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REVIEW ARTICLE

CAQ Corner

CAQ Corner: Acute liver failure management and liver transplantation

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INTRODUCTION

Acute liver failure (ALF) or fulminant hepatic failure is a rare cause of liver disease due to a multitude of etiologies with an estimated annual incidence of only 2000–3000 cases in the United States.[1] ALF is defined as the sudden onset of encephalopathy and coagulopathy (i.e., an international normalized ratio [INR] of >1.5) in an individual without preexisting liver disease in the past 8–24 weeks. The encephalopathy in ALF arises due to rapid increases in ammonia and other neurotoxins that can disrupt the blood–brain barrier with resultant cerebral edema.

The likelihood of spontaneous recovery or transplantation-free survival (TFS) is strongly related to the etiology of ALF and maximal degree of encephalopathy.[2,3] Significant improvements in TFS over the past two decades among patients with ALF are largely attributed to improvements in critical care including greater use of *N*-acetylcysteine (NAC) and continuous renal replacement therapy (CRRT) and less frequent use of blood products and mechanical intubation.[2] Nonetheless, nearly one-quarter of patients with ALF listed for liver transplantation (LT) will die awaiting an organ. Although LT is done under emergency circumstances in patients with ALF, 1- and 5-year survival rates and neurological outcomes are now excellent and approaching those of patients with cirrhosis undergoing LT.[4–6]

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ETIOLOGY AND PROGNOSIS

All patients with ALF should undergo a rapid and comprehensive diagnostic evaluation at presentation

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; APAP, acetaminophen; CMV, cytomegalovirus; CPP, cerebral perfusion pressure; CRRT, continuous renal replacement therapy; CT, computed tomography; D5W, dextrose 5% in water; DILI, drug-induced liver injury; EBV, Epstein–Barr virus; FFP, fresh frozen plasma; FiO_2, fraction of inspired oxygen; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; HELLP, hemolysis, elevated liver enzymes, low platelets; HEV, hepatitis E virus; HSV, herpes simplex virus; ICP, intracranial pressure; ICU, intensive care unit; Ig, immunoglobulin; INR, international normalized ratio; IU, international unit; LT, liver transplantation; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; NAC, *N*-acetylcysteine; OPTN, Organ Procurement and Transplantation Network; $PaCO_2$, partial pressure of arterial carbon dioxide; PCR, polymerase chain reaction; PEEP, positive end-expiratory pressure; PNF, primary nonfunction; PT, prothrombin time; ROTEM, rotational thromboelastography; TFS, transplantation-free survival; UNOS, United Network for Organ Sharing.

TABLE 1 Recommended evaluation and treatment of adults with ALF[2]

Etiology (Transplant-free survival)	Diagnostic testing	Specific treatment
APAP (60%–70%)	Serum APAP level, blood ethanol level, urine ethyl glucuronide, urine drug screen	IV or oral NAC up to 72 h Ipecac syrup and activated charcoal if single-time-point ingestion within 12 h
Idiosyncratic DILI (20%–30%)	Careful history of prescription drugs, over-the-counter medications, and herbal and dietary supplements for the past 6 months	Stop suspect agent Consider IV or oral NAC up to 72 h Consult LiverTox database
HBV (20%)	HBsAg, anti-HBc IgM, HBV DNA, anti-HDV	Tenofovir, entecavir, or tenofovir alafenamide Consider IV or oral NAC for up to 72 h
AIH (15%)	ANA, SmAb, quantitative IgG, IgM, and IgA levels Transjugular liver biopsy required for diagnosis	If histologically confirmed, methylprednisolone 20 mg IV every 8 h Consider IV or oral NAC up to 72 h
Pregnancy-related ALF (75%)	Differential: acute fatty liver disease of pregnancy, HELLP syndrome, preeclampsia/eclampsia Liver imaging, urinalysis, lactate, long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency testing of acute fatty liver of pregnancy suspected Consider APAP, HSV, HEV testing based on history	Expedited delivery of infant
Wilson's disease (<5%)	Suspect if alkaline phosphatase-to-bilirubin ratio <4, aspartate transaminase-to-alanine transaminase ratio >2.2, Coombs-negative hemolytic anemia Ceruloplasmin, 24 h urine copper, slit lamp eye examination, genetic testing Transjugular liver biopsy with copper quantification	Oral chelators: zinc, trientine Plasmapheresis Avoid penicillamine, due to risk of neurologic deterioration
Other viral hepatitis (variable)	Anti-HAV IgM HEV IgM/PCR, CMV IgM/PCR, EBV IgM/PCR, HSV IgM/PCR as clinically indicated	If HSV is suspected, start IV acyclovir 5–10 mg/kg every 8 h without delay
Budd–Chiari syndrome	Liver ultrasound with Doppler magnetic resonance imaging or CT with contrast for confirmation Possible venography and transjugular biopsy for staging Thrombophilia evaluation	Continuous heparin infusion or other anticoagulants

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ANA, antinuclear antibody; APAP, acetaminophen; CMV, cytomegalovirus; CT, computed tomography; DILI, drug-induced liver injury; EBV, Epstein–Barr virus; h, hours; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; HELLP, hemolysis, elevated liver enzymes, low platelets; HEV, hepatitis E virus; HSV, herpes simplex virus; Ig, immunoglobulin; IV, intravenous; NAC, *N*-acetylcysteine; PCR, polymerase chain reaction; SmAb, smooth muscle antibody.

because the etiology of ALF has both therapeutic and prognostic implications (Table 1).

Acetaminophen

Each year there are >60,000 instances of acetaminophen (APAP) overdose in the United States and nearly 500 individuals who progress to ALF despite NAC treatment. APAP overdose accounts for nearly 50% of all adult ALF cases and up to 20% of pediatric ALF cases (predominantly in teenagers; Figure 1).[7,8] Some patients intentionally ingest a large single dose of APAP, typically >4–6 g, as a suicide gesture, while others may unintentionally overdose on APAP containing narcotic congeners or over-the-counter products in the setting of an acute illness or chronic pain over several days. Cofactors for inadvertent APAP hepatotoxicity are increased hepatic oxidative metabolism due to chronic alcohol use and poor nutrition as well as fasting that can deplete intrahepatic glutathione stores.[7] Initial serum APAP drug levels are useful for risk stratification with single-time-point ingestions (i.e., Rumack nomogram) but often are low or undetectable in individuals with unintentional overdose.[7]

At presentation, most patients with APAP overdose have markedly elevated serum aminotransferases, a variably elevated INR, and normal or minimally elevated total bilirubin level. Lactic acidosis, acute kidney injury, hypoglycemia, and cerebral edema may develop over the first 72 h. Transplantation-free survival remains high at 60%–70% even in patients with grade 3–4 hepatic encephalopathy.[7,9] In patients with a single-time-point ingestion, ipecac syrup or gastric lavage with administration of activated charcoal is recommended within the first 12 h. Whenever APAP overdose is suspected, NAC therapy should be rapidly instituted via an enteral or intravenous route (Table 2).

Non-APAP etiologies

The majority of non-APAP ALF cases are caused by idiosyncratic drug-induced liver injury (DILI), hepatitis B virus (HBV) infection, autoimmune hepatitis (AIH), or ischemic hepatitis. Antimicrobials account for half of the DILI-related ALF cases with more recent studies demonstrating an increase in cases due to herbal and dietary supplements particularly among Asians.[10–12] The likelihood of an individual agent causing DILI can be determined by reviewing the LiverTox database and use of electronic causality assessment methods.[13,14]

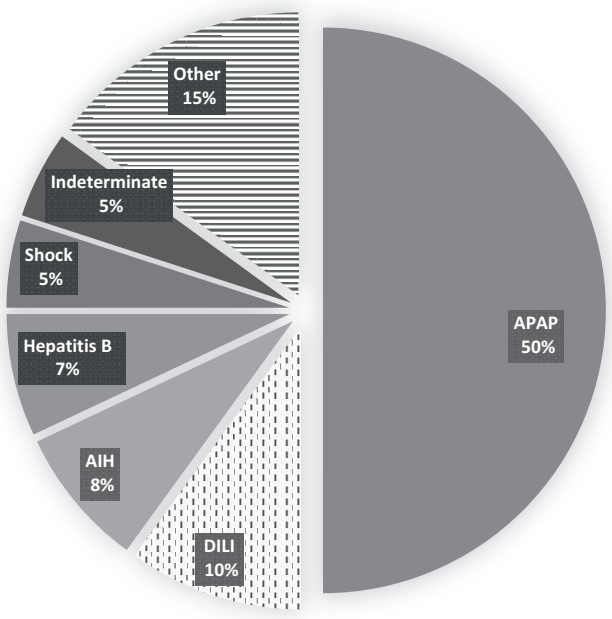

FIGURE 1 The most common causes of ALF in adult Americans. Among 2718 adults enrolled into the US multicenter ALFSG registry, APAP overdose was the most common etiology of ALF followed by idiosyncratic DILI, AIH, HBV, and indeterminate ALF[27]

A diagnosis of AIH is suggested by the presence of anti-nuclear antibody titers >1:80, anti-smooth muscle antibody titer >1:80, and an elevated immunoglobulin G (IgG) level.[15] However, not all patients with ALF AIH have detectable autoantibodies, and other forms of ALF can also be associated with detectable autoantibodies.[16] Fulminant AIH is one of the few etiologies where a liver biopsy for histological confirmation is recommended and particularly prior to initiating corticosteroids.[17,18]

HBV-related ALF is relatively uncommon but can arise from de novo infection or represent HBV reactivation that can be assessed by measuring HBsAg and quantitative anti-HBc IgM and HBV DNA levels.[19] Although anti-HBV oral nucleos(t)ide analogs are recommended, the majority of patients with HBV ALF still require urgent LT.[19–21] By contrast, hepatitis A virus (HAV)–related ALF is associated with a 50%–70% likelihood of TFS, although older individuals and those with preexisting liver disease may still need urgent LT.[22] The majority of patients with ischemia-related ALF have an identifiable cardiopulmonary insult or disease (e.g., hypotension, heart failure, arrhythmia) and will improve with supportive care and LT is rarely, if ever, indicated.[23] Other less common causes of non-APAP ALF are Wilson's disease; malignancy; and infection from Epstein–Barr virus, herpes simplex virus, hepatitis E virus, or cytomegalovirus that each account for <1% of all ALF cases.[24,25] The causes of pregnancy-related ALF are acute fatty liver of pregnancy, hemolysis,

TABLE 2 Recommended dosing of NAC in adults with APAP- and non-APAP–related ALF

Oral *N*-acetylcysteine	
Indications	**Known or suspected APAP overdose. Consider in selected patients with non-APAP ALF with grade 1–2 encephalopathy**
	Loading dose: 140 mg/kg Subsequent doses: 70 mg/kg every 4 h for up to 72 h
Precautions	As 10%–20% develop nausea and/or vomiting, consider Compazine or ondansetron prophylaxis or treatment
Intravenous *N*-acetylcysteine	
Indications	Preferred over oral NAC if functional ileus, pregnant, short gut, or gastrointestinal intolerance to oral formulation
Dosing	Dose 1. Loading dose: 150 mg/kg NAC in 200 ml D5W over 1 h Dose 2. 50 mg/kg NAC in 500 ml D5W over 4 h Dose 3. 125 mg/kg NAC in 1000 ml D5W over 19 h Dose 4. 150 mg/kg NAC in 1000 ml D5W over 24 h Dose 5. 150 mg/kg NAC in 1000 ml D5W over 24 h
Contraindications	IV NAC is contraindicated in patients with known sulfa allergy
Precautions	• Telemetry recommended during first 24 h of IV NAC infusion to detect arrythmias and anaphylactoid reactions. If hemodynamically and clinically stable, consider transition to oral NAC for completion of therapy • Anaphylactoid/ hypersensitivity reactions with rash, wheezing seen in 3% to 5% of treated patients • If patient is intolerant, hold and reduce infusion rate by 50%. Administer fluids, diphenhydramine, and steroids as needed

Abbreviations: ALF, acute liver failure; APAP, acetaminophen; D5W, dextrose 5% in water; IV, intravenous; NAC, *N*-acetylcysteine.

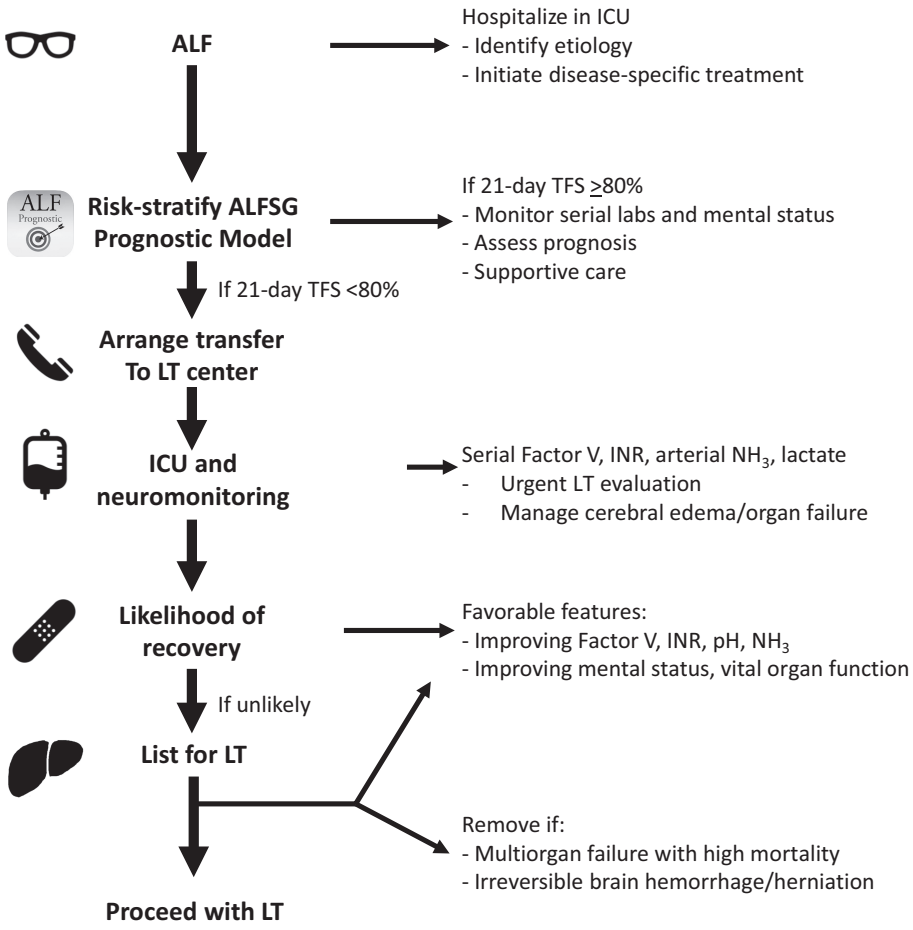

FIGURE 2 Management algorithm for adult patients with ALF. Early establishment of the etiology of ALF has therapeutic and prognostic implications. Patients with an unfavorable etiology of ALF or lower likelihood of survival should be transferred early on to an LT center for evaluation. Eligible patients with ALF who are suitable candidates for LT can be listed for LT as a high-priority, status 1a patient. Some patients with ALF may be delisted due to clinical improvement while others will require emergency LT for long-term survival.

elevated liver enzymes, low platelets (HELLP) syndrome, and preeclampsia/eclampsia. Although expedited delivery is recommended in all of these scenarios, a minority may still develop progressive ALF postpartum and require urgent LT.[26]

Despite extensive diagnostic testing, nearly 5%–10% of American adults with ALF have an indeterminate etiology.[27] These patients frequently present with a viral prodrome and jaundice but fail to improve over time necessitating urgent LT evaluation.[1,27] A 72-h course of intravenous or oral NAC should be considered in adults with DILI, HBV, AIH, and indeterminate ALF, as an improved TFS was reported in a randomized placebo-controlled clinical trial, particularly in those with grade 1–2 encephalopathy.[28] However, NAC is not recommended for children with non-APAP ALF due to inferior survival compared with placebo.[29]

Prognosis

The Acute Liver Failure Study Group (ALFSG) prognostic index can be determined at the bedside with a smartphone application ("Acute Liver Failure Prognostic" in the Apple App Store). This model incorporates the encephalopathy grade, ALF etiology, vasopressor use, and total bilirubin and INR levels to predict the likelihood of 21-day TFS.[3] The model has demonstrated superior accuracy in predicting TFS compared with the Model for End-Stage Liver Disease (MELD) score and King's College Criteria. Individuals with APAP, ischemia, and HAV-related ALF or those who are pregnant have a higher rate of TFS (50%–70%), compared with all other causes (20%–50%).[3] Patients seen in the emergency room with a <80% projected TFS who are otherwise good candidates for LT should be considered for urgent transfer to an LT center (Figure 2).

Individual patient prognosis can also be guided by serial assessment of arterial ammonia, lactate, phosphate, Factor V, and INR values every 8–12 h in the intensive care unit (ICU). The extent of hepatic necrosis on liver biopsy does not generally provide useful prognostic information in patients with ALF because of sampling artifact.[30] However, histologic confirmation of Wilson's disease, AIH, and malignant infiltration may be

required, in which case a transjugular approach is recommended to minimize the risk of bleeding. Accurate, noninvasive tests of global hepatic function such as the ^{13}C Methacetin breath test are needed to assist with bedside clinical decision making but are currently not available.[31]

COMPLICATIONS OF ALF

Patients with ALF should be cared for in an experienced ICU ideally by a multidisciplinary team of intensivists, hepatologists, and transplantation surgeons (Table 3). Initially, the patient must be stabilized (i.e., airway protection, hemodynamics) while the etiology and severity of disease are being assessed. Simultaneously, suitability for emergency LT should be undertaken particularly in patients with unfavorable etiologies and a poor prognosis. Critical decisions must be made in a short time; the median time from listing to transplantation or removal from the transplantation list due to irreversible decline or improvement is only 2–3 days.[32]

Cerebral edema

Cerebral edema arises in patients with ALF due to hyperammonemia and astrocyte swelling early on with loss of intracranial blood flow autoregulation in later stages. A fever or infection can increase the risk of cerebral edema and should be minimized with cooling blankets and preemptive antibiotics, respectively. As arterial ammonia levels rise, intracranial pressure (ICP) may rapidly surge and lead to worsening mental status and unstable hemodynamics. Therefore, a number of general measures are recommended to prevent ICP hypertension including a quiet nursing environment, minimal positive end-expiratory pressure settings, keeping the head of the bed >30°, and avoiding fluid overload (Table 3). Similarly, avoidance of sedative and analgesic drugs is recommended in patients with grade 1–2 encephalopathy as they may be hypometabolized. When patients develop grade 3 hepatic encephalopathy, elective intubation is recommended to reduce the risk of aspiration along with hyperventilation to a partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mm Hg to enhance cerebral vasoconstriction.

Invasive ICP monitoring should be considered in selected patients with ALF with grade 3–4 encephalopathy because the physical examination, papilledema, and head computed tomography (CT) are insensitive means to detect cerebral edema. Although ICP monitoring can objectively detect surges in ICP and help guide medical therapy, it has not been shown to improve clinical outcomes.[33] Because patients with ALF are coagulopathic by definition, use of prophylactic

TABLE 3 ICU recommendations for patients with ALF

Issue	Recommendation
General	• Place arterial line: lactate, arterial ammonia every 8–12 h • CBC with platelets, electrolytes, PT/INR, Factor V every 8–12 h • Glucose fingerstick every 1–2 h • IV acid suppression for gastrointestinal bleeding prophylaxis • Infection surveillance at admission and every 2–3 days (blood, urine, chest x-ray) • Preemptive broad-spectrum antibiotics (avoid aminoglycosides) • Consider antifungals if unexplained hypotension/worsening status
Neuroprotective measures	• Neuro checks, Glasgow Coma score every 1–2 h • Head of bed >30° • Avoid sedating medications (benzodiazepines, opioids, antihistamines) • Use short-acting agents for severe agitation or if intubated (midazolam, propofol) • Minimize stimulation (tracheal suctioning, straining, Valsalva, coughing, physical movement out of ICU) • Avoid lactulose since not effective and risk of colonic distention/ischemia • Minimize unnecessary IV fluids, blood transfusions • Cooling blankets to prevent/minimize fever
Elevated intracranial pressure	• Head CT if grade 3/4 encephalopathy to exclude intracranial bleed • Consider ICP monitor placement with prophylactic blood products • Hyperventilate to $PaCO_2$ of 28–30 mm Hg • Osmotic agents for surge in ICP • Hypertonic saline 30% bolus • Target Na: 140–145 mmol/L but avoid >8 mmol/L rise in 24 h • Mannitol 0.5–1 g/kg IV bolus over 5 min • Monitor serum osmolarity every 4 h (withhold if >320 mOsm/L) • Pentobarbital 100–150 mg IV bolus over 15 min, then 1–3 mg/kg/h drip • Monitor for hypotension • Target level: 20–35 mg/L (monitor levels every 8 h)

Abbreviations: ALF, acute liver failure; CBC, complete blood count; CT, computed tomography; ICP, intracranial pressure; ICU, intensive care unit; INR, international normalized ratio; IV, intravenous; $PaCO_2$, partial pressure of arterial carbon dioxide; PT, prothrombin time.

recombinant factor VIIa, plasma factors, and desmopressin prior to insertion of intraparenchymal monitors is recommended to reduce the risk of hemorrhage from 10%–20% to <5%.[34] Once an ICP monitor is in place, the cerebral perfusion pressure (CPP) can be calculated (CPP = mean arterial pressure [MAP] – ICP) and management directed to keep the CPP >60 mm Hg while avoiding ICP surges of 10–20 mm Hg. Strategies for maintaining CPP include raising the MAP via vasopressors as well as hypertonic saline or mannitol boluses to reduce ICP. In addition, some refractory patients may require a pentobarbital coma to reduce cerebral oxygen utilization (Table 3). Although there are uncontrolled studies demonstrating the utility of therapeutic hypothermia in patients with ALF with refractory ICP, this modality is not recommended because the goal temperature and how to rewarm patients is not established.[35,36]

CRRT is frequently used to address oliguria, azotemia, volume overload, and hyperammonemia in patients with ALF with acute kidney injury, which arises in up to 50% of patients.[37] Some studies have demonstrated improved 21-day TFS in those receiving CRRT compared with untreated controls.[37] By contrast, liver support systems involving albumin dialysis, plasmapheresis, and bioartificial livers have not demonstrated convincing data on improving TFS.[38–40] If the patient develops decorticate/decerebrate posturing or has abrupt deterioration in mental status, an urgent noncontrast head CT should be performed to assess for cerebral herniation and/or intracranial hemorrhage.

Transcranial Doppler flow measurements to estimate CPP are a promising noninvasive tool to assess ICP that requires further validation in patients with ALF. By contrast, optic nerve ultrasound and middle cerebral artery pulsatility index have not been shown to be useful.[41] Pupillometry using a handheld electronic device that measures the reactivity of pupils to a light stimulus shows promise in patients with head trauma but prospective studies in patients with ALF are needed.[42]

Multifactorial coagulopathy

In addition to an elevated INR, patients with ALF frequently have a multitude of other hemostatic abnormalities including thrombocytopenia, hypofibrinogenemia, and abnormal clot formation on rotational thromboelastography (ROTEM).[43,44] However, ROTEM parameters did not track with bleeding nor clotting risk in 200 adult consecutive patients with ALF but did correlate with illness severity.[44] Interestingly, the incidence of spontaneous bleeding in patients with ALF has been only 5%–10% and usually involves mucosal and cutaneous surfaces. As a result, routine administration of fresh frozen plasma (FFP) is not recommended to correct INR and in fact may worsen outcomes, obscure the prognostic value of INR/Factor V, and exacerbate pulmonary and cerebral edema. However, ICP monitor placement and transjugular liver biopsy have increased risk of procedural bleeding (up to 10%–20%). Therefore, some transplantation centers use aggressive protocols to prevent a catastrophic hemorrhage, which could undermine the patient's transplantation candidacy. Although protocols still require prospective validation, most include administration of platelets to exceed 50,000/ml, cryoprecipitate to correct fibrinogen to >100 mg/dl, and FFP or plasma factor concentrate in combination with recombinant activated coagulation factor VIIa to achieve an INR <1.5.[34,45]

Infectious complications

Infectious complications including pneumonia, urinary tract infections, line infections, and bacteremia may develop in up to 80% of patients with ALF during their hospital course. Furthermore, fungal infections may develop in up to 20% of patients.[46] Thus, patients should have two sets of blood cultures, urine culture, and a chest x-ray on admission and every 2–3 days thereafter, as well as when there is acute, unexplained worsening in mental status, laboratory parameters, or hemodynamics. Empiric broad-spectrum antibiotics to cover Gram-negative and Gram-positive organisms are recommended for most patients with ALF and especially those awaiting LT or if unexplained clinical deterioration is encountered.

Evaluation and listing for liver transplantation

Overall, 20%–30% of patients with ALF undergo emergency LT but the number of patients being waitlisted has significantly declined over the past 20 years.[2,47] Evaluation for LT includes blood tests, liver imaging, and a cardiac echo that can usually be completed in 12–24 h to ensure that there are no medical, cardiopulmonary, or psychosocial contraindications for LT. Eligible patients are then placed on the LT waiting list as a status 1 patient. In 2020, the Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) adopted a new liver allocation system that prioritizes candidates according to geographic distance from the donor hospital rather than UNOS regional boundaries. Because of their high short-term mortality, candidates with ALF qualify for status 1A listing, where they obtain the highest priority to receive an A, B, O compatible deceased brain-dead donor liver within 500 nautical miles.

To be listed as an adult status 1A for ALF, the OPTN policy requires a patient with ALF to have a life expectancy of <7 days without LT and no preexisting

diagnosis or signs and symptoms of liver disease (excluding LT recipients with primary nonfunction [PNF] or hepatic artery thromboses within 1 week of LT).[48] Patients with AIH and HBV-related ALF may still qualify if they did not have any signs or symptoms of liver disease prior to the development of ALF (Table 4). Among patients listed for LT, 60% may be removed from the list due to either improvement or development of contraindications to LT (Table 5).[4,32] Rates of waitlist removal currently vary by location as well as the etiology of ALF with APAP overdose patients being more likely to be removed for improvement, while non-APAP patients are more commonly removed due to new contraindications.[4] Progressive or refractory cerebral edema is particularly problematic because it can lead to brain herniation with or without intracranial hemorrhage, which will preclude successful LT. Patients with PNF of their LT or those with early hepatic artery thromboses may also qualify for status 1A listing, but fortunately the incidence of PNF has been declining due to improved allograft selection.[49]

LIVER TRANSPLANTATION

A whole cadaveric liver should be used for transplantation in patients with ALF whenever possible. Currently, 21-day post-LT survival is 92% and the 1-year posttransplantation survival is 80%–90%, which is slightly lower than the 1-year survival for all LT recipients (93%).[4,5,32] Compared with cirrhosis, ALF LT recipients tend to be younger and are more likely female and to be an ethnic minority.[4,32] Split, partial, and living donor livers are infrequently used in patients with ALF as there may be undue pressure to be a living donor and potentially worse outcomes in US centers.[50] Access to emergency LT can be safely expanded by using hepatitis C–positive and anti-HBV-core antibody–positive donor livers. Auxiliary partial orthotopic LT and hepatocyte transplantation remain under investigation but demonstrate promise, particularly in children.[51,52] The majority of ALF LT recipients receive an A, B, O identical or compatible graft, although some have received an A-, B-, O-incompatible graft with a higher incidence of allograft dysfunction.[53]

ALF LT recipients frequently have a slower evolution of disease, less severe encephalopathy, and lower utilization of mechanical ventilation, pressors, and CRRT compared with listed patients who died without LT.[32] Patients who develop refractory hypotension on pressors, high supplemental oxygen requirements, refractory cerebral edema, or severe multiorgan failure may not do well with LT (Table 5). Further, LT may be futile in selected patients with irreversible brain injury (e.g., bilateral nonreactive pupils, no spontaneous ventilation, brain herniation), uncontrolled sepsis/shock, and multiorgan failure (Figure 2). The leading causes of death in those waitlisted include progressive infection, cerebral edema, and multiorgan failure.

Most centers currently offer standard three-drug immunosuppression to their ALF LT recipients. However, because many of these patients are younger with intact immune systems, two or three drugs may be required for favorable long-term outcomes. A recent retrospective analysis of 3754 adult ALF LT recipients indicated poorer survival with the use of antithymocyte globulin induction compared with corticosteroids.[52] A 2-year prospective study demonstrated that ALF LT recipients were more likely to be alive compared with spontaneous APAP survivors (92% vs. 75%).[54] In addition, post-LT

TABLE 4 UNOS criteria to list a patient as status 1A

Only patients >18 years old with a life expectancy of <7 days without an LT are eligible for listing as status 1A who meet the following criteria
Patients with ALF1. Onset of hepatic encephalopathy within 56 days of the first sign/symptom of liver disease
2. Currently admitted to the ICU
3. No preexisting liver disease (unless recent prior LT)
4. Presence of any of the following:
a. ventilator dependence
b. on CRRT
c. INR >2
Prior LT recipients
Patients with primary nonfunction or hepatic artery thromboses within 7 days of LT with aspartate transaminase ≥3000 U/L and at least one of the following:
• Arterial pH ≤7.3
• Venous pH ≤7.25
• INR ≥2.5
• Lactate ≥4 mmol/L

Abbreviations: ALF, acute liver failure; CRRT, continuous renal replacement therapy; ICU, intensive care unit; INR, international normalized ratio; LT, liver transplantation; UNOS, United Network for Organ Sharing.

TABLE 5 Contraindications to emergency LT in ALF candidates

Medical contraindications
• Active malignancy
• Active human immunodeficiency virus/acquired immune deficiency syndrome
• Severe fixed mental impairment
Psychosocial barriers
• Poor compliance with medical advice, medications, follow-up
• Unremitting substance use disorder
• Lack of social support
Severe multiorgan failure
• Heart failure with reduced ejection fraction
• >90% FiO_2 ventilator support with high PEEP, acute respiratory distress syndrome, and acidosis
• Hemodynamic instability requiring two or three pressors
• Uncontrolled sepsis
Irreversible brain injury
• Cerebral herniation
• Severe intracranial bleeding

Abbreviations: ALF, acute liver failure; FiO_2, fraction of inspired oxygen; LT, liver transplantation; PEEP, positive end-expiratory pressure.

survival was associated with younger age, more days from jaundice to ALF onset, and less severe encephalopathy.[5] ALF LT recipients also had higher long-term rates of employment and lower long-term rates of psychiatric disease, substance use, and alcohol use compared with the spontaneous APAP survivors. This study and others suggest that successful long-term outcomes are related to selecting candidates with low or modifiable psychosocial risk.

KEY POINTS

- Acute liver failure (ALF) is a rare disease with an estimated annual incidence of 2000–3000 cases in the United States that is due to a multitude of etiologies, with acetaminophen (APAP) overdose being the most common cause followed by drug-induced liver injury, autoimmune hepatitis, hepatitis B virus, and indeterminate ALF.
- Rapid diagnosis of ALF etiology is required to facilitate early disease-specific therapies such as *N*-acetylcysteine for APAP overdose and to assist with prognostication.
- Assessment of serial laboratory parameters (e.g., Factor V, lactate, ammonia) along with tracking of vital organ status is recommended to assist with bedside clinical decision making.
- Cerebral edema in patients with ALF arises due to increased production and reduced clearance of putative neurotoxins that can manifest with agitation, reduced sensorium, and upper motor neuron signs.
- Management of elevated intracranial pressure in patients with ALF involves hyperventilation, osmotic agents, reducing cerebral metabolism, and use of vasopressors to maintain an adequate cerebral perfusion pressure.
- Despite the universal presence of a multifactorial coagulopathy, clinically significant bleeding is seen in only 5%–10% of patients with ALF. Therefore, prophylactic blood products are not recommended unless a moderate- or high-risk invasive procedure is planned.
- Patients with ALF receive the highest medical priority for liver transplantation (LT) as a status 1A candidate, and they currently account for 3% of annual LTs in the United States.
- Nearly 60% of waitlisted patients with ALF will not undergo LT due to either clinical improvement or development of contraindications to LT.
- Emergency LT in patients with ALF is associated with an 80%–90% 1-year survival with most early deaths attributed to infectious and neurological complications.
- Long-term outcomes in ALF LT recipients are generally favorable and possibly superior to patients with cirrhosis, but higher levels of long-term immunosuppression are frequently required.

QUESTIONS

1. A 24-year-old female with a history of depression is brought to the emergency room after being found down at home. She was last seen by her friends 48 h ago reporting suicidal ideation. She is minimally interactive and does not follow commands. Laboratory tests reveal aspartate transaminase 6000 IU/L, alanine transaminase 8000 IU/L, bilirubin 3.4 mg/dl, and international normalized ratio (INR) 8. The most important next step in management is:

   A) Call a transplantation center to discuss early transfer
   B) Give fresh frozen plasma to correct the elevated INR
   C) Placement of an arterial line for serial laboratory testing
   D) Administration of intravenous or oral *N*-acetylcysteine

2. Social work evaluates this patient and finds no evidence of prior mental health issues or substance abuse. She has a supportive family and network of friends. A head CT is negative but patient requires intubation and low dose pressors. Absolute contraindications to proceeding with transplantation in this young patient with presumed acetaminophen overdose are:

   A) High risk of bleeding due to elevated INR
   B) A possible history of tobacco use
   C) Need for mechanical ventilation and low dose pressors
   D) Evidence of biventricular heart failure on bedside echo

3. A 38-year-old Asian man with acute liver failure (ALF) is found to have hepatitis B with detectable hepatitis B surface antigen (HBsAg), anti-HBc, and hepatitis B virus (HBV) DNA. He is started on entecavir. Which of the following will likely preclude him from being listed as a status 1A for LT?

   A) His evidence of cirrhosis based on imaging findings (i.e., liver nodularity, splenomegaly), without prior signs or symptoms of liver disease
   B) His Factor V level decreased from 45% to 25%.
   C) His O_2 requirement increases with a fraction of inspired oxygen (FiO_2) 100%, positive end-expiratory pressure 15 cm H_2O, and need for three pressors.
   D) The patient is regularly hypoglycemic, requiring a D_{10} infusion.

4. A 65-year-old woman with ALF due to isoniazid hepatoxicity is hospitalized in the intensive care unit, awaiting LT. Which of the following is indicative of ongoing hepatic regeneration:

A) Stage IV encephalopathy
B) Older patient age
C) Multiple pressor requirement
D) Low serum phosphate

5. A patient with ALF with grade 4 encephalopathy has an elevated and persistent surge in intracranial pressure (ICP) to 15 mm Hg. A single dose of mannitol is administered. What neuromonitoring changes would be expected, if there is a good response to mannitol?

	Serum osmolality	Mean arterial pressure	Cerebral perfusion pressure	ICP
A)	↑	↓	↑	↓
B)	↑	↔	↑	↓
C)	↓	↔	↑	↓
D)	↓	↑	↓	↓

6. An intubated, critically ill 40-year-old patient with ALF on hospital day 4 is noted to have an increase in the white blood cell count from 13,000 to 22,000/ml, and the patient's hypotension is worsening, requiring two pressors. An infectious workup is repeated, and empiric broad-spectrum antibiotics are started. On hospital day 5, the white blood cell count is increased to 25,000/μl, and the patient is now on three pressors. There is no evidence of bleeding or cardiac dysfunction. What should be considered?

A) Hydrocortisone should be started given the worsening shock.
B) A procalcitonin, C-reactive protein, and erythrocyte sedimentation rate should be checked.
C) Accelerate the patient's listing for LT.
D) A fungal workup should be sent, and empiric antifungals started.

7. Infectious workup of a patient with ALF with autoimmune hepatitis on admission is notable for both sets of blood cultures growing *Escherichia coli*. The patient is stabilized with antibiotics for 48 h, has negative repeat blood cultures, is not requiring pressors, and the lactate level is down trending from 4 to 3 mmol/L. However, the patient's liver function is worsening, with an INR of 6 and Factor V level of 10%. The patient is fatigued and O x 2 but answering questions and has a normal creatinine. Which of the following would be recommended for this patient:

A) Immediate insertion of an ICP monitor
B) Listing for liver transplantation
C) Defer listing for transplant due to recent bacteremia
D) Initiation of CRRT

CONFLICT OF INTEREST

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