Acute Liver Failure

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KEYWORDS

• Acute liver failure • Cerebral edema • Encephalopathy • *N*-acetylcysteine
• Liver transplantation • Extracorporeal liver support system • Liver dialysis

KEY POINTS

- Acute liver failure is a life-threatening condition of heterogeneous etiology.
- Outcomes are better with early recognition and prompt initiation of etiology-specific therapy, complex intensive care protocols, and urgent liver transplantation.
- Cerebral edema and intracranial hypertension (ICH) are reasons for high morbidity and mortality.
- Hypertonic saline is suggested for patients with high-risk for developing ICH and, when ICH develops, mannitol is recommended as a first-line therapy.

INTRODUCTION

Acute liver failure (ALF) is a rare but life-threatening condition. The most widely accepted definition includes the evidence of hepatic necrosis, coagulation abnormality (International Normalized Ratio $\geq$1.5), and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with a duration of illness of less than 26 weeks. Patients with Wilson disease, perinatally acquired hepatitis B virus (HBV), or autoimmune hepatitis may be included, despite the presence of underlying cirrhosis, if their disease has only been recognized for less than 26 weeks. It is important to appreciate that ALF is a distinct entity from an acute exacerbation of chronic liver disease (or acute-on-chronic liver failure). For instance, acute alcoholic hepatitis is not considered to be ALF. ALF can be further classified based on the time interval between the development of jaundice and encephalopathy[1–4] (**Table 1**). It should be noted that the onset of encephalopathy is often sudden, may precede jaundice, asterixis may be transient, and, unlike chronic liver disease, may be associated with agitation, changes in personality, delusions, and restlessness.[5]

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Table 1
Classification of acute liver failure

	Interval Between Onset of Encephalopathy from Jaundice	Common Etiologies	Clinical Presentation	Prognosis
Hyperacute	<7 d	APAP, HAV, ischemic	Cerebral edema common	Fair (survival without LT ~36%)
Acute	7–21 d	HBV, drugs	Cerebral edema less common	Poor (survival without LT ~14%)
Subacute	22 d to <26 wk	drugs, indeterminate	Cerebral edema rare; ascites, peripheral edema and renal failure more common	Very poor (survival without LT ~7%)

Abbreviations: APAP, acetaminophen; HAV, hepatitis A virus; HBV, hepatitis B virus; LT, liver transplantation.

Over the last 3 decades, ALF has evolved from a poorly understood condition with a near entirely fatal outcome, to one with a relatively well-characterized phenotype and disease course.[6,7] Complex intensive care protocols and urgent liver transplantation (LT), as well as specific therapy according to the etiology, have been used promptly as a standard of care for ALF. Accordingly, the overall and LT-free survival rates of patients with ALF have been improving through the past few decades and the majority of patients may now be expected to survive, particularly where LT is available.[6,8]

ETIOLOGY

The etiology of ALF varies greatly by country and also has changed over time.[9–11] Over the past few decades, the most common etiology of ALF has evolved, with hepatitis A and B on the decline in incidence, while acetaminophen (APAP) and other medications related ALF have been on the increase, at least in the United States and Western Europe.[6,9–11] In the United States and the UK, APAP overdose currently accounts for 45% to 60% of cases of ALF, with viral hepatitis and idiosyncratic drug reactions each accounting for 10% to 12% of cases.[6,9–11] Notably, the incidence of APAP overdose also varies among developed countries, because it accounts for only 3% to 9% of ALF in Spain and Germany, reflecting the differences in behavior and perhaps in the national regulatory system with regard to access to large doses of APAP.[12,13] By contrast, Asia Pacific countries have a higher incidence of ALF owing to hepatitis viruses, specifically hepatitis E virus in India and Pakistan, and HBV in Japan, Hong Kong, Thailand, as well as Australia, with fewer cases of APAP overdose being observed.[6,10,11,14]

Common and uncommon etiologies of ALF are listed in **Table 2**. Apart from the well-known causes of drug-induced ALF, several recently introduced agents (eg, tyrosine kinase inhibitors, monoclonal antibodies, dabigatran, rivaroxaban, lamotrigine, levetiracetam, pregabalin, venlafaxine, duloxetine, sertraline, darunavir, and maraviroc) and herbal supplements (eg, black cohosh, germander, chaparral, kava kava, Chinese herbs, and anthraquinones) have also been reported to cause ALF.[15,16] Important clinical characteristics, prognosis, and specific therapies of selected etiologies of ALF, including viruses,[17–24] medications,[25–27] autoimmune,[28,29] Wilson disease,[30]

Table 2
Etiology of acute liver failure

Infections	Viral hepatitis A, B, C, D, E Herpes simplex virus, varicella zoster virus Epstein-Barr virus, cytomegalovirus Tropical infections (eg, Dengue virus, leptospirosis, scrub typhus, malaria)
Drug and toxins	Acetaminophen Carbon tetrachloride Idiosyncratic drug reactions (eg, modern medications,[a] herbal supplements) Mushroom poisoning (eg, *Amanita phalloides*) Sea anemone sting
Ischemia	Ischemic hepatitis, hypoperfusion, cardiogenic shock Heat stroke Cocaine, methamphetamines, ephedrine, ecstasy
Vascular	Acute Budd-Chiari syndrome Sinusoidal obstruction syndrome
Miscellaneous	Autoimmune hepatitis Wilson disease Reye syndrome Malignant infiltration Acute fatty liver of pregnancy, eclampsia, HELLP syndrome Primary graft nonfunction after liver transplantation Indeterminate

Abbreviation: HELLP, hemolysis, elevated liver enzymes, low platelets.

[a] Isoniazid, rifampicin, pyrazinamide, sulfonamides, trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, dapsone, ketoconazole, ofloxacin, didanosine, efavirenz, allopurinol, diclofenac, halothane, isoflurane, phenytoin, valproic acid, nicotinic acid, statins, imipramine, propylthiouracil, disulfiram, lisinopril, labetalol, methyldopa, amiodarone, flutamide, metformin, etoposide, gemtuzumab.

mushrooms,[31–34] ischemia,[35] and Budd-Chiari syndrome,[36] are summarized in **Table 3**.[3,5,10,11] Indeterminate etiology, despite extensive workup, continues to be a sizable ALF group (12%–43% of cases), even in the Western world.[4,6,12]

DIAGNOSIS

A thorough medical history should be obtained and physical examination should be done promptly. A history of potential exposures to viral infections, drugs, herbs, and other toxins should be explored. If encephalopathy is present, the history may be unavailable or can only be provided by the family. Early testing should include routine chemistries, arterial blood gas, complete blood counts, blood typing, APAP level, screening for other drugs and toxins, viral serologies, tests for Wilson disease, autoantibodies, and a pregnancy test in females. Thus, testing for complications such as acute pancreatitis should also be performed[3,4] (**Box 1**).

APAP–protein adducts are released into blood during hepatocyte lysis and the concentration of adducts in the serum has been noted to correlate with the degree of APAP hepatotoxicity. Thus, it may be a rapid and useful diagnostic test for ALF of unknown cause or unclear history, and for patients who present more than 1 day after APAP overdose.[25,37,38] Interestingly, up to 19% of indeterminate cases in the US Acute Liver Failure Study Group (US-ALFSG) study demonstrated adducts in serum suggesting that unrecognized APAP toxicity caused or contributed to ALF in these patients.[39] Liver biopsy, most often done via the transjugular route, is generally not recommended in the setting of ALF.[40,41] It is indicated only when certain conditions such

Table 3
Clinical characteristics, prognosis and specific therapy of selected etiologies of ALF

Etiologies	Clinical Characteristics	Prognosis of ALF	Specific Therapy
Hepatitis A	• Lives in or traveled to endemic area • Ingestion of contaminated food and water, particularly shellfish • ALF develops in ~0.35% of acute hepatitis A (more common in older patients and those with preexisting liver disease)	• Mortality ~40% without LT	• Not available
Hepatitis B	• Lives in or traveled to endemic area • Known or unknown HBV, recovered HBV infection and exposed to immunosuppressant, B-cell–depleting agents, and cancer chemotherapy • ALF develops in 0.4%–4% of acute hepatitis B	• Mortality >60%–80% without LT (higher mortality if reactivated by immunosuppressive therapy, B-cell–depleting agents, and cancer chemotherapy)	• Nucleos(t)ide analogues (preferably entecavir or tenofovir)
Hepatitis E	• Lives in or traveled to endemic area • Ingestion of contaminated water in endemic areas • ALF develops in 0.2%–0.5% of acute hepatitis E (increased dramatically to 15%–25% in pregnant women, particularly in the third trimester)	• Mortality 45% without LT (better prognosis compared with other etiologies of ALF in India)	• Not available
APAP	• Ingestion of APAP >7.5–10 g (4–10 g in high-risk population; eg, alcoholics, cirrhotics, taking CYP2E1 inducers) • Marked elevation of ALT (often >3000 IU/L and AST > ALT), starts increasing 24–36 h after overdose • Relatively low level of bilirubin • Early metabolic acidosis and elevated lactate • ARF (10%–50%) and pancreatitis (0.3%–5%) may develop	• More favorable outcomes compared with other causes of ALF, but it still has a high mortality (~30%) • Low phosphate may be seen as a good prognostic maker (but replacement is required)	• NAC IV: 150 mg/kg load, then 12.5 mg/kg/h × 4 h, then 6.25 mg/kg/h • Activate charcoal if presented within 4 h after ingestion

Non-APAP DILI	• Exposures to certain medications or herbs (in the United States, the most common implicated agents were antimicrobials) • More often in older patients • Latent period typically 4 d to 8 wk • Hypersensitivity reactions may be present in more than one-third of patients) • May have subacute clinical course mimicking cirrhosis	• Mortality ~70% without LT • CAM-induced ALF is associated with higher rates of LT and lower LT-free survival compared with prescription medicine	• Discontinuation of suspicious agent(s) • Corticosteroids may be of benefit in selected patients with hypersensitivity reactions
Autoimmune hepatitis	• Often subacute presentation • Young or middle-age women • High serum gamma-globulins • Positive serum autoantibodies	• Mortality >50% without LT	• Prednisolone 40–60 mg/d and discontinue in 7–10 d if no improvement (in the context of ALF, steroids are often ineffective and may favor septic complications)
Wilson disease	• Child or young adults • Coombs-negative hemolytic anemia • Rapid progression to renal failure • Relative mild rises in ALT (often AST > ALT) • Normal or subnormal ALP (typically <40 IU/L) • TB (mg/dL)/ALP (IU/L) ratio >2	• Usually fatal without LT	• LT must be promptly considered • Albumin dialysis, hemofiltration or plasmapheresis may lower serum copper and limit further hemolysis • D-Penicillamine is not recommended in ALF
Mushroom poisoning	• Ingestion of wild mushroom, mainly *Amanita phalloides, A verna, A virosa* • Preceded by muscarinic effects, such as profuse sweating, vomiting and diarrhea within 6–12 h after ingestion, then clinical hepatotoxicity often develops after 24–48 h	• Mortality 30%–60% without LT • LT should be strongly considered if interval between ingestion and diarrhea <8 h, PT index[a] <10% or PT index <25% + Cr ≥1.2 mg/dL from d 3–4 after ingestion	• Penicillin G: 1 g/kg/d IV • Silibinin 5 mg/kg IV q4h • NAC (as for APAP)
Herpes simplex virus	• Immunocompromised host and pregnant women (but can also occur in normal host) • Classic triad: high fever, leukopenia, marked elevation of ALT • Mucocutaneous vesicles present in ~50%	• 74% progressed to death or LT (51% in acyclovir-treated patients and 88% in untreated patients)	• Acyclovir: 5–10 mg/kg IV q8h

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Table 3
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Etiologies	Clinical Characteristics	Prognosis of ALF	Specific Therapy
Epstein-Barr virus	• Young adults • 25% immunosuppressed • Classical symptoms of infectious mononucleosis may not be present • 50% have cholestatic injury	• Mortality 50%–75% without LT	• Antiviral agents (eg, acyclovir, ganciclovir, famciclovir) • Corticosteroids
Ischemic hepatitis	• Associated with cardiac or pulmonary disease (~30% of patients) • Cardiopulmonary precipitant was identified in 70% • Marked elevation of ALT (>1000 IU/L; AST > ALT), increased LDH and Cr; with normalization soon after stabilization of hemodynamic instability	• Mortality ~30% without LT • Higher serum phosphate and grade 3 or 4 encephalopathy are associated with poor outcomes	• Optimizing hemodynamic status and cardiopulmonary conditions
Budd-Chiari syndrome	• 84% female • 63% have hypercoagulable state • Abdominal pain, hepatomegaly, ascites • AST/ALT ratio >1 • Diagnosis: Doppler ultrasound imaging (loss of hepatic venous signal of reverse flow in PV), computed tomography, MRI	• Mortality 50%–60% even with the availability of LT • Higher peak ALT and Cr are associated with poorer outcomes	• Early anticoagulation followed by TIPS and/or LT
Malignant infiltration	• Common malignancies are lymphoma, leukemia, breast and colon cancer • History of cancer (75% for breast cancer, but only 10% for lymphoma or leukemia) • Massive hepatomegaly • Elevated ALP and/or other tumor markers • About 50% have liver mass on imaging • Liver biopsy may be required for diagnosis	• Near 100% mortality (90% died within 3 wk)	• Chemotherapy

Abbreviations: ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APAP, acetaminophen; ARF, acute renal failure; AST, aspartate aminotransferase; CAM, complementary and alternative medicines; Cr, creatinine; DILI, drug-induced liver injury; HBV, hepatitis B virus; IV, intravenous; LDH, lactate dehydrogenase; LT, liver transplantation; NAC, *N*-acetylcysteine; PV, portal veins; TIPS, transjugular intrahepatic portosystemic shunt.

[a] PT index; prothrombin time control plasma/prothrombin time patient plasma] × 100.

Box 1
Initial laboratory tests in patients with acute liver failure

- Chemistries: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, albumin, creatinine, blood urea nitrogen, lactate dehydrogenase, creatinine kinase
- Urine output (hourly)
- Complete blood count, blood type and screen
- Prothrombin time, International Normalized Ratio, fibrinogen
- Arterial blood gas
- Arterial lactate
- Ammonia (arterial if possible)
- Acetaminophen level, toxicology screen
- Viral hepatitis serologies: anti-hepatitis A virus IgM, hepatitis B surface antigen, anti-hepatitis B core antigen IgM, anti-hepatitis E virus,[d] anti-hepatitis C virus, hepatitis C virus RNA[a], herpes simplex virus-1 IgM, varicella zoster virus
- Ceruloplasmin level[b]
- Pregnancy test (females)
- Autoimmune markers: antinuclear antibody, anti-smooth muscle antibody, anti-soluble liver antigen, anti-neutrophil cytoplasmic antibody, immunoglobulin levels
- Human immunodeficiency virus-1, human immunodeficiency virus-2[c]
- Amylase and lipase
- Tests for tropical infections[d]

[a] Done to recognize potential underlying infection.
[b] Done only if Wilson disease is a consideration (eg, in patients <40 years without another obvious explanation for acute liver failure [ALF]); in this case, the uric acid level and bilirubin to alkaline phosphatase ratio and serum copper may be helpful as well. Ceruloplasmin may be falsely low in non-Wilson ALF owing to massive hepatic necrosis or may be increased owing to it being an acute phase reactant. Because Wilson disease has a low prevalence in the ALF population, there is a great likelihood that any test for Wilson disease would have a high negative predictive value but a low positive predictive value.
[c] Implications for potential liver transplantation.
[d] If clinically indicated.
Data from Lee WM, Stravitz, Larson AM. AASLD position paper: the management of acute liver failure: update 2011. The American Association for the Study of Liver Diseases. Available at: https://www.aasld.org/sites/default/files/guideline_documents/alfenhanced.pdf and European Association for the Study of the Liver. J Hepatol 2017;66(5):1047–81.

as autoimmune hepatitis, metastatic liver disease, lymphoma, or herpes simplex virus are suspected.[3] Liver histology also could predict the outcomes in ALF, because greater than 50% hepatocyte necrosis is associated with a 3-fold higher mortality.[40,41] Liver imaging studies may disclose malignant infiltrations or Budd-Chiari syndrome, but are seldom definitive.

PROGNOSTIC FACTORS AND SCORING SYSTEM

It is well-known that ALF is a severe and life-threatening condition, and the chance of spontaneous recovery is variable according to the presentation and etiology. A

number of factors influence survival of patients and one of the most important predictors of outcome is the etiology of ALF: LT-free survival is greater than 50% for ALF associated with APAP, hepatitis A, ischemia, and pregnancy, compared with less than 25% for other causes.[5,42] In addition, the severity of encephalopathy also impacts survival significantly (spontaneous recovery: 65%–70% with grade 1 or 2, 40%–50% with grade 3, and <20% with grade 4 encephalopathy).[5,43] Those who survive rarely develop cirrhosis. Two-year outcomes in initial survivors are generally good, but non-APAP patients have a significantly lower survival (75.5% compared with 89.5% in APAP overdose survivors), which may be related to preexisting medical comorbidities.[44] In contrast, spontaneous survivors with APAP overdose experience substantial morbidity during follow-up from ongoing psychiatric and substance abuse issues.[44]

LT is the only life-saving procedure for some patients with ALF. Identifying the right patient for LT in a timely manner is vital and therefore several prognostic scoring systems have been developed. The Kings College Criteria (KCC) was the first validated scoring system (introduced in 1989) and is currently the most widely used prognostic tool for ALF (**Table 4**). It has good specificity (82%–94%), but has limited sensitivity (68%–82%).[5,43,45,46] The positive predictive values are reasonable (70%–90%), but negative predictive values are variable (25%–90%). Therefore, a significant number of patients who do not fulfill the KKC will eventually die without LT.[5,43,45,46] In addition, the KCC performs best in groups with high-grade encephalopathy and in historically earlier studies suggesting that modern medical management of ALF may modify performance of KCC because its sensitivity was reduced in studies published after 2005 (46%–71%) compared with studies before 1995 (76%–82%).[46] Arterial blood lactate greater than 3.5 mmol/L is an early predictor of mortality in APAP-associated ALF (sensitivity 67%, specificity 95%, positive predictive value 79%, negative predictive value 91%) and may increase the predictive accuracy of the KCC.[47]

Other prognostic systems for ALF have been proposed including the Model for End-stage Liver Disease (MELD) score,[48] Clichy criteria,[49–51] and Acute Physiology and Chronic Health Evaluation II score.[52] In a systematic analysis of the MELD score in ALF, 526 patients with ALF from 6 studies (all did not have LT support, which may not be a good representation of the Western populations) were included and overall

Table 4
King's College criteria

Acute liver failure owing to acetaminophen	• Arterial pH <7.3 or lactate >3 mmol/L after adequate fluid resuscitation and >24 h since ingestion • All 3 following criteria: ○ Grade III or IV encephalopathy ○ Serum creatinine >3.4 mg/dL (>300 μmol/L) ○ INR >6.5 (PT >100 s)
Acute liver failure not owing to acetaminophen	• INR >6.5 (PT >100 s) • 3 out of 5 following criteria: ○ Unfavorable etiology: indeterminate, Wilson disease, idiosyncratic drug reaction ○ Age <10 y or >40 y ○ Jaundice for >7 d before development of encephalopathy ○ Bilirubin >17 mg/dL (>300 μmol/L) ○ INR >3.5 (PT >50 s)

Abbreviations: INR, International Normalized Ratio; PT, prothrombin time.

304 died (58%). By using a MELD score cutoff of 30.5 to 35, the pooled sensitivity was 77% (95% CI, 72%–82%) and specificity was 72% (95% CI, 62%–80%). The positive likelihood ratio was 2.76 (95% CI, 1.97–3.87) and negative likelihood ratio was 0.31 (95% CI, 0.25–0.40).[41] The differences between KKC and MELD are slight, although it seems that the KCC is more specific and the MELD score is more sensitive.[40,41] Accordingly, the American Gastroenterological Associates suggests using the MELD score rather than the KCC as a prognostic scoring system in patients presenting with ALF (a cutoff MELD score of 30.5 should be used for prognosis and higher scores predict a need for LT).[40] A more recent European Association for the Study of the Liver guideline recommends that LT be considered in those patients fulfilling either the KCC or Clichy criteria.[4] A factor V level of less than 20% may indicate a poor prognosis necessitating consideration of LT in patients of 30 years of age or younger, and a higher threshold of less than 30% is of equivalent significance in older patients.[49–51] Recently, by using data from the US-ALFSG, a logistic regression model to predict LT-free survival has been developed using admission variables include hepatic encephalopathy (HE) grade, ALF etiology, vasopressor use, bilirubin, and International Normalized Ratio.[53] In the validation cohort, this model was noted to be superior to KCC and MELD, with a c-statistic value of 0.84, 66.3% accuracy, 32.5% sensitivity, and 95.3% specificity; however, external validations are required.[53]

Apart from these scoring systems, other serum laboratory parameters (eg, alfa-fetoprotein,[54] Gc-globulin,[55] phosphate,[56] galectin-9,[57] procoagulant microparticles,[58] soluble CD163,[59] and liver-type fatty acid binding protein[60]) and etiology-specific prognostic systems (eg, hepatitis A virus,[20] idiosyncratic drug reaction,[61,62] Wilson disease,[30] autoimmune hepatitis,[29] and *Amanita phalloides* poisoning[31,32]) for predicting outcomes in ALF have also been proposed.[10]

MANAGEMENT

ALF is considered a “hepatology emergency” in that early discussion with a transplant team and/or rapid transfer to an experienced center that has LT availability is advisable once a patient is stabilized. Acute onset of jaundice and elevated transaminases and prolonged International Normalized Ratio, but without encephalopathy, is acute liver injury and not ALF. Most patients with APAP-associated acute liver injury recover, whereas patients with non–APAP-associated acute liver injury more readily may evolve on to ALF.[63] Levels of alanine aminotransferase do not necessarily correlate with the severity of liver injury and do not have to be markedly elevated in ALF (particularly in ALF related to acute fatty liver of pregnancy and Wilson disease), and International Normalized Ratio, bilirubin, and severity of HE are the key indicators of clinical severity.[4] Certain etiologies of ALF may require specific therapies promptly (see **Table 3**). Given the severity and rarity of the disease, most of these interventions have not been evaluated in a well-designed study, and the use of them is often based on the basis of pathogenesis, studies in animals, or in patients without ALF. Therefore, the true benefit of these interventions in patients with ALF is unclear, recognizing that patients with ALF can spontaneously recover.

Because ALF often leads to infections and multiple organ failures, admission to the intensive care unit should be considered as early as possible, especially when HE and/or coagulopathy is progressing. Careful monitoring and general management to prevent and treat infections and the use of organ support systems, where applicable and available, are very important and should follow the principles as in generally critically ill patients, but with some special considerations (**Table 5**).[3,64–66] Of note, an easy-to-

Table 5
Intensive care unit management of ALF

Cerebral edema and intracranial hypertension	Grade I/II encephalopathy • Consider transfer to liver transplant facility and listing for transplantation • CT brain: rule out other causes of altered mental status • Avoid stimulation; avoid sedation if possible • Lactulose, possibly helpful Grade III or IV encephalopathy • Continue management strategies listed above • Intubate trachea (may require sedation) • Elevate head of bed (~30°) • Consider placement of ICP monitoring device in selected cases • Immediate treatment of seizures required; prophylaxis of unclear value • Mannitol (0.25–1 g/kg IV bolus): use for severe elevation of ICP or first clinical signs of herniation • Hypertonic saline to increase serum sodium to 140–150 mmol/L • Hyperventilation: effects short lived; may use for impending herniation
Infections	• Surveillance for and prompt antimicrobial treatment of infection required (low threshold for empiric antibiotics if hemodynamic deterioration and/or increasing encephalopathy with inflammatory phenotype) • Antibiotic prophylaxis possibly helpful but not proven • Antifungal coverage for patients not responding to broad spectrum antibiotics and with infection/sepsis physiology
Bleeding and coagulopathy	• Vitamin K (10 mg IV or SC): give at least 1 dose • FFP: give only for invasive procedures or active bleeding • Cryoprecipitate: for fibrinogen <100 mg/dL and bleeding • Platelets: give only for invasive procedures or active bleeding • Hemoglobin target for transfusion is 7 g/dL • Recombinant activated factor VII (40 μg/kg bolus): possibly for invasive procedures (expensive and has a risk of thrombosis) • Prophylaxis for stress ulceration: give PPI or H2RA (consider stopping prophylaxis when feeding has been established)
Hemodynamics and renal failure	• Volume replacement • Vasopressor support (norepinephrine is the vasopressor of choice) as needed to maintain adequate MAP (target MAP ≥60–75 mm Hg) • Vasopressin or terlipressin recommended in hypotension refractory to volume resuscitation and norepinephrine (but should be used cautiously in patients with ICH) • Hydrocortisone therapy does not reduce mortality, but does decrease vasopressor requirements in patients with vasopressor resistant shock • Avoid nephrotoxic agents • Continuous modes of hemodialysis if needed
Pulmonary	• Sedation for endotracheal intubation and suctioning to prevent increased ICP • Ventilator management: tidal volumes 6 mL/kg, low PEEP
Metabolic Concerns	• Follow closely: glucose, potassium, magnesium, phosphate, lactate, blood gas • Glucose infusions (10%–20%): glycemic target ~140 mg/dL • Consider nutrition: enteral feedings if possible or total parenteral nutrition

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Table 5 (*continued*)	
Extracorporeal liver support systems	• Should only be used in selected patients or within the context of a clinical trial • MARS and high-volume plasma exchange have been most studied in ALF

Abbreviations: ALF, acute liver failure; CT, computed tomography; FFP, fresh-frozen plasma; H2RA, histamine-2 receptor antagonists; ICH, intracranial hypertension; ICP, intracranial pressure; IV, intravenous; MAP, mean arterial blood pressure; MARS, molecular adsorbent recirculating system; PEEP, positive end-expiratory pressure; PPI, proton-pump inhibitors; SC, subcutaneously.

Data from Lee WM, Stravitz, Larson AM. AASLD position paper: the management of acute liver failure: update 2011. The American Association for the Study of Liver Diseases. Available at: https://www.aasld.org/sites/default/files/guideline_documents/alfenhanced.pdf and European Association for the Study of the Liver. J Hepatol 2017;66(5):1047–81.

use checklist for the management of ALF in the intensive care unit developed by the US-ALFSG is helpful and has been accepted by several centers in North America.[67]

Specific Treatment According to the Etiology

N-acetylcysteine (NAC), a glutathione precursor, is an established antidote for APAP poisoning and should be administered in all patients with APAP hepatotoxicity and APAP-induced ALF, and in those at significant risk for developing hepatotoxicity (based on the amount of APAP ingestion and/or serum APAP levels). Intravenous NAC has shown to improve LT-free survival by 20% to 30% among patients with APAP-induced ALF.[68,69] Apart from detoxifying *N*-acetyl-para-benzoquinoneimine, an intermediate metabolite of APAP, the potential mechanisms of NAC in this state include improving hepatic perfusion and oxygen delivery, scavenging reactive oxygen and nitrogen species, and refining mitochondrial energy production.[25] Intravenous administration (loading dose is 150 mg/kg in 5% dextrose over 15 minutes; maintenance dose is 50 mg/kg given over 4 hours followed by 100 mg/kg administered over 16 hours or 6 mg/kg/h) is recommended for patients with ALF. About 10% to 20% of patients may develop some side effects, such as nausea, vomiting, and anaphylactoid reactions.[3,25] Controversy exists over when to stop the use of NAC; whether a standard 72-hour period is optimal or continuation until liver chemistry values have improved is preferred.[3] The European Association for the Study of the Liver experts suggest that the use of NAC be limited to a maximum duration of 5 days, given its antiinflammatory effects, which are unlikely to be impacted and, further, may increase risk of infections in the later phase of ALF.[4]

The role of NAC for non–APAP-associated ALF has also been evaluated. In an randomized, controlled trial of intravenous NAC for non–APAP-associated ALF (n = 173), NAC did not improve LT-free survival at 3 weeks. However, a subanalysis revealed improved LT-free survival in 114 patients with early stage encephalopathy (grades I or II; 52% compared with 30% for placebo; $P = .01$).[70] In contrast, a multicenter, observational study of 155 patients with non–APAP-associated ALF from Egypt (85 were given NAC; 70 were not) reported that NAC significantly reduced mortality (LT-free survival: 96.4% vs 23.3%; $P<.01$), need for LT, and encephalopathy.[71] In a randomized, controlled trial in non–APAP-associated ALF in pediatric patients (n = 184), NAC did not improve 1-year survival and, in addition, noted a lower LT-free survival among those less than 2 years of age.[72]

Corticosteroids have been proposed as a potential therapeutic intervention for patients with ALF owing to autoimmune hepatitis, hypersensitivity drug reaction, and Epstein-Barr virus based on a presumed immune-mediated pathogenesis.[21,29,73,74]

In a retrospective analysis of 361 patients with ALF (66 with autoimmune etiology, 164 with indeterminate etiology, and 131 with drug-induced ALF) in the US-ASLFG from 1998 to 2007, corticosteroid use was not associated with improved overall survival (61% vs 66%; $P = .41$), nor with improved survival in any diagnosis category. Further, the use of corticosteroid was associated with diminished survival in those with very high MELD score (>40; survival of 30% vs 57%; $P = .03$).[75] Despite the lack of demonstrable benefit of anti-HBV therapy in the US-ALFSG HBV-induced ALF cohort, potent nucleos(t)ide analogues should be strongly considered in all patients with HBV-induced ALF (also impending ALF), particularly in LT candidates. Viral suppression may potentially help recovery and, if LT is necessary, it likely will prevent HBV recurrence after grafting.[76,77]

Hepatic Encephalopathy and Cerebral Edema

Cerebral edema (CE) and intracranial hypertension (ICH) have long been recognized as cardinal features and major causes of death in ALF (brainstem herniation). These manifestations may also contribute to ischemic and hypoxic brain injury, which may result in long-term neurologic deficits in survivors.[3] The incidence of CE and ICH has been decreasing over the time and may reflect improvements in the preventive care and use of early LT. However, once CE has developed in ALF, it is still associated with very poor survival and thus complex critical care management is required.[6,9]

The pathogenesis of CE and ICH in ALF is multifactorial and includes hyperammonia (causing accumulation of glutamine within astrocytes, which leads to an osmotic stress and cytotoxic edema), loss of cerebrovascular autoregulation, neuroinflammation, systemic inflammatory response syndrome, disruption of the blood–brain barrier (causing vasogenic edema), endothelial dysfunction, and other contributing causes (eg, metabolic disturbances, medications, and hypoxia).[3,6,78,79] The strong risk factors for CE and ICH in ALF are severity of HE (ICH in 25%–35% with HE grade III and >65%–75% with HE grade IV) and duration of illness (highest with hyperacute liver failure where >70% developed ICH).[3,5,80] Other risk factors include female gender, young age, acute renal failure, and requirement for vasopressors and renal replacement therapy.[3,9,81] Blood ammonia levels, preferably arterial, may also be helpful; levels greater than 150 to 200 μmol/L have been shown to correlate with CE and ICH, whereas levels less than 75 μmol/L may preclude the development of severe HE or ICH.[81,82] The blood sample should be drawn without using a tourniquet and transported within 20 minutes of the blood draw on ice.[83]

CE and ICH should be suspected clinically in patients with ALF with new-onset systemic hypertension, bradycardia, progression of hyperventilation and encephalopathy, alterations in pupillary and oculovestibular reflexes, myoclonus, or decerebration.[3,79,80] However, most of these clinical signs are not specific or sensitive and may evolve in patients even in those with grade IV HE and without ICH.[80] Non–contrast-enhanced computed tomography scanning is often performed mainly to exclude intracranial pathology, particularly bleeding. Features of CE with or without signs of herniation may be observed on computed tomography scans (**Fig. 1**); however, the absence of these findings does not exclude CE and ICH, especially at the early stages.[3,79,80]

The use of intracranial pressure (ICP) monitoring devices in patients with ALF remains controversial, and practices vary widely among centers. A survey performed among 24 LT centers in the US-ALFSG revealed that ICP monitoring device was used in 92 of 322 patients (28%) with ALF and severe HE from 1998 to 2004. Intracranial hemorrhage occurred in 10.3% (one-half of these complications were incidental radiologic findings) and the 30-day survival after LT was similar in both the monitored

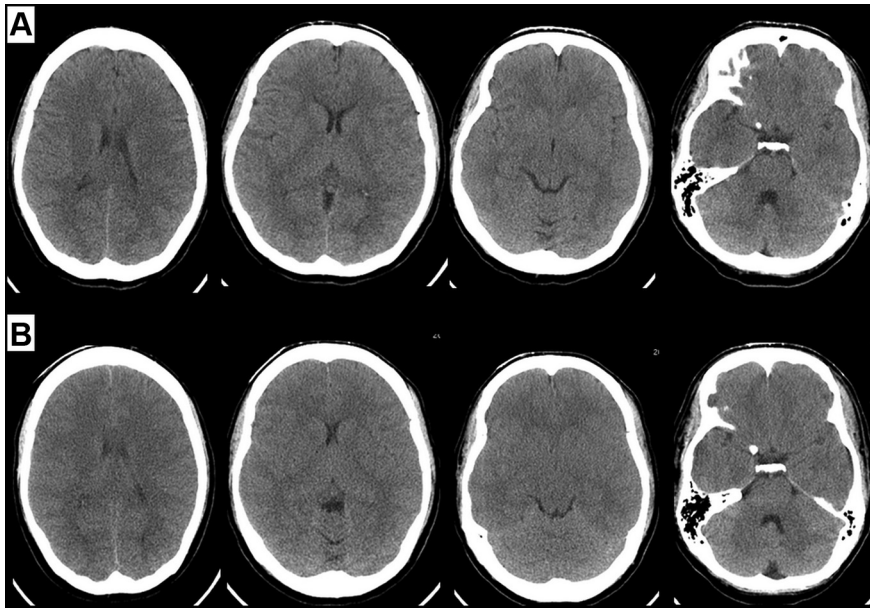

Fig. 1. (*A*) Computed tomography (CT) scan of the brain of a patient with acute liver failure and grade III encephalopathy showed mild cerebral edema with loss of sulci and gyri, blurring of grey-white junctions and mild narrowing of ventricles. (*B*) CT of the brain of the same patient (5 days later) showed progression of cerebral edema and impending brain herniation.

and the nonmonitored cohorts (85% vs 85%).[84] In Europe, there has been heterogeneity in the use of ICP monitoring in ALF; greater than 60% at King's College Hospital, 20% to 30% in Birmingham (UK) and Copenhagen, approximately 16% in Spain, and usually not used in France.[85] The main rationale for monitoring ICP is to allow assessment of cerebral perfusion pressure (CPP; calculated as the mean arterial pressure [MAP] minus the ICP), to avoid cerebral hypoperfusion during ICH by targeting CPP at greater than 60 mm Hg and ICP to less than 20 mm Hg either by administering osmotically active agents and/or vasopressors.[3] In addition, refractory ICH and/or decreased CPP may be considered relative contraindications for LT because of concern about poor neurologic recovery.[3,85] The European Association for the Study of the Liver guideline recommends that invasive ICP monitoring be considered in highly selected subgroup of patients with grade III or IV coma, who are mechanically ventilated and deemed at high risk of ICH based on the presence of more than 1 of the following criteria: (1) young patients with hyperacute or acute ALF, (2) an ammonia level greater than 150 to 200 μmol/L that does not decrease with initial treatment interventions, (3) renal impairment, and (4) vasopressor support (>1.0 μg/kg/min).[4] Noninvasive assessments of ICP and CPP, such as transcranial Doppler ultrasonography,[83,86] ocular ultrasonography,[83,87] and near-infrared spectrophotometry,[88] have also been evaluated in patients with ALF, but their use is center specific and guidelines on their use consistently across various centers have not been harmonized.

Patients with mild HE may benefit with lactulose as suggested in a retrospective study from the US-ALFSG (increased median survival time from 7 to 15 days while awaiting LT without changes in mortality or need for LT).[89] Caution is to be exercised in the overuse of lactulose because the pathogenic mechanisms of HE differ in ALF

from those with chronic liver disease; further overuse may lead to bowel dilation challenging the LT procedure. A double-blind, randomized, controlled trial included 201 patients with ALF (mainly owing to hepatitis E virus) demonstrated that L-ornithine L-aspartate infusion did not lower ammonia, or improve the level of consciousness or survival.[90]

As patients progress to grade III or IV encephalopathy, intubation and mechanical ventilation are mandatory.[3] Small doses of propofol may be used for sedation because it may reduce cerebral blood flow. As prophylactic measures to reduce the risk of development of ICH, patients should be positioned with the head elevated at 30°, and stimulation and pain should be minimized.[3] If ICH develops, either as seen on ICP monitoring or by obvious neurologic signs, osmotic agents such as mannitol are often effective in decreasing ICH by creating a gradient across the blood–brain barrier that forces water movement from the edematous brain to the intravascular space. Mannitol has been shown in small series to correct episodes of elevated ICP in patients with ALF, and also to improve survival (supported by a randomized, controlled trial).[3,80,91] However, its effect is short lived, and may not be effective for patients with severe ICH (ICP >60 mm Hg).[3,64,80,91] The dose may be repeated as needed if the serum osmolality is less than 320 mOsm/L. Potential adverse events are hyperosmolarity, hypernatremia, and volume overload for which the patients be closely monitored.[3] Hyperventilation to a $Paco_2$ of 25 to 30 mm Hg restores cerebrovascular autoregulation, resulting in vasoconstriction and reduction of ICP. If severe ICH is not controlled with mannitol, hyperventilation may be instituted acutely to delay impending herniation.[3,64,80] However, the effect of hyperventilation on cerebral blood flow is transient and there has been some concern that vasoconstriction may cause cerebral hypoxia. A randomized, controlled trial of prophylactic continuous hyperventilation in patients with ALF revealed no reduction in the incidence of CE and ICH and no survival benefit, although onset of cerebral herniation seemed to be delayed in the hyperventilated group.[92]

Based on studies in patients with traumatic brain injury, hypertonic saline boluses have been found to have a similar or even superior efficacy to mannitol.[93,94] In a randomized, controlled trial of patients with ALF and grade III or IV encephalopathy (n = 30), prophylactic induction of hypernatremia (aim for serum sodium of 145–155 mEq/L for 72 hours) with 30% hypertonic saline reduced the incidence and severity of ICH compared with normonatremic standard of care.[95] Although a survival benefit with induced hypernatremia was not demonstrated, the American Association for the Study of Liver Diseases Practice Guideline recommends the use of hypertonic saline as a prophylactic measure in patients at greatest risk of developing CE and ICH.[3] However, serum sodium greater than 150 mmol/L may be associated with cell damage and should be avoided. Therefore, hypertonic saline infusions should be targeted to maintain serum sodium at 140 to 145 mmol/L.[4] There has been no study that evaluated hypertonic saline as a treatment for established ICH in ALF. Therapeutic hypothermia (cooling to core temperature of 33°C–34°C) may prevent or control ICH in patients with ALF, but its potential harmful effects include increased risk of infection, coagulation disturbance, arrhythmias, and reduced liver regeneration.[3,96] Although 2 uncontrolled studies from the UK suggested some benefits of hypothermia in ALF,[97,98] a subsequent randomized, controlled trial of moderate hypothermia in patients with ALF and grade III or IV encephalopathy (n = 46) found no benefit on improving survival or preventing ICH.[99] Similarly, a retrospective analysis from the US-ALFSG (97/1232 patients received therapeutic hypothermia) found no survival benefit from moderate hypothermia, although a survival benefit was observed in young patients (<25 years of age) with APAP-associated ALF.[100]

In situations where the patient has cerebral hyperemia and signs of ICH persist despite mannitol and hypertonic saline, a bolus of intravenous indomethacin may be considered.[4,101]

Seizures increase ICP and should be controlled promptly with short-acting benzodiazepines plus phenytoin or levetiracetam. Although seizure activity in patients with ALF can be subclinical, the prophylactic use of phenytoin is not recommended currently, because available randomized, controlled trials have shown conflicting results.[102,103]

Infections

Patients with ALF have an increased susceptibility for infections as a result of excessive systemic inflammation, mainly from cytokine storm, multiple organ dysfunction, and functional immunoparesis, particularly impaired function of leukocytes, macrophages, and complement systems.[104,105] Risks of infection are further amplified by the presence of indwelling lines, catheters, and tubes.[104,105] Microbial infections have been documented in up to 80% of ALF cases; approximately 50% pneumonia, 15% to 26% bacteremia, and approximately 30% fungal infections (mainly candidiasis).[106–108]

The classic signs of infection such as fever and leukocytosis, however, can be absent in up to 30% of patients with ALF.[105,108] In addition, although serum procalcitonin seems to be a helpful assay for detecting bacterial infections in general, there has been poor discrimination between patients with ALF with or without bacterial infection, presumably because of the massive liver injury.[109] Sepsis leads to negative outcomes among patients with ALF. Bacteremia and systemic inflammatory response syndrome are associated with an increased severity of HE, coagulopathy, and renal failure.[105] Sepsis can affect the outcome of LT adversely, and increases mortality in patients with ALF, with the reported attributable mortality ranging from 10% to 52%.[105–107]

Although prophylactic antimicrobial therapy reduces the incidence of infection in certain groups of patients with ALF, prophylactic antibiotics and antifungals have not been shown to improve overall outcomes in ALF and, therefore, cannot be advocated in all patients, particularly those with mild HE.[3,105,106] Strict implementation of infection prevention control measures and periodic surveillance for infections (eg, chest radiography and periodic cultures of sputum, urine, and blood for fungal and bacterial organisms) should be undertaken. Antibiotics should be initiated promptly based on surveillance culture results, or at the earliest clinical signs of active infection or clinical deterioration.[3,4,105]

Acute Kidney Injury

AKI develops in 56% to 70% of patients with ALF and has been associated with decreased short-term and long-term overall survival.[110,111] AKI is often multifactorial, and is more common with certain etiologies, including ischemic hepatitis, Wilson disease, acute fatty liver of pregnancy, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, heat stroke, hepatitis A virus, *Amanita* poisoning, or hepatotoxicity owing to APAP, phenytoin, trimethoprim–sulfamethoxazole, or macrolides.[64,111] Most patients with ALF with AKI fully recover renal function either after LT or spontaneously.[4] Renal replacement therapy is required in approximately 30% of cases and the classic indications including severe acidosis, hyperkalemia, and/or fluid overload. Additional indications include the removal of toxic substances, and difficult to treat hyponatremia or hyperthermia.[64,110] Continuous modes of renal replacement therapy are preferred because they have been shown in a randomized, controlled trial to result

in improved stability in cardiovascular and intracranial parameters compared with intermittent modes.[3,4,112]

Extracorporeal Liver Support Systems

The rationale for using an extracorporeal liver support system (ELSS) in ALF is to help maintain homeostasis while the liver regenerates or until an organ is available for LT. Several strategies have been developed to remove toxins and maintain biosynthesis, which can broadly be divided into artificial and bioartificial liver support systems.[64,113] Artificial support systems are cell-free systems that can be subdivided further into conventional extracorporeal procedures (eg, hemodialysis, hemofiltration, plasmapheresis, and hemodiabsorption) and albumin dialysis (eg, molecular adsorbent recirculating system [MARS], single pass albumin dialysis, or fractionated plasma separation and adsorption [Prometheus; Fresenius Medical Care, Bad Homburg vor der Höhe, Germany]). Bioartificial systems incorporate hepatocytes, with or without the artificial systems described, include the extracorporeal liver assist device, which uses aggregates from C3a hepatoma cell lines, and HepatAssist (AirBios Systems, Inc, Waltham, MA), which uses porcine hepatocytes together with a charcoal column.[41,113]

Among several techniques reported, only 2 artificial ELSS have been studied in ALF with well-designed randomized, controlled trials, namely MARS and high-volume plasma exchange (HVP). In a randomized, controlled trial in France (n = 102), MARS has not been shown to improve 6-month survival in ALF (75.5% with conventional treatment vs 82.9% with MARS in the per-protocol population; P = .50). However, a confounder may have been the short median listing to LT time, which was only 16 hours (75% of enrolled patients underwent LT within 24 hours).[114] A recent metaanalysis of 11 trials (n = 781 patients) evaluating ELSS in ALF and acute-on-chronic liver failure showed a statistically significant improvement in overall survival (relative risk [RR], 0.86; 95% CI, 0.74–1.00).[41] When focusing on ALF (7 trials involving 415 patients), there was no improvement in survival in the artificial support system group (RR, 0.86; 95% CI, 0.70–1.06).[20,30–34] Five randomized, controlled trials reported that adverse events were similar between the ELSS and usual care, but 1 randomized, controlled trial found that 2 of 12 patients randomized to an extracorporeal liver assist device withdrew owing to fever and bleeding.[41,115] In a post hoc analysis looking at trials within the past 20 years in ALF (presumably techniques have improved and patient populations different), there was a marginally statistically significant benefit of artificial support systems in 4 trials (RR, 0.75; 95% CI, 0.57–0.99).[114–117] Four randomized, controlled trials (n = 228) assessing traditional extracorporeal methods showed no decrease in mortality (RR, 0.94; 95% CI, 0.74–1.20). Four randomized, controlled trials (n = 340) assessing MARS compared with usual care showed no statistically significant decrease in mortality with MARS, although there was a trend to benefit (RR, 0.79; 95% CI, 0.60–1.06).[41]

It should be noted that there was a subsequent randomized, controlled trial (n = 182) evaluating HVP versus standard medical therapy in ALF, which was not included in the aforementioned metaanalysis.[118] In this randomized, controlled trial, treatment with HVP (15% of ideal body weight representing 8–12 L/d for 3 days) improved outcome in patients with ALF by increasing LT-free survival (overall hospital survival, 58.7% vs 47.8%; hazard ratio, 0.56; 95% CI, 0.36–0.86; P = .0083).[118] In those who underwent LT (n = 56), HVP did not improve survival compared with standard medical therapy alone (P = .75). A parallel proof-of-principle study demonstrated that HVP attenuates innate immune activation and ameliorates multiorgan dysfunction.[118] Therefore, HVP may be of greater benefit in patients who are treated early and thus ultimately may be able to avoid undergoing LT.[4] In summary, the overall benefits of ELSS in ALF remain uncertain. ELSS may reduce overall and LT-free survival in

select patients, but also may harm in some and therefore ELSS should not be routinely used in ALF until more data became available.

Liver Transplantation

Urgent LT is the only definitive treatment for patients with ALF when prognostic indicators suggest a high likelihood of death. Decisions to list and transplant must be made early in all patients with ALF, particularly in those with APAP-associated failure in whom ALF outcomes evolve rapidly, and where they either survive without LT or die.[119] Overall 1-year survival after LT has been reported to be lower for patients with ALF in comparison to patients with cirrhosis (most deaths after LT for ALF occur within the first 3 months from infections and neurologic complications); however, after the first year this trend has been to be reversed and patients with ALF have a better long-term survival.[120–122] Nevertheless, the 21-day survival rate after LT for ALF has significantly improved over the past 16 years: from 88.3% to 96.3% ($P<.01$).[8] ALF is one of few conditions for which a patient can be listed as a United Network for Organ Sharing status 1A (urgent) in the United States and "super urgent" in the UK.[3] Based on the largest series from US-ALFSG, of 617 patients with ALF listed for LT (36% of overall ALF), 117 (19%) spontaneously survived, 108 (17.5%) died without LT, and 392 (63.5%) underwent LT.[119] Cadaveric donor LT has been the standard in ALF, but living-donor or auxiliary LT may also be considered if organ support is limited, although its use remains controversial and should be done only in large-volume centers.[3,64,123,124] The use of ABO-incompatible grafts showed less favorable outcomes (30%–60% 1-year graft survival).[125,126]

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