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Acute Liver Failure: Diagnosis and Management

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Abstract

Acute liver failure is life threatening liver injury with coagulopathy and hepatic encephalopathy within 26 weeks and generally, in the absence of preexisting liver disease. Fulminant liver failure occurs when hepatic encephalopathy occurs within 8 weeks of jaundice. The majority of patients with ALF are women with the median age of 38 years. In the United States, drug induced liver injury including acetaminophen causes the majority of ALF cases. The etiology of ALF should be determined, if possible, because many causes have a specific treatment. The mainstay for ALF is supportive care and liver transplantation, if necessary. There are multiple prognostic criteria available. Prognosis can be poor and patients should be referred to a liver transplantation center as soon as possible.

Keywords

acute liver failure, diagnosis of acute liver failure, management of acute liver failure

Introduction and Definition

Acute liver failure (ALF) is defined as life-threatening liver injury in the absence of preexisting liver disease with coagulopathy (prothrombin time >15 seconds or international normalized ratio [INR] $\geq$ 1.5) and hepatic encephalopathy (HE) that develops within 26 weeks of initial symptoms.[1-3] The definition excludes underlying liver disease except in cases of Wilson disease, autoimmune hepatitis, or reactivation of hepatitis B.[2] Further terminology has been used based on the onset of any encephalopathy after the development of jaundice. The term ''fulminant hepatic failure'' (FHF) is used when HE develops within 8 weeks of jaundice.[1,2,4] Williams suggested further grouping of patients. He used the terms ''hyperacute liver failure'' when HE develops within 7 days of jaundice, ''ALF'' when HE occurs 8 to 28 days after jaundice, and ''subacute liver failure'' when the onset of HE was greater than 4 weeks (29-72 days) after the development of jaundice.[2] In general, only the terms FHF and ALF are used.

Epidemiology and Etiologies

The annual incidence of ALF is 5.5 per million (Table 1).[1] Demographics vary according to etiology, but overall, 76% of patients who present with ALF are women and Caucasian.[5] The median age on presentation is 38 years.[5] Unlike in developing countries where viral hepatitis is the primary etiology of ALF, in the United States and the United Kingdom, drug-induced liver injury (DILI) including acetaminophen (APAP) overdose causes the majority of ALF cases.[4,5] The etiology has changed over the years with APAP only accounting for 28% of ALF cases in 1998 but up to 51% in 2003.[6] Acetaminophen overdose now causes up to 65.4% of ALF but is unintentional in about half of the cases.[1,4-8] The mean age of APAP overdose is 33 years.[4]

Other drugs account for 11% to 13% of ALF cases.[5,9] Similar to the demographics of all cases of ALF, the majority of patients with DILI were female (70.6%) and Caucasian (57.1%), however, with a mean age of 43.8 years.[9] Antimicrobials caused most of the DILI ALF cases. Isoniazid, sulfur-containing drugs, especially trimethoprim–sulfamethoxazole, and nitrofurtanoin were common causes of DILI ALF. Antifugals, particularly terbinafine and azoles, were also relatively common causes. About 10% of the cases were caused by nonprescription medications, dietary supplements, weight loss treatments, illicit substances such as cocaine or methylenedioxymethamphetamine (or ecstasy), and complementary and alternative medicines.[9] Several cases of DILI ALF were also caused by phenytoin and psychotropic drugs.[9] Statins were used in less than 10% of ALF DILI cases.[9] The most frequent medications causing DILI requiring liver transplant (LT), however, include

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Table 1. Acute Liver Failure Etiologies and Clinical Characteristics.

Viral	Etiology	Characteristics
	Hepatitis A	Fecal-oral transmission History of international travel or food outbreak
	Hepatitis B	Reactivation of chronic HBV History of high-risk behavior
	Hepatitis C	Rare History of high-risk behavior
	Hepatitis E	Fecal-oral transmission Pregnant patient
	Herpes simplex virus	Immunocompromised or pregnant patient Fever Normal or only mildly increased bilirubin
	Cytomegalovirus	Immunocompromised patient
	Epstein-Barr virus	Rare, generally pediatric population
	Parvovirus	Rare, generally pediatric population
Metabolic	Autoimmune hepatitis	Female predominance History of other autoimmune disorders Positive autoantibodies
	Wilson's disease	Hemolytic anemia Low alkaline phosphatase Low serum ceruloplasmin
Drug	Acetaminophen	History May be unintentional Lower dose required in chronic alcohol users
	Other	History
Pregnancy specific	Acute fatty liver of pregnancy	Persistent nausea and vomiting HTN Jaundice AKI AST/ALT in hundreds Bilirubin <5 Prolonged PT/PTT
	HELLP	Abdominal pain and vomiting Headache Thrombocytopenia Elevated ALT/AST Hemolytic anemia HTN Edema
Other	Ischemic hepatitis	History of hypotension Rapid rise in ALT > 1000 IU/mL
	Mushroom (amanita phalloides) poisoning	History Watery diarrhea
	Malignancy	History of cancer Infiltration on imaging
	Budd-Chiari syndrome	Hypercoagulable state Hepatic outflow obstruction on imaging
	Rhabdomyolysis	Related to hyperthermia or drugs

Abbreviations: AKI, acute kidney injury; AST, aspartate transaminase; alanine transaminase; HBV, hepatitis B virus; HELLP, hemolysis elevated liver enzymes, low platelets; IU, International unit; PT, prothrombin time; PTT, partial thromboplastin time; HTN, hypertension.

isoniazid, propylthiouracil, phenytoin, and valproate. These 4 drugs alone account for 42% of LT for non-APAP DILI ALF. Herbal supplements or mushrooms account for an additional 11.7% of ALF requiring LT in the non-APAP group.[9]

In the past few decades, cases of ALF from viral hepatitis have decreased in the United States and the United Kingdom. In 1973 to 1978, viral hepatitis accounted for 55.9% of all non-APAP ALF cases; in 2004 to 2008, it only caused 16.6% of non-APAP ALF cases. Hepatitis A and hepatitis B account for 3% to 4% and 7% of ALF cases, respectively.[5,10-12] The decrease in cases of acute hepatitis A is likely related to vaccinations and improved sanitation.[10] The decrease in ALF from hepatitis B is also likely related to vaccination. Reactivation of hepatitis B virus (HBV) infection can occur in patients with positive hepatitis B surface antigen (HBsAg) who undergo chemotherapy for cancer or immunosuppression for autoimmune diseases.[13] Patients with antibodies against hepatitis B core antigen or HBsAg and appear to have cleared the virus can also have viral reactivation.[13]

Other etiologies of ALF include ischemic hepatitis, autoimmune hepatitis, Wilson disease, toxic mushroom poisoning, particularly *Amanita phalloides*, infection with herpes simplex virus (HSV), malignant carcinoma or lymphoma, and Budd Chiari syndrome which overall account for 2% to 6% of ALF cases.[5,10] Acute liver failure can also rarely be caused by heat stroke, sepsis, acute cocaine intoxication, and rhabdomyolysis, as well as cytomegalovirus, Epstein-Barr virus, and parvovirus.[5,14-17] Indeterminate etiology accounts for 17% to 43% of all ALF cases and up to a third of FHF cases.[3,5,18-20]

Certain etiologies specific to pregnancy should be considered in pregnant patients with ALF. Acute fatty liver of pregnancy (AFLP) is a rare cause of ALF and occurs in 1 per 10 000 births but has a high mortality of 10% to 33%.[21-23] Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, preeclampsia, and eclampsia are other rare causes of ALF in pregnant patients. Preeclampsia occurs in 5% to 10% of pregnancies, and HELLP occurs in 0.17% to 0.8% of pregnancies. In developing countries, infection with HEV should be considered in any pregnant patient presenting with jaundice and leads to high maternal mortality when presenting with FHF.[24,25]

Diagnosis and Presentation

Except in the cases of Wilson disease, autoimmune hepatitis, and hepatitis B, the diagnosis of ALF generally requires the exclusion of underlying liver disease. Exclusion of chronic liver disease can be difficult because patients with ALF can present with clinical findings similar to chronic liver disease. Almost 30% of patients with ALF will have ascites and 17.7% develop spontaneous bacterial peritonitis (SBP).[26] Imaging may demonstrate nodular liver surface suggesting cirrhosis, ascites, splenomegaly, and collateral vessel formation.[27] Evidence of portal hypertension and a nodular liver surface can be seen in patients whose symptoms developed over 1 to 4 weeks.[27] The nodularity on imaging correlated with massive hepatic necrosis and wrinkled capsules on explants.[27]

Determining the etiology of ALF is important because several etiologies have specific medical treatments. Often, the underlying etiology can be found without invasive procedures; however, the use of transjugular liver biopsy has been found to be safe and may clarify the etiology of ALF.[28] A careful history of APAP use should be obtained when possible and an APAP level should always be measured.[3] Only 4.5% of patients with acetaminophen overdose results in hepatotoxicity, but ALF from APAP is unintentional in about 50% of cases.[29] Compared to those who intentionally overdose, patients with unintentional APAP overdose tend to have a history of alcohol abuse, lower serum APAP levels, and lower ALT but more severe HE on admission.[6,29] Most of the unintentional overdose patients reported taking the APAP for pain.[6] The median dose ingested was 13.2 to 24 g/d with 83% of patients ingesting more than the recommended 4 g/d.[5,6] A history of taking 2 preparations of APAP is common.[6] Patients present a median of 2.0 days after symptoms developed.[6] There are some data to suggest that despite negative APAP levels and no history of APAP use, a number of indeterminate cases may be due to APAP toxicity. Acetaminophen–protein adducts, products of APAP metabolism that have a 100% specificity and sensitivity for APAP toxicity, have been detected in 18% to 19.4% of indeterminate ALF cases.[3,30] This group of APAP-protein adduct positive, previously indeterminate ALF patients had similar demographics and clinical presentation (short duration of illness, high aminotransferase levels, and low bilirubin levels) as the known APAP toxicity group who also had detectable adduct levels.[3,30]

Non-APAP DILI accounts for a large number of ALF, but the offending agent may not be obvious. In 20.3% of DILI ALF cases, only one drug was being used, but in 77.4% of causes, several other drugs with potential hepatotoxicity were also being taken.[9] Furthermore, the duration of the drug use prior to development of ALF varies from 1 week up to 8 months. In a few cases, the culprit medication was used for 1 to 3 years.[9] Drug-induced liver injury may be independent of dose.[14] Rash and/or eosinophilia occurs in less than 10% of patients with DILI ALF and in one study, only 1.5% had both.[9] Significant titers of autoantibodies may be present.[9] Unlike ALF from APAP overdose, DILI ALF is characterized by only moderate aminotransferase elevations. Patients may also present with deep jaundice from hyperbilirubinemia, fluid retention, coagulopathy, and coma.[9]

To predict which patients with DILI develop ALF, Hy's law, which incorporates admission and upper limit of normal (ULN) alanine aminotransferases (alanine transaminase [ALT] or aspartate transaminase [AST]), total bilirubin (TBL), and alkaline phosphatase (Alk phos), can be used. One study compared the ratio value (R) of ALT × ULN/ALP × ALN to the new ratio (nR) value of ALT or AST, whichever is highest, × ULN/Alk phos × ULN. Using the Spanish DILI registry, the study found that an nR value of 5 or greater was the most predictive to predict ALF compared to R of 5 or greater, TBL greater than 2× ULN, and ALT greater than 3× ULN.[31]

Autoimmune hepatitis (AIH) is an uncommon cause of ALF although acute presentation of the disease can occur in up to 25% of cases.[32,33] It is speculated that AIH may account for some of the indeterminate cases as well.[32] The diagnosis may be difficult because ALF from AIH does not necessarily present similar to the classic AIH. Compared to the chronic form of the disease, patients with acute AIH FHF have lower albumin and higher bilirubin and globulins, and prevalence of autoantibodies.[32,33] Findings on liver biopsy may differ as well. Rather than the classical histological features of AIH that include portal tract-based necroinflammatory process with interface hepatitis and lobular involvement, biopsies in AIH FHF may demonstrate severe centrilobular inflammation and necrosis involving zone III.[33] Central perivenulitis, plasma cell-rich inflammatory infiltrate, an autoimmune type of massive hepatic necrosis, and lymphoid aggregates may also be seen on biopsy.[33]

Ischemic hepatitis is an uncommon cause of ALF but should also be considered, especially in patients with a rapid rise in serum ALT >1000 IU/mL. One study on ischemic hepatitis in patients with ALF found that only 31% had known cardiovascular disease and only 55% had documented hypotension. Cardiopulmonary decompensation was noted in 69%, but the remaining cases were due to noncardiac causes including sepsis, seizures, vascular occlusion of the porta hepatitis, and intravascular volume depletion.[34]

Amanita phalloides, an exceedingly rare cause of ALF, should be considered with history of recent ingestion of wild mushrooms and development of watery diarrhea within 12 hours after ingestion. Diarrhea has been described as watery and cholera like.[35]

Herpes simplex virus is another rare cause of ALF and primarily noted only in case reports, however, with a high mortality rate. Risk factors include pregnancy and immunosuppression, either by disease or medication. Practitioners should have a higher index of suspicion of this etiology of ALF when the bilirubin is normal or mildly elevated but with very high transaminases, especially if AST is greater than the ALT. Thirty percent of patients will not have identifiable oral or genital lesions, and diagnosis may require a liver biopsy.[36]

Acute fatty liver of pregnancy should be considered in pregnant patients who present with persistent nausea and vomiting, hypertension, and/or abdominal pain and ALF. Risk factors include first pregnancy, multiple gestations, and male fetus.[24] On presentation, patients are usually in their third trimester but up to 20% are <34 weeks of gestation. Abnormal liver tests include hepatic transaminases in the several hundreds, elevated bilirubin up to 15 mg/dL, with a mean of 3.7 mg/dL, and coagulopathy.[23] Patients also have anemia, leukocytosis, and low platelets. Seventy-six percent will develop acute kidney injury (AKI).[23] Patients with AFLP may also present with pancreatitis.[38] On examination, patients may have jaundice, edema, hypertension, and HE.[37] It is unclear whether AFLP and HELLP are part of the same spectrum of pregnancy-specific liver disorders or separate entities. The clinical presentation may overlap. As the name indicates, patients with HELLP syndrome develop hemolysis, elevated liver enzymes, and thrombocytopenia.[24,37] Risk factors for HELLP include Caucasian race, older age, being multiparous, and HELLP syndrome during previous

pregnancies.[24] Patients may have similar symptoms to those with AFLP including abdominal pain, malaise, headache, and nausea and vomiting with or without preeclampsia. On examination, patients typically present with hypertension and edema. Maternal complications can include seizures, disseminated intravascular coagulopathy, abruption placentae, AKI, subcapsular hematoma, and cardiopulmonary distress.[24,37] Compared to patients with HELLP syndrome, those with AFLP generally have higher INR levels, bilirubin, creatinine, and platelet counts, and lower AST levels.[38] Liver biopsies are usually not necessary to diagnose these pregnancy-specific liver disorders.[24] If liver biopsies are done for AFLP, frozen section with oil red-O or Sundan III should be sent and typically demonstrate microvesicular fatty infiltration in centrilobular hepatocytes.[24] Histopathology in HELLP is characterized by periportal necrosis and hemorrhage with fibrin deposits.[24]

Preeclampsia and eclampsia are characterized by hypertension, edema, and proteinuria and generally occur in the second or third trimester. Postpartum presentations have also occurred.[24] Liver function tests (LFTs) can be abnormal in preeclampsia and is elevated in up to 90% of those with eclampsia. Transaminases may be up to 100 times normal, but bilirubin is usually less than 5 mg/dL.[24] Acute liver failure is very rare in these disorders.

Wilson disease is uncommon, but the fulminant presentation is almost always fatal without liver transplantation (LT). The disease should be considered in young patients with acute onset of hemolytic anemia with very low Alk phos but bilirubin >20 mg/dL, which can be both indirect and direct.[39] Serum ceruloplasmin is usually low (typically <20 mg/dL) but can be normal in up to 15% of cases. Ceruloplasmin can be low in other causes of ALF as well. An Alk phos–TBL ratio <4 and an AST–ALT ratio >2.2 are highly sensitive and specific predictors of fulminant Wilson disease.[40] Patients may also have a high serum and urinary copper levels and hepatic copper measurements by biopsy. Patients may develop renal insufficiency from copper injury to the kidney.[39]

Management

The mainstays for ALF are supportive care, treatment for specific etiologies, and LT, if necessary. All patients with ALF and HE should be admitted or transferred to the intensive care unit (ICU) and ideally referred to the nearest LT center.[39,41] Transplantation evaluation should be started as soon as possible because rapid deterioration may occur.[39] Computed tomography (CT) head may be used to exclude other causes of rapid change in mental status such as an intracranial hemorrhage.[39] Any patient with Wilson disease and ALF should be referred for LT.[42]

Medications

Certain treatments are standard based on the etiology. *N*-Acetylcysteine (NAC) is standard of care for APAP overdose.[43,44] Low or undetectable APAP levels do not necessarily rule out APAP overdose.[39] Although the efficacy is best when given within 8 hours of acute ingestion, NAC is still recommended up to 72 hours after the overdose although efficacy may be decreased.[39,41,43] Older studies were based on an oral regimen that was given over 72 hours. Oral NAC may be given in patients with grade 1 HE but intravenous (IV) NAC should be given in patients with more severe HE or unstable hemodynamics. Intravenous *N*-acetylcysteine is generally better tolerated than the oral form.[41] The IV dose may vary according to institution protocol but is generally 150 mg/kg over 1 hour followed by an infusion of 12.5 to 15 mg/kg/h for 4 hours then 6.25 to 7.5mg/kg/h for at least 16 hours. *N*-Acetylcysteine is continued until hepatic function improves and may be continued for several days.[41]

A prospective randomized double blind placebo controlled trial found promising results in the use of NAC for non-APAP causes of ALF.[45] The study found similar overall 3-week survival between treatment and placebo groups, but transplant-free survival was significantly higher in the treatment group (40% vs 27% P .043). The largest difference in transplant-free survival was seen in patients with coma grade I to II. There was no significant difference in transplant-free survival in coma III to IV group. The study also found a trend toward shorter hospital stays in the NAC group, but the difference was not significant. There was no difference in adverse events. Overall, the study suggests a survival benefit in patients with ALF treated with NAC who have early stages of HE.[45]

For mushroom poisoning, several methods of treatment are used but based on limited data. Gastric lavage with a nasogastric tube to remove any remaining mushroom pieces, activated charcoal, pencillin G, and *Silybum marianum* (*milk thistle*) are generally used with NAC.[16,41,46] Penicillin G is given in doses of 300 000 to 1 million units/kg/d, while silymarin can be given either via IV or orally 30 to 40 mg/kg/d for an average of 3 to 4 days.[39]

For HSV hepatitis, acyclovir has been used successfully with a survival rate of 72% and should be started promptly. The dose is not standard but 10 mg/kg for 10 to 14 days has generally been used.[36] If strong clinical suspicion for HSV ALF is present, empiric treatment should be started before the diagnosis is confirmed.[36]

Management of pregnancy-specific liver disease generally requires delivery of the fetus.[23,24,37] Patients with AFLP usually have clinical recovery within 3 to 4 days after delivery. Aminotransferases generally improve within days after delivery, and if remain very elevated, may indicate sepsis or ischemic liver damage.[23] Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency in the fetus may play a role in the pathophysiology of AFLP, and screening for infants born to mothers with AFLP has been advocated. Patients with preeclampsia and eclampsia quickly improve after delivery.[24] Patients with HELLP syndrome should be closely monitored after delivery because mothers may have worsening thrombocytopenia up to 48 hours after delivery.[37] Plasmapheresis can be considered if platelet counts do not improve within 72 hours after delivery.[24]

Evidence regarding treatment for acute hepatitis B has varied. One prospective study of patients with severe acute or fulminant hepatitis B treated with lamivudine resulted in higher rate of spontaneous survival compared to historical controls who were not treated (82.4% vs 20% $P < .0001$).[47] None of the treated patients had an adverse event from lamivudine.[47]

Another small study showed that 6 patients with ALF from HBV infection improved on entecavir treatment. None required LT, all patients had a rapid decrease in HBV DNA with near or complete normalization within 3 months of presentation. Seroconversion of anti-HBsAg occurred in 5 of 6 patients.[48] A large retrospective review, however, found no difference in spontaneous and overall survival in patients with ALF from hepatitis B infection who were and were not treated with a nucleoside(-tide) analogue.[49]

The role of corticosteroids in AIH ALF is unclear. Immunosuppression, usually steroids followed by azathioprine, is recommended for chronic AIH; however, the use in ALF is controversial.[39] In patients with severe and fulminant forms of AIH, studies have demonstrated little mortality benefit and may lead to infection.[50] Prednisolone in addition to NAC was not shown to reduce 6-month mortality in patients with severe alcoholic hepatitis; however, mortality was significantly lower at 1 month.[51]

Unlike in known chronic forms of Wilson disease, penicillamine is not recommended in ALF.[39] Plasmapheresis and continuous hemofiltration may acutely reduce copper levels; however, LT is generally required for survival.[39]

The role of lactulose therapy for HE in ALF is unclear. One study demonstrated that compared to patients who did not receive lactulose, there was no difference in final outcome; however, the lactulose group had a significantly longer median survival time.[52] The main concern for giving lactulose is that it may cause abdominal distention and therefore obscure the surgical view during LT.[39,41]

Prophylactic phenytoin seems to have little benefit in patients with ALF. Subclinical seizure activity has been recorded in up to 32% of patients with ALF. The use of prophylactic phenytoin failed to demonstrate significant difference in pupillary abnormalities, seizure activity, elevated intracranial pressure (ICP), or survival.[53]

Adrenal insufficiency has been demonstrated to be associated with poor outcome in patients with ALF who may benefit from IV steroids.[54] However, a retrospective analysis of patients with ALF from autoimmune, indeterminate, and drug-induced ALF demonstrated that IV steroids were not associated with improved overall survival.[55] Steroid use was associated with decreased survival in patients with model for end-stage liver disease (MELD) >40.[55]

Supportive Care

Supportive care preferably in an ICU setting is essential for patients with ALF. Patients' intravascular volume and systemic perfusion should be maintained with IV fluids. If vasopressors are necessary, norepinephrine is preferred.[14] If patients with ALF require renal replacement therapy, continuous forms are recommended to limit the changes in cardiac index, mean arterial pressure, and increase in ICP that can occur with intermittent dialysis.[56] Intubation should be considered by HE grade 3 to manage the airway.[14,41] Adequate sedation and pain control are essential to limit intracranial hypertension, however, sedatives and narcotics may worsen HE.[41] Propofol is recommended over benzodiazepines because of the shorter half-life and that it may lower ICP.[57] Similarly, analgesics with a shorter half-life such as fentanyl are preferred over those with longer half-lives.[41]

Spontaneous, significant bleeding is uncommon in ALF.[14,41] Although prothrombin time (PT) and INR are increased in patients with ALF, procoagulants are also elevated and a heparin-like effect can also be seen in this patient population.[58] Vitamin K subcutaneously or intravenously can be given in case there is a component of vitamin K deficiency; however, prophylactic transfusion of fresh frozen plasma is not recommended except in the case of invasive procedures and profound coagulopathy.[14,39,41] A platelet count of 10 to 20 000/mm^3 is generally safe unless an invasive procedure is planned in which case platelets should be transfused for a goal of 50 to 70 000/mm^3.[39] In the setting of an invasive procedure such as a central line placement, fresh frozen plasma (FFP) should be transfused. Recombinant factor VIIa (rFVIIa) can be given after the FFP and immediately before the procedure at the dose of 40 μg/kg; however, it is contraindicated in patients with deep vein thrombosis, cerebrovascular accident (CVA), myocardial infarction (MI), pregnancy, Budd-Chiari syndrome, or malignant infiltration of the liver.[41,59] Cryoprecipitate should be given if fibrinogen <100 mg/dL. Gastrointestinal prophylaxis with H2 blocker or proton pump inhibitor (PPP) is also recommended.[39]

Management should include a high index of suspicion for infection since sepsis is a leading cause of death from ALF.[14,60] Infection control to prevent nosocomial infection is strongly recommended.[14] Eighty percent of patients with ALF have bacteriologically proven infection while 32% have concomitant fungal infection. Respiratory and urinary tract infections account for almost 70% of all infections with the majority occurring within 3 days of admission. Only 32% of patients with bacterial infection have both leukocytosis and fever, and about 30% have neither feature.[60] The lung is the most common site of infection followed by urinary tract. Acute renal failure is significantly associated with bacterial infection.[60]

Acute kidney injury develops in 70% of patients with ALF and is more often seen in patients with APAP ALF.[61] Thirty percent of patients with ALF require dialysis, but only 4% of patients who survive require dialysis more than 3 months after discharge. Patients with AKI have decreased rates of spontaneous survival; however, the difference in survival rates are nonsignificant for non-APAP ALF patients.[61]

The systemic inflammatory response syndrome (SIRS) is common in ALF, and 56.8% develop SIRS during hospitalization, but in 40% a microbiologically confirmed infection is not found.[62] Systemic inflammatory response syndrome on admission was associated with death. Patients with SIRS during their hospitalization were more likely to have worsening HE, even when infection could not be found. Infected patients, however, are more likely to develop a severe SIRS and worsening encephalopathy.[62] Higher number of components of SIRS on admission predicts worsening of HE to stage III or IV.[63] Prophylactic antibiotics are not routinely recommended although should be considered in patients with worsening HE, SIRS, or hypotension, and those listed for LT.[39,41]

Intracranial Hypertension Management

Forty-one percent of patients with ALF have signs of intracranial hypertension (ICH), which is defined as an ICP of greater than 20 mm Hg.[7,41,64] The etiology of ALF has not been associated with the development of ICH; however, episodes may be preceded by fever, psychomotor agitation, and arterial hypertension.[65] Patient stimulation should be avoided.[41] The benefits of ICP monitoring is unclear and institution dependent. Intracranial pressure monitoring allows detection and management of elevated ICP and may aid in decision making.[66] A large prospective registry of patients with ALF (US ALF study group) found that 27.7% of patients with grade III to IV HE had ICP monitoring.[67] Compared to the unmonitored group, this group was significantly younger, and 66.3% had grade IV encephalopathy. The frequency of utilization differed significantly between individual institutions. Subdural transducers were the most commonly used followed by parenchymal and then epidural. Fresh frozen plasma was given in 91% of cases of ICP insertion. In 59% of cases, the patients received other products such as platelets, cryoprecipitate, and rFVIIa. Intracranial pressure monitoring was maintained for a median of 4 days. The transducer was removed because of improvement in 59% of cases and death in 33% of patients. There were complications in 10% of cases, which was a decrease from prior studies.[67] All of the cases were intracranial hemorrhage. Only 5.2% of the ICH had clinical symptoms. Three cases were diagnosed by CT. Three died, one after LT. Patients who had ICP monitoring were more likely to have mannitol, barbiturates, and vasopressors. Thirty-day survival post LT was similar with or without ICP even controlling for center and etiology.[67]

Measures to reduce ICP include head-of-bed elevation and controlled hypocapnia.[41] Based on older studies, IV mannitol (in small number of boluses of 0.5 to 1 g/kg) and controlled hyperventilation are generally used to reduce ICP.[40,68,69] The goal ICP is below 20 to 25 mm Hg with cerebral perfusion pressure (CPP) above 50 to 60 mm Hg.[41] Systemic hypernatremia via hypertonic saline infusion (3%) has been shown to significantly reduce ICP and incidence of ICH.[70]

Therapeutic hypothermia is increasingly used to reduce body core temperature and treat uncontrolled ICH prior to orthotopic liver transplant (OLT) with some success.[71] During therapeutic hypothermia, patients are cooled to 32°C to 33°C for 8 to 14 hours. Improvement in mean ICP, mean arterial pressure, and CPP has been demonstrated.[71,72] Protocols recommend therapeutic hypothermia to be achieved with external cooling rather than endovascular devices, cooling to a core temperature of 32°C to 33°C and to avoid over cooling, and for patients to be rewarmed slowly.[71] The optimal duration of hypothermia is unclear although patients with ALF have tolerated being cooled for up to 5 days.[71]

A protocol-driven management of ICH has been shown to be beneficial in patients with FHF and stage 3 or 4 encephalopathy. One prospective series evaluated the use of an ICP management protocol in patients with ALF, all of whom had an intraparenchymal ICP monitor. Activated factor VII and desmopressin were routinely used prior to ICP placement. The protocol for ICP >20 mm Hg for >5 minutes included keeping CPP >60 mm Hg with norepinephrine or phenylephrine infusion, mannitol bolus, hyperventilation to target P_{CO_2} 30 to 35 mm Hg, hypothermia using cooling blanket to core temperature of 33°C to 34°C with the initiation of neuromuscular blockade if necessary with cisatracurium, phenobarbital bolus with repeated boluses as necessary to titrate to ICP effect, and finally 3% saline to achieve serum sodium in 145 to 155 mEq/L range.[64] Seventy-seven percent of included patients had bleeding complications. Three had intracranial hemorrhage associated with the site of the ICP monitor. Almost all of the patients (95%) had ICH when the ICP was placed or during the hospitalization. The mean peak ICP during an ICH episode was 33 mm Hg. Ninety-five percent of episodes resolved with the above protocol treatment; however 4 patients died within 1 hour of an ICH episode. The primary causes of death in these 3 were determined to be severe sepsis or hypoxia from acute respiratory distress syndrome. The overall survival was 55%.[64]

Investigational Treatments

Liver dialysis systems have not been shown to provide benefit to patients with ALF. Albumin dialysis systems were developed to eliminate albumin-bound toxic molecules. The prospective, open label, parallel assignment randomized controlled multicenter trial evaluating efficacy and safety of molecular adsorbent recirculating system (MARS) found no significant difference between 6-month survival, 6-month transplant-free survival, 1-year patient survival, and adverse events, and between conventional treatment and those who had at least 1 session of MARS >5 hours.[73] Similarly, a pilot-controlled trial for the extracorporeal liver assist device (ELAD) failed to demonstrate a difference in survival in patients with ALF who were randomly allocated to ELAD as a bridge to transplantation compared to controls.[74] A phase II/III prospective, randomized, multicenter controlled trial examining the use of extracorporeal liver perfusion using a bioartificial liver (BAL) was also unable to find a 30-day survival benefit or prolongation of survival with the BAL in patients with fulminant or subfulminant liver failure.[75] Hepatocyte transplantation was investigated in 5 patients who were not candidates for LT.[75] All 5 died; however, clinical improvement was seen after 48 hours in 3 patients who had engraftment of donor hepatocytes demonstrated by fluorescence in situ hybridization (FISH) and histology.[76] There have been only a few reported cases of patients with ALF who were successfully bridged to LT with hepatocyte transplant.[77]

Criteria

Multiple prognostic criteria have been proposed and studied to evaluate which patients would benefit most from LT.[14] The King's College Hospital (KCH), MELD, Acute Physiology and Chronic Health Evaluation II score (APACHE II), and Sequential Organ Failure Assessment (SOFA) score are some of the

more common scoring systems for patients with APAP ALF (see Table 2).[78]

For the management of APAP ALF, an MELD score greater than 18 was shown to predict development of HE with a positive predictive value (PPV of 44%) and negative predictive value (NPV) of 99%.[79] Once HE developed, however, MELD was not able to discriminate between survivors and nonsurvivors of APAP ALF.[79] In a similar group of patients, KCH, APACHE II, SOFA, and MELD were compared to predict outcome. King's College Hospital criteria had the most specificity (83%) but lowest sensitivity (47%); MELD had the highest sensitivity (89%) but the lowest specificity and PPV of only 25% and 0.49, respectively.[78] The discriminative ability as demonstrated by the area under the curve (AUC) was also the lowest at 0.61.[78] Compared to the other 3 scoring systems, the SOFA had the highest discriminative ability that likely reflects the score's inclusion of multiorgan dysfunction.[78] A meta-analysis of 15 studies evaluating FHF from APA found that the KCH criteria had similar high specificity (92%) but sensitivity of 69%.[80] In this article, the APACHE II criteria had a similar specificity to the KCH but with a higher sensitivity of 81%. As mentioned in previous studies, one main disadvantage of the APACHE II is that it includes multiple factors and is cumbersome to calculate.[80]

Serum lactate has been shown to predict mortality in ALF.[81-84] One study of patients with APAP ALF demonstrated that arterial lactate early after admission and at onset of HE was higher in nonsurvivors compared to survivors.[81] Arterial blood lactate concentrations of >4.0 mmol/L predicted mortality with a sensitivity of 74% and specificity of 62% early after admission and sensitivity of 67% and specificity of 80% at onset of HE.[81] Another study of patients with APAP ALF demonstrated that compared to KCH criteria, a lactate level of 3.5 mmol/L on presentation and 3.0 mmol/L after resuscitation had higher sensitivity and similar specificity, accuracy, positive and negative likelihood ratio, and identified patients earlier.[82] The combination of KCH criteria and postresuscitation lactate >3.0 mmol/L had higher sensitivity and lower negative likelihood ratio than KCH alone.[82] It also correlated with SOFA scores and number of SIRS components, all of which were strongly associated with death.[81]

In patients with non-APAP-induced ALF, similar scoring systems have been investigated. One study compared the KCH, MELD, and the Clichy scores.[85] Using an MELD >35, no significant difference was found when compared with the Clichy score, KCH, and MELD scores in terms of specificity, sensitivity, NPV, PPV, and AUC.[85] A meta-analysis of 17 studies in nonparacetamol-induced ALF found that the KCH had a sensitivity of 68% and specificity of 82%, which were similar to the numbers found with the APAP group.[86]

A retrospective analysis of patients admitted with FHF, mostly from acute viral hepatitis, and did not have an LT due to unavailability at the hospital, was reviewed for clinical data and compared MELD, KCH, and clinical prognostic indicators (CPI).[87] The study found that 6 independent predictors of outcome including age >50 years, jaundice to encephalopathy

Table 2. Acute Liver Failure Prognostic Criteria.

Criteria	Factors
King's College Hospital	*Acetaminophen-iduced ALF*
	Arterial lactate
	pH
	Hepatic encephalopathy
	INR
	Creatinine
	Nonacetaminophen-induced ALF
	INR
	Encephalopathy
	Age
	Duration of jaundice
	Bilirubin
	Unfavorable etiology, such as Wilson disease, idiosyncratic drug reaction, and seronegative hepatitis
MELD	Creatinine
	Bilirubin
	INR
	Dialysis within the past week
APACHE II	Temperature
	Mean arterial pressure
	Heart rate
	Respiratory rate
	Aa gradient or Po_2
	pH or HCO_3
	Na
	K
	Creatinine
	Hematocrit
	WBC
	Glasgow score
	Age
	Presence of a chronic disease
SOFA	Pao_2/Flo_2 (mm Hg)
	Sao_2/Flo_2
	Platelets $\times$ $10^3/mm^3$
	Bilirubin
	MAP
	Use of vasopressors
	Glasgow score
	Creatinine or urine output
CLICHY	Age
	Encephalopathy grade
	Factor V level
Clinical prognostic indicators	Age >50 years, Jaundice to encephalopathy interval greater than 7 days, grade 3 or 4 encephalopathy, presence of cerebral edema, prothrombin time $\geq$35 seconds, and creatinine $\geq$ 1.5 mg/dL
ALFSG	Admission coma grade
	Bilirubin
	INR
	Phosphate
	Log 10M-30
ALFED	Hepatic encephalopathy grade
	INR
	Arterial ammonia
	Total bilirubin

Abbreviations: Aa gradient, alveolar-arterial gradient; ALF, acute liver failure; Flo_2, fraction of inspired oxygen; HCO_3, bicarbonate; INR, international normalized ratio; K, potassium; MAP, mean arterial pressure; Na, sodium; Sao_2, oxygen saturation; WBC, white blood cell.

interval greater than 7 days, grade 3 or 4 encephalopathy, presence of cerebral edema, PT $\geq$ 35 seconds, and creatinine $\geq$1.5 mg/dL were indicative of poor outcome.[87] The presence of any 3 of these CPI predicted mortality with higher specificity, PPV, NPV, and diagnostic accuracy than MELD $\geq$33. Sensitivity of MELD was slightly higher at 75.1% compared to 73.9% for any 3 CPI predictors. MELD $\geq$33 better predicted mortality than the KCH mortality in terms of sensitivity, PPV, NPV, and diagnostic accuracy but with less specificity.[87]

Arterial ammonia (NH_3) on admission has also been investigated in ALF from any cause and was found to be significantly higher in patients with ALF who developed ICH and HE.[88-90] Arterial NH_3 concentration on admission was significantly higher in patients who developed ICH and also predicted development of severe HE requiring intubation. A NH_3 concentration greater than 200 μmol/L had a specificity of 92% to predict ICH but only with a sensitivity of 25%.[88] In one study of patients with ALF, although both arterial NH_3 and the partial pressure of the gaseous NH_3 (pNH_3) were correlated with HE grade, on the multiple regression model, only the pNH_3 was a significant independent predictor on the HE grade.[90]

More recently, a prognostic index combining levels of M30, a marker of hepatocyte cell death increased in ALF and clinical variables in the ALF study group (ALFSG) index has been investigated. The ALFSG index predicts death or need for LT with a sensitivity of 85.6% and specificity of 64.7%.[91] The specificity and sensitivity were similar regardless of etiology and better identified patients compared to the KCH and MELD score.[91]

While the majority of the prognostic criteria are based on admission parameters, the ALF early dynamic model (ALFED) is based on early changes. Variables on admission as well as persistent or progression to HE grade >2 are as follows: INR $\geq$5, arterial NH_3 $\geq$123 μmol/L, and TBL $\geq$15 mg/dL. Patients were then given increasing risk scores from 0 to 6. Scores $\geq$4 had a high PPV of 85% and NPV 87%.[92] Compared to MELD and KCH, the ALFED had better discrimination.[92]

Model for end-stage liver disease and a new logistic model based only on INR and TBL predicted 1-month mortality in patients with pregnancy-specific liver disease.[93] Higher admission serum lactate level and encephalopathy have also been shown to identify patients with pregnancy-related liver disease that were more likely to detect patients who died or required LT.[38]

Prognosis

Acute liver failure has a poor prognosis with an overall mortality of 40% to 62.2%.[1,5,7] The spontaneous survival is 25% to 43%, and the overall survival is 67%.[1,4,5,94] The main causes of death in patients with ALF are cerebral edema, sepsis, and multiorgan failure.[5,18,62] Cerebral edema also causes 71.4% of deaths in the pretransplant and immediate (<24 hour) posttransplant period.[18] Of patients who present with ALF, 71% meet the criteria for transplant, 22% to 43% are listed, but only 29% to 56% are transplanted.[4,5,95] Liver transplant waiting list mortality is 6.3% to 27.7%.[1,5,6,18,95] The majority who were listed but not transplanted died waiting for a liver while the remainder was considered too sick for transplant when an organ was available.[95]

Liver transplant is the gold standard for ALF management. Acute liver failure was the etiology of 8% of LT in Europe between 1988 and 2009 and 7% in the United States between 1999 and 2008.[19] The median time from listing to actual transplant was 3.5 days.[5] Post LT for ALF survival rates have improved but are still under rates for cirrhosis.[18,19] Thirty-day posttransplant survival was similar between APAP and non-APAP causes for transplant.[96] Posttransplant 3-week survival in 1 large US study was 84%.[5] One-year graft survival was not significantly different in the APAP and non-APAP DILI groups.[8] Transplant for drug-related ALF accounted for 15% of LT between 1990 and 2002.[8] In that period of time, patient and graft survival improved. One year patient survival increased from 74% to 82%, 5 year survival increased from 69% to 76%, and 1 year graft survival increased from 63% to 71%.[18,19,96] Improved survival is likely multifactorial including change in etiology of ALF from viral hepatitis to drug induced, improvement in intensive care, and improvement in immunosuppression thus decreasing rejection.

Prognosis varies according to clinical presentation. Mean age and sex do not affect survival or transplantation rate.[4] More than half of the patients with ALF develop at least grade 3 encephalopathy requiring intubation and mechanical ventilation.[95] Patients who progress from stage I to II HE to III to IV have significantly lower rates of spontaneous survival.[4,63] Half of the patients presented with grade I or II hepatic coma on admission and 52% of these patients had spontaneous survival at 3 weeks. Only 33% of those who were admitted with grade III or IV hepatic coma survived 3 weeks without transplantation.[5] Prognosis and the percentage of patients undergoing transplant vary depending on etiology. Spontaneous survival was 50% or greater in cases of APAP overdose, hepatitis A virus infection, shock liver, and pregnancy-related ALF.[5] Short-term transplant-free survival was lower in patients with indeterminate causes, non-APAP DILI, hepatitis B, AIH, Wilson disease, Budd-Chiari, or cancer.[5] Ninety-four percent of patients with ALF from Wilson disease had LT, while only 6% to 13% of acetaminophen overdose patients were transplanted.[4,5,96] Acetaminophen overdose has the highest spontaneous survival rate with 65% spontaneous survival.[4,5,6,96] About half of APAP fulfill transplant criteria, 26% percent of patients with APAP ALF are listed for transplant, but only 8% are transplanted.[5] Compared to patients who intentionally overdose on APAP, prognosis is poorer for patients with unintentional APAP ingestion.[29] Patients with ALF from DILI have worse prognosis than the APAP group. Only 27.1% of patients with ALF DILI recover spontaneously without LT.[9]

The prognosis for viral hepatitis depends on the virus. Patients who present with ALF from hepatitis A have a 55% to 69% spontaneous survival and an overall survival

of 88%.[10] The group with spontaneous survival was more likely in female than male and had higher ALT and Alk phos. Spontaneous survivors were also less likely to require blood pressure support, hemodialysis, or mechanical ventilation.[10] Serum ALT <2600 International units/L, creatinine >2.0 mg/dL, intubation, and pressor use were associated with transplant or death.[10] Of those with hepatitis A, 44% to 48% were listed for LT but only 19% to 31% were actually transplanted.[10] On the other hand, 77% of patients having ALF with hepatitis B are listed for LT and 50% to 62% have the surgery.[11,12] The ALF from hepatitis B has an overall survival of 67% to 69% and a spontaneous survival rate of 19% to 25%.[11,12]

Ischemic hepatitis, while an uncommon cause of ALF, generally has a high likelihood of spontaneous recovery with a 3-week spontaneous survival of 71%. Of the 51 patients included in 1 retrospective analysis of ALF from ischemic hepatitis, only 2% or 4% had an LT. Multivariate analysis found that advanced encephalopathy and elevated serum phosphate predicted adverse outcomes of transplant or death in 3 weeks.[34]

Mortality from *Amanita phalloides*, a rare cause of ALF, ranges from 10% to 30%.[35] A retrospective study from France found that development of diarrhea in less than 8 hours from ingestion was significantly associated with mortality. Most patients who died also had rapid deterioration and not all patients developed encephalopathy.[35]

Those who survive ALF, with or without LT, may have reduced quality of life compared to US population controls. A quality of life study from the ALFSG found that patients with ALF from APAP and had spontaneous survival were significantly more likely to report fair or poor general health and had more days of pain and depression than spontaneous survivors from non-APAP causes and LT recipients and the general public. They have been found to have similar quality of life scores but less likely to resume employment than LT recipients from cirrhosis.[94]

Conclusion

There are many etiologies of ALF, but currently DILI, especially from APAP, is the most common cause. Early diagnosis of ALF is essential and the underlying cause should be found, if possible since many etiologies have specific treatment. Acetylcysteine may be beneficial even in non-APAP cases. Due to the complexity of these patients, a multidisciplinary team is often needed to help care for them. Supportive care and, if needed, liver transplantation continues to be the gold standard of care.

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