Acute Liver Failure: Peritransplant Management and Outcomes

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Acute liver failure (ALF) is a rare but often devastating syndrome characterized by the sudden loss of liver function in a patient without preexisting liver disease or cirrhosis.¹ ALF is defined by coagulopathy [international normalized ratio (INR) ≥ 1.5] and hepatic encephalopathy (an altered mental status of any degree), usually within 1 to 2 weeks of jaundice; however, the disease course can progress over a more prolonged period of up to 26 weeks.¹ ALF can result from a variety of etiologies (Table 1), but acetaminophen is the most common cause in the United States and Europe with a prevalence $> 40\%$.^{1,2} ALF is considered an orphan disease, and with an estimated annual prevalence of only 2000 cases in the United States, much of what is known about its management and outcomes comes from large centers or collaborative, multicenter networks dedicated to its study.^{1,3}

Most patients with ALF rapidly become critically ill, and many succumb to multiorgan system failure, complications of cerebral edema, or infection. Despite aggressive intensive care and a limited number of specific therapies (Table 2), approximately one-third of these patients do not survive without liver transplantation. In addition to the need for and availability of liver transplantation, survival for patients with ALF decisively depends on critical care management by an experienced multidisciplinary team. Because the progression of ALF can be rapid, early consultation with a liver transplant center is essential to ensure appropriate initial management and a timely transfer.⁴ Any patient without known preexisting liver disease who develops an elevated INR and even subtle changes in his or her mental status should be transferred to a hospital with a liver transplant program.

Intracranial Hypertension (ICH)

After initial resuscitation, the management of ALF is often focused on the prevention or treatment of ICH, which can cause death due to cerebral herniation (Table 3). Intracranial pressure (ICP) monitoring is a controversial practice that has not been shown to result in an overall survival benefit, although the risks associated with ICP monitoring appear to be decreasing, and monitoring has been associated with increased use of ICP-lowering therapies.⁵ There has been an apparent decrease in the incidence of ICH, which is no longer the leading cause of death but is still associated with high mortality.³

Fluid Management, Infection, and N-Acetylcysteine (NAC)

Other essential priorities in the management of ALF include aggressive fluid management and surveillance for infection.⁴ Patients often require early use of continuous renal replacement therapy and empiric or prophylactic antibiotics.^{3,6,7} In addition to the proven benefit of NAC for acetaminophen toxicity, adults presenting with ALF of non-acetaminophen etiologies (particularly with early grades of encephalopathy) may also benefit from NAC.⁸

Coagulopathy and Bleeding Risk

Although coagulopathy is a defining feature, ALF patients rarely develop clinically significant bleeding. Studies show that ALF patients maintain generally preserved hemostasis despite a high INR.⁹ Correcting the INR in ALF patients in the absence of clinically significant bleeding is, therefore, an inappropriate yet prevalent practice. Correcting the INR before invasive procedures remains controversial.

Abbreviations: ALF, acute liver failure; ICH, intracranial hypertension; ICP, intracranial pressure; INR, international normalized ratio; NAC, N-acetylcysteine; TJLB, transjugular liver biopsy.

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Listing for Liver Transplantation

Assessing a patient's need and suitability for liver transplantation must occur concurrently with the treatment of the underlying etiology and the management of complications. Patients with ALF meeting specific criteria can be placed on the transplant waiting list as status 1A (Table 4).¹⁰ In keeping with the sickest-first rule, status 1A patients are assigned the highest priority, and livers are allocated to them before patients with chronic liver disease.

TABLE 1 ALF Etiologies

Category	Examples
Drugs/toxins	Acetaminophen (most common), anti-epileptics, antibiotics, nonsteroidal anti-inflammatory drugs, isoniazid, <i>Amanita</i>
Viral	Hepatitis A virus, hepatitis B virus, hepatitis E virus, herpes simplex virus, Epstein-Barr virus
Vascular	Budd-Chiari syndrome, ischemia (shock liver)
Metabolic	Wilson's disease
Autoimmune	Autoimmune hepatitis
Pregnancy-related	Acute fatty liver of pregnancy; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
Malignancy	Lymphoma, metastatic
Indeterminate	

TABLE 2 Specific Therapies for ALF

Etiology	Therapy
Acetaminophen	NAC
<i>Amanita</i>	Silibinin, NAC, penicillin G
Hepatitis B virus	Nucleoside/nucleotide analogues
Herpes simplex virus	Acyclovir
Autoimmune	Corticosteroids
Acute fatty liver of pregnancy; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome	Delivery of fetus

TABLE 3 Prevention and Treatment of ICH

Prevention	Treatment	Mechanism
Fluid management, continuous renal replacement therapy	Mannitol (osmotic diuretic)	Maintains a negative fluid balance (other potential benefits of continuous renal replacement therapy include clearance of ammonia and proinflammatory cytokines).
Facilitation of cerebral venous drainage (elevation of head of bed, head in midline)	Pressors	Pressors increase cerebral perfusion pressure by increasing the mean arterial pressure.
Minimization of stimulation (minimization of tracheal suctioning and sternal rubbing, maintenance of darkened room)	Sedation	Psychomotor agitation contributes to ICH; propofol specifically decreases cerebral blood flow and lowers ICH.
Hypertonic saline	Hypertonic saline	Increases serum osmolality to decrease intracellular volume.
Permissive hypothermia	Therapeutic hypothermia	Decreases splanchnic ammonia production, restores normal regulation of cerebral hemodynamics, and lowers oxidative metabolism within the brain.
Permissive hypocapnia	Hyperventilation	Hyperventilation-induced hypocapnia induces cerebral vasoconstriction, decreases ICP, and may improve cerebrovascular autoregulation.
	Barbiturate coma	Cerebral vasoconstriction

Determining the Prognosis

One of the most difficult challenges in ALF is determining whether a patient is likely to spontaneously survive or urgently need a liver transplant. The main determinant of the prognosis is the etiology of the liver injury, and etiologies such as acetaminophen, hepatitis A, and ischemia are associated with relatively high rates of spontaneous survival (>60%), whereas drugs other than acetaminophen, autoimmune hepatitis, Wilson's disease, and indeterminate etiologies are associated with relatively low rates (<30%).^{1,2} Across etiologies, the encephalopathy grade is also a strong predictor of survival.²

In addition to etiology and encephalopathy, multiple prognostic models, including factor V, serum phosphate, and the Model for End-Stage Liver Disease, have been studied.⁴ The King's College criteria (Table 5) are the most widely used, but they are limited in accuracy; therefore, the development of reliable prognostic models remains an area of important and needed research.¹¹

Role of Liver Biopsy

Transjugular liver biopsy (TJLB) can provide important diagnostic and prognostic information, but its role in the management of ALF remains controversial. Some studies advocate the idea that the amount of necrosis seen on TJLB is a strong predictor of mortality; however, these have been retrospective studies limited by selection bias, with biopsy findings influencing the decision whether or not to proceed with transplantation.^{12,13} TJLB is perhaps most useful for establishing the etiology of ALF, particularly in indeterminate cases, and should be encouraged in such cases despite concerns about coagulopathy. In some cases, TJLB can confirm the absence of fibrosis or establish the presence of cirrhosis when this is unclear from noninvasive studies.

TABLE 4 Criteria for Status 1A Listing for Liver Transplantation in the United States

1. Fulminant hepatic failure (defined as the onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease)
2. Life expectancy without a liver transplant < 7 days
3. Absence of preexisting liver disease
4. Must be in the intensive care unit
5. One of the following three criteria:
 - a. Ventilator dependence
 - b. Need for dialysis, continuous venovenous hemofiltration, or continuous venovenous hemodialysis
 - c. INR > 2.0

The information in this table was taken from the Organ Procurement and Transplantation Network.¹⁰

TABLE 5 King's College Criteria

Acetaminophen Overdose	Nonacetaminophen Overdose
Arterial pH < 7.30 or all of the following: <ul style="list-style-type: none">• Prothrombin time > 100 seconds (INR > 6.5)• Creatinine level > 3.4 mg/dL• Grade 3/4 encephalopathy	Prothrombin time > 100 seconds (INR > 6.5) or any three of the following: <ul style="list-style-type: none">• Non-A, non-B hepatitis; idiosyncratic drug reaction; halothane etiology• Time from jaundice to encephalopathy > 7 days• Age < 10 years or > 40 years• Prothrombin time > 50 seconds (INR > 3.5)• Bilirubin level > 17.4 mg/dL

Survival and Posttransplant Outcomes

Overall survival for patients with ALF exceeds 60% at 21 days, and this is a significant improvement in comparison with the pretransplant era when the mortality rate was >80%.^{1,3} Survival has steadily improved over time because of earlier referrals, improvements in intensive care and liver transplantation, and a shift toward etiologies with higher rates of spontaneous survival.^{1,3}

Approximately a quarter of ALF patients undergo liver transplantation. Posttransplant survival rates have improved over time, but 1-year survival rates remain lower (approximately 84%) than rates after transplantation for chronic liver disease.¹⁴ The most common etiologies resulting in

liver transplantation for ALF include drug-induced liver injury, autoimmune hepatitis, and indeterminate causes.¹⁵ Although acetaminophen accounts for almost half of all ALF cases, relatively few of these patients are listed for liver transplantation or undergo transplantation if they are listed; this reflects both the high rate of spontaneous recovery and the psychosocial barriers commonly associated with drug overdose in this group. Across etiologies, long-term survival after liver transplantation appears to be significantly better than survival after spontaneous recovery for reasons as yet unclear.¹⁵

Artificial Liver Support and Living Donor Transplantation

Because of the limited supply of donor organs, artificial liver support devices, including nonbiological and bioartificial devices, offer the promise of supporting the failing liver until regeneration can occur or bridging the patient to liver transplantation if sufficient regeneration is not possible. Unfortunately, these devices have failed to show survival benefit in patients with ALF.¹⁶ Living donor liver transplantation is another approach to mitigating the organ scarcity, but the condensed time frame for evaluating a potential donor limits this option to only a minority of patients.¹⁷

Conclusion

Advances in the management of ALF have led to significant improvements in spontaneous survival and posttransplant outcomes; however, ALF is still associated with high mortality, and many patients do not survive without liver transplantation. Outcomes can be maximized by early referral and aggressive treatment in the intensive care setting within experienced transplant centers. Substantial progress in our understanding of the pathophysiology, prognosis, and management of ALF will continue to depend on collaborations between centers and across disciplines. ■

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