letting the allograft be rejected. Thus the patient can live with his/her own liver without lifelong immunosuppressive medication use. This operation is technically more challenging, however, and issues related to maintaining the blood supply to the graft and recipient native liver are more complex.

OUTCOMES OF PATIENTS WITH ACUTE LIVER FAILURE

Survival of patients who have ALF depends on the etiology of ALF, with spontaneous or nontransplant recovery being the best in patients with acetaminophen-induced injury who receive timely treatment with NAC. For those patients who undergo emergent liver transplantation, the outcomes are good for long-term survival but below those for patients who have chronic liver diseases or liver cancer. The 1-, 3-, and 5-year graft survivals following transplant in a published series from a single center with a large experience in transplantation for acute liver failure were 63.2%, 58.0%, and 56.6%, respectively.⁸⁵ This is approximately 10% to 20% lower than transplantation for chronic liver diseases where 5-year survivals are typically 70% to 80%. Causes of graft loss in the patients who had ALF were patient death from sepsis, neurologic complications, and primary graft nonfunction, the last occurring at a much higher frequency (13.2%) than for nonemergent transplantation. The cause for this is likely because of donor and host factors: the use of more marginal grafts due to the urgency of transplantation and the placement of grafts into patients with multiorgan failure. The risk of transplantation must be weighed against the risk of death without transplantation and presence of any contraindications to transplantation. This risk-benefit analysis must be thought through carefully for each individual patient before deciding to move toward transplant or to continue with conservative management alone.

The early identification of ALF and the etiology of the liver failure along with the judicious use of transplant and the advances in ICU management of these patients have contributed greatly to the improved overall survival of patients who have ALF. Survival now approaches 66%, compared with a once dismal 20% survival. Further advances in ICU management including the future use of liver support devices, advances in techniques and organ distribution for liver transplant, and the early recognition of liver failure by medical personnel will contribute to even better future outcomes.

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