CME

Acute Liver Failure Guidelines

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Acute liver failure (ALF) is a rare, acute, potentially reversible condition resulting in severe liver impairment and rapid clinical deterioration in patients without preexisting liver disease. Due to the rarity of this condition, published studies are limited by the use of retrospective or prospective cohorts and lack of randomized controlled trials. Current guidelines represent the suggested approach to the identification, treatment, and management of ALF and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence was reviewed using the Grading of Recommendations, Assessment, Development and Evaluation process to develop recommendations. When no robust evidence was available, expert opinions were summarized using Key Concepts. Considering the variety of clinical presentations of ALF, individualization of care should be applied in specific clinical scenarios.

KEYWORDS: Acute liver failure; liver transplantation; fulminant liver failure; acute liver injury; jaundice; coagulopathy; hepatotoxicity; multi-organ failure; hepatic encephalopathy

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INTRODUCTION

Acute liver failure (ALF) is a life-threatening condition that occurs in patients with no preexisting liver disease and is characterized by liver injury (abnormal liver tests), coagulopathy (international normalized ratio [INR] >1.5), and hepatic encephalopathy (HE). It has a multitude of etiologies and a variety of clinical presentations that can affect virtually every organ system. It is imperative for clinicians to recognize ALF early in patient presentation because initiation of treatment and transplant considerations could be lifesaving. The current guideline represents the summary of existing data on diagnosis and management of patients with ALF.

The guideline is structured in the format of statements that were considered to be clinically important by the content authors. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process was used to assess the quality of evidence for each statement (Table 1) (1). The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect (2). A strength of recommendation is given as either strong (recommendations) or conditional (suggestions) based on the quality of evidence, risks vs benefits, feasibility, and costs taking into account perceived patient-based and population-based factors (3). Furthermore, a narrative evidence summary for each section provides important definitions and further details for the data supporting the statements.

Under the auspices of the American College of Gastroenterology (ACG) Practice Parameters Committee, a group of experts in the area of ALF were identified for the writing group. The proposed writing group was reviewed by the ACG Practice Parameters Committee and the ACG leadership, and the final approved writing group consisted of the current authorship team, which includes hepatology experts across a broad range of practice settings and different stages of clinical and research career development. Regular meetings were conducted among this writing group throughout the guideline development process to formulate PICO questions that guided the subsequent literature search, development of recommendation statements and key concepts, GRADE assessments, and the preparation of the full guideline document.

We conducted an electronic search using MEDLINE, EMBASE, and the Cochrane Library through January 2022. We limited the search to English language and fully published articles. For each PICO question developed, we comprehensively reviewed the existing literature, with a focus on studies of the highest quality of evidence (e.g., when available, systematic reviews and meta-analyses, followed by randomized controlled trials, followed by observational studies).

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Table 1. Grading of recommendations assessment, development, and evaluation quality criteria

Quality of evidence	Study design	Factors lowering the quality of evidence	Factors increasing the quality of evidence
High	Randomized trial	Risk of bias: −1: serious risk of bias −2: very serious risk of bias Consistency: −1: serious inconsistency −2: very serious inconsistency	Strong Association: +1: strong, no plausible confounders +2: very strong, no major threats to validity +1: evidence of a dose response gradient +1: all plausible confounders would have reduced the effect
Moderate		Directness:	
Low	Observational study	−1: serious indirectness	
Very low	Any other evidence	−2: very serious indirectness	
		Precision:	
		−1: serious imprecision	
		−2: very serious imprecision	
		Publication bias:	
		−1: likely presence of reporting bias	
		−2: very likely presence of reporting bias	

In addition to guideline recommendations, the authors have highlighted key concept statements that were not included in the GRADE assessment. Key concepts are statements that the GRADE process has not been applied to and can include both expert opinion recommendations and definitions/epidemiological statements. Table 2 is a summary of recommendations, whereas Table 3 summarizes the key concept statements.

DEFINITION AND PRESENTATION OF ACUTE LIVER FAILURE

ALF is a rare, acute, potentially reversible condition resulting in severe liver impairment and rapid clinical deterioration in patients without preexisting liver disease (4,5). First described in 1970, its definition has been refined over the years (5). The definition of what constitutes ALF varies globally. The most used

Table 2. Recommendations

Statement	GRADE quality	Strength of recommendation
System-specific management: CNS		
1. In patients with ALF and grade 2 or higher encephalopathy, we suggest early CRRT for management of hyperammonemia even in the absence of conventional RRT indications	Conditional	Very low
System-specific management: coagulopathy		
2. In patients with ALF, in the absence of active bleeding or impending high-risk procedure, we recommend against routine correction of coagulopathy	Conditional	Very low
System-specific management: infection		
3. In patients with ALF, we recommend against the routine use of prophylactic antimicrobial agents, given no improvement in either rate of bloodstream infection or 21-day mortality	Conditional	Low
System-specific management: hemodynamics and renal failure		
4. In patients with ALF, we recommend norepinephrine as the first-line vasopressor for hypotension refractory to fluid resuscitation	Strong	Moderate
5. In patients with ALF with hypotension not responsive to norepinephrine, we suggest adding vasopressin as a secondary agent	Conditional	Low
Etiology-specific management		
6. In patients with suspected APAP toxicity, we recommend early administration of N-acetylcysteine	Strong	Low
7. In patients with non-APAP ALF, we suggest the initiation of intravenous NAC	Strong	Moderate
8. In patients with ALF due to reactivation of HBV, we recommend starting antiviral therapy	Strong	Low
9. In patients with ALF due to mushroom poisoning, we recommend initiation of IV silibinin as soon as possible. IV penicillin G may be used if IV silibinin is unavailable	Conditional	Very low
Liver transplantation: prognostic models		
10. In patients with ALF, we recommend using either the KCC criteria or MELD score for prognostication. Patients meeting the KCC criteria or presenting with MELD >25 are at high risk of poor outcomes.	Conditional	Low

ALF, acute liver failure; APAP, N-acetyl-p-aminophenol; CNS, central nervous system; CRRT, continuous renal replacement therapy; HBV, hepatitis B virus; IV, intravenous; KCC, King's College Criteria; MELD, Model for End-Stage Liver Disease; NAC, *N*-acetylcysteine; RRT, renal replacement therapy.

Table 3. Key concepts

General management
Comprehensive testing to elucidate a diagnosis and exclude underlying chronic liver disease is essential in the evaluation of ALF (Table 7).
Biomarkers (ETG or PETH) should be used in addition to psychosocial assessment when alcohol-induced liver disease is suspected.
Grade 2 encephalopathy should prompt transfer to intensive care unit (ICU) while intubation for airway protections should be considered for grade 3 and 4 HE.
Referral for consultation by hepatology or gastroenterology as soon as possible after identification of ALF. Early communication with the transplant center is crucial to patient management.
When to biopsy
Liver biopsy may help exclude infiltrative disease and malignancy and to identify patients with contraindication to LT.
Liver biopsy may help diagnose autoimmune hepatitis, which may respond to immunosuppressive therapy and potentially spare patients the long-term complications of LT.
There is insufficient evidence to recommend the routine use of liver biopsy in other settings.
When considering liver biopsy in the evaluation of patients with ALF, we suggest using transjugular liver biopsy over other methods.
System-specific management: CNS
ALF patients with grade 2 or higher encephalopathy should be monitored in an ICU setting.
Patients with ALF with grade 3 and 4 encephalopathy should be intubated for airway protection.
There is no conclusive evidence to recommend for or against the use of lactulose or rifaximin for the treatment of encephalopathy in patients with ALF.
There is no conclusive evidence to recommend routine ICP monitor placement in patients with ALF.
There is no conclusive evidence to recommend routine use of hypothermia to control intracranial pressure in patients with ALF.
System-specific management: coagulopathy
The INR does not accurately reflect bleeding risk in patients with ALF.
Viscoelastic tests may provide a more accurate assessment of coagulopathy in patients with ALF.
System-specific management: infection
In patients with ALF, early assessment for infection is prudent because clinical signs of infection are frequently absent.
There is insufficient evidence in patients with ALF to recommend the use of procalcitonin as a biomarker of infection.
Empiric antibiotic and antifungal therapy may be considered in the setting of clinical deterioration of the patient.
In patients with ALF, we suggest regular surveillance cultures; however, the optimal frequency is unknown.
In patients with ALF and hypotension, intravenous fluid resuscitation should be initiated.
Renal replacement therapy should be considered early in patients with acute kidney injury, electrolyte or metabolic abnormalities, and/or volume overload.
In patients with ALF requiring renal replacement therapy, we recommend CRRT over intermittent hemodialysis.
System-specific management: nutritional and metabolic support
In patients with ALF, monitoring and correction of glucose, fluid, and electrolyte imbalances should be performed.
In patients with ALF, enteral nutritional support should be started if the patient is unable to resume oral intake within 5–7 d.
System-specific management: other management considerations
There is insufficient evidence to recommend for or against the routine use of high-volume plasma exchange or artificial/bioartificial liver support devices in patients with ALF
Etiology-specific management: acetaminophen hepatotoxicity
In patients with APAP-ALI or APAP-ALF, the duration of NAC treatment should be individualized based on the patient's clinical condition and laboratory values.
In patients with APAP overdose, we recommend single-dose activated charcoal administration if ingestion is known to have occurred within 4 hr.
Etiology-specific management: viral hepatitis
In patients presenting with ALF, grade 2 encephalopathy and features suggestive of HSV infection, we suggest empiric treatment with IV acyclovir until confirmatory testing with HSV PCR is obtained.
Etiology-specific management: mushroom poisoning
In patients presenting with mushroom poisoning and acute liver injury, Escudie criteria can be used to predict the need for liver transplantation even before the development of encephalopathy.
Gastric lavage and activated charcoal should be administered within the first few hours after ingestion, provided no contraindications exist.
Etiology-specific management: Wilson disease
In patients presenting with ALF due to suspected or confirmed Wilson disease, liver transplantation evaluation should be initiated during diagnosis because of the lack of effective medical therapy
Etiology-specific management: AIH
In patients presenting with AS-AIH, we suggest the use of IV corticosteroids.
In patients with AS-AIH, which has progressed to ALF, we recommend early evaluation for liver transplantation

Table 3. (*continued*)

Etiology-specific management: pregnancy-related ALF
In patients with pregnancy-related ALF, supportive care and multidisciplinary management is essential, and prompt delivery of the fetus is crucial
In patients with pregnancy-associated ALF, who fail to improve after delivery of the fetus, we suggest prompt evaluation for liver transplantation
Etiology-specific management: Budd-Chiari syndrome
In patients with Budd-Chiari syndrome leading to ALF, TIPS is the preferred intervention in those who fail anticoagulation
In patients with Budd-Chiari syndrome–induced ALF, we recommend heparin as initial therapy in the absence of contraindications to anticoagulation.
In patients with Budd-Chiari syndrome–induced ALF, who do not respond to medical and therapeutic interventions, we recommend liver transplantation
Liver transplantation: prognostic models
Identifying patients with ALF at risk of poor outcomes is important and should trigger transfer to a transplant center early in presentation.
Liver transplantation: transplant evaluation
Multidisciplinary discussion involving the transplant team to determine individual transplant candidacy should be undertaken at the transplant center.
Liver transplantation: graft considerations
In patients with ALF, listed as status 1A priority, LDLT may be considered in centers with LDLT experience when DDLT is not readily available
In patients with ALF, listed as status 1A priority, we suggest consideration of ABO-I grafts in a rapidly declining patient.

ABO-I, ABO incompatible; AIH, autoimmune hepatitis; ALF, acute liver failure; ALI, acute liver injury; APAP, N-acetyl-p-aminophenol; AS-AIH, acute severe autoimmune hepatitis; CRRT, continuous renal replacement therapy; ETG, ethyl glucuronide; HE, hepatic encephalopathy; HSV, herpes simplex virus; ICP, intracranial pressure; INR, international normalized ratio; IV, intravenous; LDLT, living donor liver transplantation; LT, liver transplantation; NAC, *N*-acetylcysteine; PCR, polymerase chain reaction; PETH, phosphatidyl ethanol.

definition in the United States and Europe is an illness duration of <26 weeks duration in a patient without preexisting liver disease or cirrhosis associated with any degree of mental status alteration (encephalopathy) and coagulopathy (an INR ≥1.5) (5). There are exceptions to the requirement for lack of underlying liver disease. Conditions that may have an acute presentation in the setting of already advanced hepatic fibrosis include autoimmune hepatitis (AIH), Budd-Chiari syndrome (BCS), and Wilson disease (WD).

The presentation of ALF has been further differentiated (O'Grady classification) based on the rapidity of onset of HE (Table 4) (4,6). Hyperacute ALF is predominantly seen in the setting of viral hepatitis A, viral hepatitis E (HEV), acetaminophen (N-acetyl-p-aminophenol [APAP]) toxicity, and ischemic injury. Although this subtype of ALF carries a high risk of cerebral edema (CE), it has the best prognosis without transplantation (7). The acute subtype can be seen in the setting of hepatitis B virus (HBV) infection and subacute ALF is more often seen with non-APAP drug–induced liver injury. The more indolent acute and subacute categories carry some degree of overlap; therefore, their utility can be less useful in clinical management (8). Although these categories have a lower risk of CE, their outcome is poorer without transplantation. Care must be taken not to mistake subacute ALF for chronic liver failure.

Etiology of ALF varies geographically. In North America, Japan, and Europe, the most common causes in adults include drug-induced liver injury (DILI), viral hepatitis, and cryptogenic liver failure with no identifiable cause (indeterminate ALF) (9–12). The percentage of ALF attributed to an indeterminate cause varies globally, ranging from 5% to 70% (13–15) In developing countries, acute viral hepatitis (AVH) remains the predominant etiology (16).

The etiology is an essential indicator for prognosis and treatment strategy, especially for the necessity for liver transplantation (LT). A recent national cohort study from the United States suggests ALF etiology is an independent predictor of waitlist mortality but not of post-LTx outcomes. After adjusting for the severity of ALF at listing, waitlist mortality and spontaneous survival for DILI, AIH, and HBV were lower than those for acetaminophen toxicity (17). Common etiologies of ALF are listed in Table 5 and expanded upon in the Management section of the guideline.

ALF carries a high morbidity and mortality without LT (9–11). Overall and transplant-free survival have improved over the past few decades with improvement in specialty care management (18). It remains imperative to identify the disease so that the patient is referred to a liver transplant center in a timely fashion.

Table 4. **ALF presentations**

Type of ALF	Time frame	Examples	Risk of cerebral edema	Risk of death
Hyperacute	<7 d	Acetaminophen hepatitis A & E ischemic injury	High	Low
Acute	7–21 d	Hepatitis B	Intermediate	Intermediate
Subacute	>21 d and <26 wk	Nonacetaminophen DILI	Low	High

ALF, acute liver failure; DILI, drug-induced liver injury.

Table 5. Etiologies of acute liver failure

Etiology	Clinical features	Prognosis
Acetaminophen hepatotoxicity	• Hyperacute presentation • Often occurs after ingestion of >10 g as a suicide attempt or inadvertently over several days • Labs–predominantly hepatocellular pattern of injury with marked transaminase elevation and relatively low bilirubin • Rapid progression to ALF accompanied by hypoglycemia, lactic acidosis, and renal failure with 72–96 hr	Favorable
Idiosyncratic drug-induced liver injury	• Acute-to-subacute presentation • Not necessarily dose dependent, and latency period is highly variable • Labs–pattern of liver injury is variable • Antimicrobials, followed by complementary and alternative medications are the most common culprits	Poor
Viral hepatitis	• Hyperacute-to-subacute presentation • Hepatitis A, B, and E virus infections are most common causes • Hepatitis B reactivation represents acute presentation of chronic liver disease • Labs–Predominantly hepatocellular pattern of liver injury with marked transaminase elevation • Viral prodrome with symptoms of acute gastroenteritis or generalized malaise often precedes onset of ALF	Variable (favorable for HAV, but poor for HBV, and HEV during pregnancy)
Pregnancy related	• Acute presentation • Hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome and acute fatty liver of pregnancy (AFLP) are most common causes, both occurring in the third trimester or immediately postpartum • Labs–hepatocellular pattern of injury with median AST/ALT >10× ULN • Half of cases with ALF in pregnancy are due to conditions observed in nonpregnant individuals, particularly acetaminophen hepatotoxicity	Favorable
Autoimmune hepatitis	• Acute-to-subacute presentation • May occur de novo or represent fulminant exacerbation of chronic liver disease • Labs–predominantly hepatocellular pattern of injury with marked transaminase elevation, accompanied by elevated ant-nuclear antibody, anti-smooth muscle actin antibody and elevated immunoglobulin G levels • Characteristic findings on liver biopsy include centrilobular hemorrhagic necrosis and confluent necrosis superimposed on chronic hepatitis and a plasma cell-rich infiltrate	Poor
Wilson disease	• Acute-to-subacute presentation • May represent fulminant exacerbation of chronic liver disease or occur after discontinuation of copper-chelating therapy • Labs–predominantly hepatocellular pattern of injury with modest transaminase elevation and normal or very low alkaline phosphatase • Patients often young and present with Coombs-negative hemolytic anemia with features of acute intravascular hemolysis and rapid progression to renal failure	Poor
Mushroom poisoning	• Acute presentation • Most associated with ingestion of Amanita species among mushroom foragers • Labs–predominantly hepatocellular pattern of injury with marked transaminase elevation • Patients present with severe gastroenteritis symptoms 6–12 hr after ingestion, with evolving hepatotoxicity within 24–36 hr and onset of progressive liver and multiorgan failure within 4–7 d	Favorable
Budd-Chiari syndrome	• Acute-to-subacute presentation • Most commonly affects women in their fourth to fifth decades of life • Often associated with hypercoagulable states • Obstruction of hepatic venous outflow tract causes severe intrahepatic ischemia and massive hepatocyte necrosis • Labs–predominantly hepatocellular liver injury pattern with marked transaminase elevation in the 1000s and AST:ALT ratio often exceeds 1 • Patients present with abdominal pain and ascites	Favorable

Table 5. (*continued*)

Etiology	Clinical features	Prognosis
Ischemic liver injury	• Acute presentation • Often occurs in the setting of congestive heart failure, sepsis, traumatic injury, or major surgery • Labs–predominantly hepatocellular pattern of injury with marked AST elevation >10,000 IU/L • Bilirubin and INR often worsen despite improvement in transaminase levels	Favorable (with restoration of hemodynamic stability)
Malignant infiltration	• Acute presentation • Lymphoma, leukemia, breast cancer, and colon cancer are most common causes • Patients often present with abdominal pain, jaundice, hepatic encephalopathy, and hepatomegaly • Labs–mixed hepatocellular and cholestatic pattern of injury, often with elevated alkaline phosphatase, gamma-glutamyl transferase along with marked transaminase elevation approximately 40× ULN • Diagnosis largely relies on liver or bone marrow biopsy	Poor

ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HEV, viral hepatitis E; INR, international normalized ratio.

What Acute Liver Failure Is Not

ALF may be confused with acutely decompensated cirrhosis or acute on chronic liver failure. Cirrhosis is highly prevalent leading to approximately 1 million deaths annually worldwide (19). The compensated patient with cirrhosis will ultimately develop decompensation with complications such as ascites, variceal hemorrhage, and HE (20,21). Therefore, it is much more likely that the hospitalized patient with liver failure will have decompensated cirrhosis than ALF. These patients are generally easily distinguishable from true patients with ALF, and their management differs significantly.

Acute on chronic liver failure (ACLF) presents with acutely decompensated cirrhosis and carries a very high short-term (<28 days) mortality (22,23). It most often develops in the patient with cirrhosis in the setting of superimposed liver injury leading to profound systemic inflammation (i.e., viral infection, DILI, alcohol-associated hepatitis, and bacterial infection). ACLF is characterized by 3 major elements: intense systemic inflammation, a close temporal relationship to the precipitating events, and it is associated with single-organ or multiple-organ failure (22). It can at times be difficult to distinguish ACLF from ALF if the underlying cirrhosis is unknown or unrecognized. It is critical, however, to make this distinction because the management of each is significantly different (Table 6).

EPIDEMIOLOGY

ALF remains rare, and data regarding its true incidence are not robust. Published studies are limited by the use of cohorts, the source of patient population (e.g., general population vs insurance databases), or the inclusion of only a single cause of ALF (i.e., DILI). Very few population studies have been published. Most of the available data are from large registries in the United States and Europe. In addition, data often are tainted by inaccurate coding of decompensated cirrhosis or ACLF as ALF.

Overall, the incidence has been reported to be approximately 1–6 cases per million population in developed countries (24). In the United States, estimates suggest that there are approximately 2,000–3,000 cases per year (8,25–27). In population-based cohorts in the United Kingdom and Scotland, the incidence is up to 0.8 per 100,000 person-years (PY) and ~0.62 per 100,000 PY, respectively (28,29). Recent data from a state-insured cohort in Germany suggested that the incidence was up to 1.13 per 100,000 PY (30,31). The incidence of drug-induced ALF in a US-based health system was 0.161 per 100,000 PY (32). These figures are lower than those reported in Taiwan (8.02 per 100,000 PY) and Thailand (6.29 per 100,000 PY) (15,33). Even less data exist on the economic burden of the disease. To date, there are few controlled clinical trials on management. With a lack of solid data, all ALF guidelines and position papers—including our own—are predominantly based on expert opinion, rather than evidence-based medicine (8).

GENERAL MANAGEMENT

Initial assessment and diagnostic evaluation

A critical aspect of the initial evaluation should focus on distinguishing between acute and chronic or acute-on-chronic liver failure. Extensive laboratory and imaging tests will help in making that differentiation. Obtaining a complete history is of utmost importance when considering a patient with ALF, specifically focused on the timeline of symptom development, history of chronic liver disease, alcohol consumption, viral risk factors, and a thorough prescription and over-the-counter medication review. A review of the patient's prescription history, use of complementary and alternative medications (CAM), and review of controlled substance monitoring databases should be performed promptly. All attempts should be made to contact next of kin or those who had contact with the patient before the presentation if patient history is not obtainable.

Patients with ALF should be referred for consultation by hepatology or gastroenterology as soon as possible after identification. Prognostic assessment and decision related to transfer and LT should be made as early as possible. For patients unlikely to survive with medical treatment alone, early referral to a liver transplant center is essential because a transfer may take time to arrange and patients may deteriorate quickly (34).

A thorough physical examination should focus on vital signs, presence of jaundice, signs of chronic liver disease, and a careful assessment of mental status. Encephalopathy due to ALF, also known as type A HE, can be graded according to the West-Haven Criteria (Table 7) (35,36). Grade 2 encephalopathy should

Table 6. Differences between ALF and ACLF

	ALF	ACLF
Age	Younger	Older
Chronic liver disease	Absent	Present Signs of portal hypertension
Precipitating factors (by frequency)	DILI, viral hepatitis, autoimmune hepatitis	Infection, alcohol, GI bleeding,
Clinical signs	Liver injury, INR>1.5, HE	Coagulopathy, elevated bilirubin, shock, multiorgan dysfunction
Liver biopsy	Necrosis and collapse	Fibrosis
CNS	Increased intracranial pressure Use CRRT early for HE	HE responds to lactulose/Rifaximin
Infection	Late (<5 d)	Early (<5 d)
Renal failure	Hypoperfusion, ATN	HRS-AKI
Respiratory	ARDS rare	ARDS common
Liver transplantation	KCC, MELD Status 1A listing	MELD No priority in MELD system

ACLF, acute on chronic liver failure; ALF, acute liver failure; ARDS, acute respiratory distress syndrome; ATN, acute tubular necrosis; CNS, central nervous system; CRRT, continuous renal replacement therapy; DILI, drug-induced liver injury; GI, gastrointestinal; HE, hepatic encephalopathy; HRS-AKI, hepatorenal syndrome-acute kidney injury; INR, international normalized ratio; KCC, King's College Criteria; MELD, Model for End-Stage Liver Disease.

prompt transfer to intensive care unit (ICU), while intubation for airway protections should be considered for grades 3 and 4 HE. Coagulopathy should be assessed in every patient. Initial laboratory and diagnostic evaluation are further outlined in Table 8.

Imaging studies can help identify patients with underlying chronic liver disease or ACLF with findings such as shrunken liver size, presence of regenerative nodules, and irregular liver surface (37). However, liver may also appear shrunken in the setting of ALF due to a massive collapse (Romero, 2014 #1759). Chronic alcohol consumption adversely affects outcomes in ALF (38). Therefore, tests to diagnose underlying chronic liver diseases, including cirrhosis, and alcohol-induced liver diseases, should be performed. Urine and serum toxicology screenings should be obtained, including urinary ethyl glucuronide or serum phosphatidyl ethanol (PETH), which help identify the evidence of alcoholic consumption using laboratory-provided cutoff values.

Key concepts

- Comprehensive testing to elucidate a diagnosis and exclude underlying chronic liver disease is essential in the evaluation of ALF (Table 8).
- Biomarkers (ethyl glucuronide or PETH) should be used in addition to psychosocial assessment when alcohol-induced liver disease is suspected.
- Grade 2 encephalopathy should prompt transfer to ICU while intubation for airway protections should be considered for grades 3 and 4 HE.
- Referral for consultation by hepatology or gastroenterology as soon as possible after identification of ALF. Early communication with the transplant center is crucial to patient management.

When to biopsy

Liver biopsy can be helpful in diagnosing the etiology of ALF and predicting outcomes in selected patients. An accurate diagnosis helps in the management. Liver biopsy can help to rule out infiltrative disease or malignancy and to identify patients with contraindication to LT. In addition, liver biopsy can aid in the diagnosis of AIH, which may respond to immunosuppressive therapy and potentially spare patients the long-term complications of LT. There have been concerns that the risks of liver biopsy are greater in patients with coagulopathy, and serious adverse events have been reported after percutaneous liver biopsy including bleeding, organ perforation, sepsis, and death (39). Similar to findings reported in the American Gastrological Association 2017 technical review (40), we did not identify any studies that specifically compared the diagnostic accuracy or the outcome of liver biopsy with the clinical diagnosis only. On the contrary, several small observational studies suggested that liver biopsy, especially transjugular liver biopsy (TJLB), is safe and effective in the diagnosis and potentially the prognosis of patients with ALF.

TJLB is currently a frequently used technique to obtain liver tissue (41). Mini laparoscopy with liver biopsy in patients with ALF and severe coagulopathy is safe, although this invasive method is not widely available in many centers (42). A small retrospective study compared 102 TJLB with 112 mini-laparoscopic liver biopsies and 100 percutaneous liver biopsies, although only 32 patients had ALF (43). Despite a smaller biopsy sample in TJLB, data suggest that it is safe and valuable in determining hepatocellular necrosis in patients with ALF. In 66 patients with ALI/ALF from Europe, 5 patients with suspected liver involvement by extrahepatic disease were confirmed and 8 excluded through the biopsy (44). Hepatocellular necrosis has been reported to be a predictor of a higher rate of death; thus, TJLB may be valuable in non-APAP ALF in deciding whether and when to perform an LT (43,45,46). Newer techniques such as endoscopic ultrasound–guided liver biopsy and portal pressure measurements have not been studied or validated in this patient population (46,47).

Table 7. Management according to grade of hepatic encephalopathy (West-Haven Criteria) (36)

Grade of HE	Symptom description	Management in ALF
Grade 1	Trivial lack of awareness Shortened attention span Impairment of addition or subtraction Altered sleep rhythm	• Contact transplant enter and initiative transfer • Obtain baseline CT head
Grade 2	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis	• Transfer to the intensive care unit • Neuro checks q1 hr
Grade 3	Somnolence to semistupor Responsive to stimuli Confusion Gross disorientation Bizarre behavior	• Intubation if appropriate • Repeat CT head • Avoid opioids and benzodiazepines for sedation • Consider propofol due to short half life
Grade 4	Coma	• Repeat CT head • Consider intracranial pressure monitor if transplant candidate • Initiate treatment for cerebral edema

ALF, acute liver failure; CT, computed tomography. HE, hepatic encephalopathy.

Table 8. Initial diagnostic workup

	Laboratory analysis	Imaging	Consultations
All patients	General • CBC, CMP, Mg PO4, LDH, CK • INR, Fibrinogen, PT • ABG, arterial lactate • Blood culture, urine culture • ABO match and screen • Serum beta-hCG (all females) Viral • HAV IgM, HBsAG, HBcIgM, HBV PCR, HCV PCR, HEV PCR (if endemic) • EBV PCR, CMV PCR, HSV PCR, VZV PCR Toxicology • Serum acetaminophen • Serum ASA • Urine drug screening Autoimmune • ANA, F-Actin • IgG, IgM, IgA Metabolic • Ceruloplasmin • Ferritin	ECG CXR Abdominal ultrasound with Doppler CT head (if encephalopathy) Consider contrasted imaging	Hepatology Gastroenterology ICU Contact transplant center
Transplant candidate	HIV, QuantiFERON gold, cryptococcal antigen, treponemal antibody, second ABO match, and screening	Contrasted imaging if renal function allows TTE Repeat CT head with any change in mental status Consider ICP monitor	Psychiatry Social work Hepatobiliary surgery

ANA, antinuclear antibody; CBC, complete blood count; CK, creatinine kinase; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HEV, viral hepatitis E; HSV, herpes simplex virus; ICP, intracranial pressure; ICU, Intensive Care Unit; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; PT, prothrombin time; TTE, transthoracic echocardiogram; VZV, varicella zoster virus.

Key concepts

- Liver biopsy may help exclude infiltrative disease and malignancy and to identify patients with contraindication to LT.
- Liver biopsy may help diagnose AIH, which may respond to immunosuppressive therapy and potentially spare patients the long-term complications of LT.
- There is insufficient evidence to recommend the routine use of liver biopsy in other settings.
- When considering liver biopsy in the evaluation of patients with ALF, we suggest using TJLB over other methods.

When to refer for liver transplantation

LT is a lifesaving procedure for some patients with ALF, but it relies on graft availability, requires significant resources, has significant morbidity and mortality, and commits patients to lifelong immunosuppression. No studies address whether a transfer to or the timing of transfer to a liver transplant center affects outcome. Approximately half of patients with ALF will undergo liver transplant; the 1-year survival rates are 79% in Europe and 84% in the United States (46).

Several prognostic scoring systems have been validated for ALF (48). The 2 most studied systems are King's College Criteria (KCC) and Model for End-Stage Liver Disease (MELD). A meta-analysis suggests KCC more accurately predicts hospital mortality among patients with acetaminophen-associated ALF, whereas MELD scores more accurately predict mortality among patients with nonacetaminophen-associated ALF (49). See "Prognostic Models" and "Liver Transplant" sections below for more information (Table 11).

SYSTEM-SPECIFIC MANAGEMENT

CNS

The neurological manifestations of ALF range from hyperammonemia to HE and ultimately CE with increased intracranial pressure (ICP) resulting in neurological injury and death (50). Continuous renal replacement therapy (CRRT) has been shown to effectively lower ammonia levels in patients with ALF (51). Analysis of data from a large cohort of patients in the US ALF Study Group (US ALFSG) showed that this reduction in serum ammonia level is associated with reduced mortality and increased transplant-free survival (TFS) at 21 days (52). The decrease in intracranial hypertension (ICH) and CE was associated with an increased use in CRRT in APAP-induced ALF (53).

Ornithine phenylacetate reduces ammonia levels with ornithine acting as a substrate to trap ammonia by forming glutamine. Glutamine is then combined with phenylacetate, and the phenylacetate-glutamine complex is excreted in the kidneys (54). This was hailed as a potential new therapy for reducing ammonia in the setting of HE (55). However, recent data from a randomized controlled trial of 231 patients with cirrhosis failed to show any improvement compared with standard of care and placebo; therefore, its use in the ALF setting cannot be endorsed (56).

The progression to grade 2 encephalopathy necessitates the move to an ICU setting for closer monitoring and intervention. The nonabsorbable disaccharide lactulose remains the first-line therapy for HE in chronic liver disease. Oral administration has been adopted for those patients with ALF alert enough to maintain a safe airway (grade 1–2 encephalopathy). One must be mindful of the timing of anticipated liver transplant surgery because bowel gaseous distention can be problematic intraoperatively.

Rifaximin in addition to lactulose is more effective than lactulose alone in patients with chronic liver disease (57,58). Extrapolating from these data, many transplant centers have adopted the use of rifaximin in the setting of ALF. Data for this practice are lacking in the setting of ALF.

Those with advanced grade 3–4 HE should undergo endotracheal intubation for airway protection. Lactulose should be discontinued in this setting.

The overall incidence of increased ICP is declining in ALF but when present, the associated mortality remains high (53). First-line treatment of increased ICP includes hyperosmolar therapy (mannitol, hypertonic saline), hyperventilation, and CRRT (59). Hyponatremia should be avoided. It is a common practice to target serum sodium concentration of 145–150 mmol/L; however, we failed to identify any supporting literature for this practice. When correction is undertaken, it should be accomplished at a slow rate, not exceeding 6–8 mmol/L in 24 hours as it is recommended for other disease entities. Hypertonic saline is sometimes used to counteract the effect of CE. General recommendations are for 3% saline in a bolus of 250–500 mL volume or a continuous infusion to maintain serum sodium levels below 160 mmol/L (60–62).

The utility of ICP monitoring has been called into question, especially given the increased use of CRRT resulting in lower rates of ICH. One group demonstrated that patients with APAP-induced ALF had outcomes comparable with those observed with traditional management without the use of ICP monitoring or LT (63). Recent reviews show no survival advantage for ICP monitoring and favor general use of ICP-lowering strategies (64). ICP monitoring may be considered in centers with expertise and in highly selected patients.

A recent review that included randomized controlled trials, case reports, and observational studies analyzed the use of therapeutic hypothermia to improve refractory ICH and improve patient outcomes in the setting of ALF (65). They concluded that the studies were heterogenous and intervention did not improve overall patient survival despite efficiency and a low risk of bleeding.

Key concepts

- Patients with ALF with grade 2 or higher encephalopathy should be monitored in an ICU setting.
- Patients with ALF with grade 3 and 4 encephalopathy should be intubated for airway protection.
- There is no conclusive evidence to recommend for or against the use of lactulose or rifaximin for the treatment of encephalopathy in patients with ALF.
- There is no conclusive evidence to recommend routine ICP monitor placement in patients with ALF.
- There is no conclusive evidence to recommend routine use of hypothermia to control ICP in patients with ALF.

Recommendation

1. In patients with ALF and grade 2 or higher encephalopathy, we suggest early CRRT for the management of hyperammonemia even in the absence of conventional RRT indications. GRADE recommendation: conditional, very low quality of evidence.

Coagulopathy

The exact mechanism of coagulopathy in ALF is complex and remains incompletely understood; multiple factors contribute to changes of hemostasis in ALF (66). Despite the frequently extreme elevation of the INR and the prognostic significance of prolonged prothrombin time, INR is not an accurate predictor of bleeding risk in ALF (67). Current evidence suggests a rebalanced state of hemostasis in ALF (66, 68, 69). Clinically significant bleeding is uncommon in patients with ALF accounting for death in only approximately 5% of cases (69). A recent large cohort study suggests that bleeding in ALF may be related to systemic inflammation and not a primary coagulopathy (70). The elevated INR value in ALF is often misinterpreted as a marker of increased hemorrhagic tendency, which may lead to improper prophylactic transfusion of blood products. The use of fresh frozen plasma, cryoprecipitate, platelets, or other correction in routine settings may lead to the increased risk of death or need for LT partly due to the associated risk of transfusion reaction, thrombosis, and transfusion-related acute lung injury (69,71).

Other means of assessing the need for transfusion before invasive procedures are being evaluated. Viscoelastic testing (VET) (most commonly rotational thromboelastometry and rotational thromboelastography) may allow for a more global assessment of the procoagulant and anticoagulant pathways, hyperfibrinolysis, platelet function, and clot formation (72). Stravitz et al prospectively reviewed 51 patients with ALI/ALF of which 62% had normal mean rotational thromboelastography parameters despite a mean INR of 3.4 ± 1.7 (72). Rotational thromboelastometry data were evaluated in 200 patients from the ALF Study Group and were shown to be associated with disease severity, while association with bleeding events was less clear. One limitation may be that VET lacks the ability to adequately assess the activity of protein C and von Willebrand factor, which are key to anticoagulant balance. More studies are needed before being able to uniformly recommend the use of VET in ALF. Currently, the Society of Critical Care Medicine recommends the use of VET instead of INR for the assessment of bleeding and thrombosis risk in critically ill patients with ALF (73).

Correction of coagulopathy may be necessary before invasive high-risk procedures, such as ICP monitoring, because invasive ICP monitoring is believed to be associated with the risk of intracranial hemorrhage. FFP and platelet transfusions have inherent volume overload risk, and Factor VII has been used in these settings (74). However, a retrospective multicenter cohort study suggested bleeding is uncommon (7%) and cannot account for mortality trends (75). A recent experience from a tertiary referral center together with a comprehensive literature review suggests ICP monitors can be placed safely in ALF when clinical protocol is followed, including aggressively correcting coagulopathy (74).

Key concepts

- The INR does not accurately reflect bleeding risk in patients with ALF.
- Viscoelastic tests may provide a more accurate assessment of coagulopathy in patients with ALF.

Recommendation

2. In patients with ALF, in the absence of active bleeding or impending high-risk procedure, we recommend against routine correction of coagulopathy. GRADE recommendation: conditional, very low quality of evidence.

Infection

Patients with ALF have a high incidence of bacterial infections associated with a high mortality (76,77). Fungal infections account for up to 32% of infections (77). For that reason, there has been a tendency to prophylactically treat with antimicrobials. This intervention has not been supported by data. In a large retrospective cohort report from the US ALFSG, Karvellas et al reviewed 1,551 patients to examine the effects of prophylactic antimicrobials and development of blood stream infection. The results showed that antimicrobial prophylaxis did not reduce the rate of bloodstream infection or 21-day mortality (75). It would be helpful to have reliable predictors for early detection of infection. The usual indicators of leukocytosis and fever are absent in up to 30% of cases with ALF with infection (77). To identify biomarkers that might be an early indication of infection, Rule et al (78) compared procalcitonin levels in the sera of patients with ALF with those with chronic liver disease. Procalcitonin levels in most of the samples of both groups were elevated, but there were no differences between the uninfected group and the group with documented infection. Procalcitonin seems to indicate inflammation and is a poor indication of infection. In the absence of surrogate indications of infection, it is recommended that regular surveillance of blood, urine, and sputum cultures be performed (77). If antimicrobial prophylaxis is undertaken, this should keep in mind local microbial resistance patterns.

Key concepts

- In patients with ALF, early assessment for infection is prudent because clinical signs of infection are frequently absent.
- There is insufficient evidence in patients with ALF to recommend the use of procalcitonin as a biomarker of infection.
- Empiric antibiotic and antifungal therapies may be considered in the setting of clinical deterioration of the patient.
- In patients with ALF, we suggest regular surveillance cultures; however, the optimal frequency is unknown.

Recommendation

3. In patients with ALF, we recommend against the routine use of prophylactic antimicrobial agents, given no improvement in either the rate of bloodstream infection or 21-day mortality. GRADE recommendation: conditional, low quality of evidence.

Hemodynamics and renal failure

The hemodynamic profile in ALF resembles that of septic shock exhibiting a hyperdynamic circulation with high cardiac output, low systemic vascular resistance, and decreased effective circulating volume (79). As such, most of the recommendations for hemodynamic management are similar to those of patients with sepsis. Intravenous (IV) fluid resuscitation is the primary intervention to maintain adequate tissue perfusion. To avoid volume overload and potential increase in ICP, Audimoolam et al (80) propose using pulse pressure variation measurements to assess fluid responsiveness and guide the need for vasopressor use. This intervention requires local expertise, and further validation is needed to recommend its use. When IV fluid administration is ineffective, vasopressor use is the next reasonable step to maintain a satisfactory mean arterial pressure (MAP). The target range of MAP is to maintain a cerebral perfusion pressure of

60–80 mm Hg. Norepinephrine is the preferred vasopressor due to its association with survival benefit and decreased adverse outcomes (73,81). Vasopressin may be added to potentiate the effects of norepinephrine if needed (73).

Acute kidney injury, as defined by the acute kidney injury network criteria (Table 9), is common in the setting of ALF (82). Up to 70% of patients in the US ALFSG experienced AKI with 30% requiring renal replacement therapy (RRT) (83). One European center reported an incidence of AKI in 63.4% of patients with ALF admitted to the ICU (84). The pathogenesis is multifactorial and includes direct nephrotoxicity, sepsis, or hemodynamic instability. According to Organ Procurement and Transplant Network data, 56% of 2,280 patients with ALF listed for transplantation from 2002 to 2012 had renal dysfunction, and the increased severity was associated with increased mortality (85). Most patients in the US ALFSG cohort with AKI did not require ongoing renal support after resolution of ALF (83).

Indications for RRT include acid-base disturbances, oliguria, and volume overload (86). CRRT is the preferred modality because it is associated with a lower risk of cardiovascular instability and CE compared with intermittent hemodialysis (87,88). CRRT effectively lowers ammonia level; therefore, hyperammonemia has become an increasing indication for RRT independent of AKI (89). In this setting, early CRRT improves survival by preventing severe hyperammonemia and the associated complications (89). Therefore, it is important to consider RRT for other indications independent of AKI.

Key concepts

- In patients with ALF and hypotension, IV fluid resuscitation should be initiated.
- RRT should be considered early in patients with acute kidney injury, electrolyte or metabolic abnormalities, and/or volume overload.
- In patients with ALF requiring RRT, we recommend CRRT over intermittent hemodialysis.

Recommendations

4. In patients with ALF, we recommend norepinephrine as the first-line vasopressor for hypotension refractory to fluid resuscitation. GRADE recommendation: strong, moderate quality of evidence.
5. In patients with ALF with hypotension not responsive to norepinephrine, we suggest adding vasopressin as a secondary agent. GRADE recommendation: conditional, low quality of evidence.

Nutritional and metabolic support

There is severe loss of hepatocellular function in ALF resulting in abnormal carbohydrate, protein, and lipid metabolism. At the same time, it has been shown that the energy expenditure increases by 18%–30% compared with healthy controls (90,91). It is recommended that patients with ALF be provided with nutritional support if they are not expected to resume oral intake in a 5- to 7-day period (92). Oral nutrition can be considered in cases of mild mental status alterations. Otherwise, enteral support is preferred when feasible and patient safety allows. Standard supplements should suffice because there is insufficient data to recommend disease-specific formulas.

Increased protein intake has not been shown to worsen encephalopathy in patients living with cirrhosis, and administration of 1.0–1.5 gm/kg of protein daily is recommended (93). There is concern regarding increased protein intake in the setting of severe hyperammonemia (>150 μMol/L) and HE in ALF. Consideration can be given to delayed supplementation for the first 24–48 hours with restarting at a lower range (1.0 gm/kg) daily and with close monitoring of serum ammonia levels.

The short duration of ALF may make nutritional support less crucial. A focus on glucose, fluid, and electrolyte support is of more urgent concern. Hypoglycemia is a frequent manifestation in patients with ALF due to decreased hepatic glycogen stores, impaired gluconeogenesis, and insulin resistance. Hypoglycemia can contribute to encephalopathy and has been associated with an increased mortality; therefore, monitoring of mental status every 1–2 hours is recommended. For hypoglycemia, a constant infusion of dextrose 10% solution should be used to maintain blood sugar level in the range of 150–180 mg/dL (94). Infusion of hypotonic solutions should be avoided because of the risk of hyponatremia and the development or worsening of CE. Magnesium and phosphorus levels should be monitored every 8–12 hours and replenished as needed.

Key concepts

- In patients with ALF, monitoring and correction of glucose, fluid, and electrolyte imbalances should be performed.
- In patients with ALF, enteral nutritional support should be started if the patient is unable to resume oral intake within 5–7 days.

Other management considerations

High-volume plasma exchange (HVPE)—plasmapheresis of 8–12 L or 15% of ideal body weight with fresh frozen plasma—has been associated with improved transplant-free survival (95). A retrospective review of 32 patients with ALF awaiting LT found the

Table 9. Acute Kidney Injury Network criteria (Lafaine)

	Creatinine criteria	Urine output criteria
An acute rise in SCr within 48 hr		
Stage 1	Increase in SCr ≥ 1.5× baseline or SCr ≥ 0.3 mg/dL (≥26.4 μmol/L)	UO < 0.5 mL/kg per hr × 6 hr
Stage 2	Increase in SCr ≥ 2.0× baseline	UO < 0.5 mL/kg per hr × 12 hr
Stage 3	Increase in SCr ≥ 3.0× baseline or SCr ≥4.0 mg/dL (354 μmol/L) Initiation of RRT	UO < 0.3 mL/kg per hr × 24 hr or anuria × 12 hr

RRT, renal replacement therapy; SCr, serum creatinine.

overall survival was 94% in the treated group vs 69% in those who did not receive HVPE. After HVPE, coagulopathy, bilirubin, and ammonia levels were improved (96). However, there remains concern regarding its applicability across the varying etiologies of ALF (95).

Artificial liver support systems deserve special mention in the discussion of management of ALF. There is great interest in support devices that can be a bridge to transplant or liver recovery. There are 2 types of extracorporeal liver support devices: artificial liver support and bioartificial liver support. Currently, none have received US marketing approval from the US Food and Drug Administration (FDA) but are available for investigational or compassionate use. The best-known artificial systems are plasma exchange and those based on albumin dialysis, the Molecular Adsorbent Recirculating System, the Single-Pass Albumin Dialysis system, and Fractionated Plasma Separation and Adsorption system FPSA (FPSA; Prometheus). Martinez et al (97) presented efficacy data that found a lack of evidence to support any particular system. In the only randomized clinical trial of 102 patients, there was improved 6-month survival only in the APAP-induced ALF group (98).

Key concept

- There is insufficient evidence to recommend for or against the routine use of HVPE or artificial/bioartificial liver support devices in patients with ALF.

ETIOLOGY-SPECIFIC MANAGEMENT

In addition to the general management of the patient described earlier, the clinician needs to be aware of time-sensitive, etiology-specific interventions that should be instituted (Table 10).

Drug-induced liver injury

Acetaminophen hepatotoxicity. The analgesic-antipyretic agent acetaminophen (paracetamol; APAP) has become ubiquitous to nearly every household across the world. Although safe at the usual therapeutic dosage of up to 4,000 mg every 24 hours, the drug has emerged as the leading cause of DILI and ALF in the United States and many western countries (99,100). APAP-induced ALF may occur after a single intentional overdose of greater than 10–15 g, usually as part of a suicide attempt. Unintentional overdoses also occur with ingestion of large quantities (>10 g) over several days, generally for the treatment of acute or chronic illness and often involve multiple APAP-containing products. Fasting or ingestion of alcohol may further contribute to toxicity, even at the use of recommended dosages (99,100).

Acetaminophen hepatotoxicity occurs in a dose-dependent fashion. High doses overwhelm favorable sulfation and glucuronidation metabolism pathways. APAP is then shunted toward cytochrome P450-mediated oxidase pathways resulting in the formation of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI reacts with cellular proteins to NAPQI-protein adducts that induce oxidative hepatocyte injury and inflammatory processes leading to hepatic necrosis (99,100). APAP levels may be undetectable at presentation, and the detection of NAPQI-protein adducts may aid in the identification of APAP-induced liver injury when they become clinically available (101,102).

Patients with APAP-induced ALF may be asymptomatic or have nonspecific, constitutional symptoms on initial presentation, with relatively rapid progression to liver failure within 72–96 hours after toxic ingestion. Laboratory studies characteristically show a predominantly hepatocellular pattern of liver injury with marked transaminase elevations often exceeding 3,000 U/L with coagulopathy and relatively mild hyperbilirubinemia.

Most patients with APAP-induced ALF will recover with aggressive medical management, particularly when an overdose has been identified early and treatment initiated promptly. However, APAP-induced ALF is associated with an approximately 28% mortality rate, and up to a third of patients will require LT (103).

Management of acetaminophen hepatotoxicity. Patients with suspected APAP hepatotoxicity should receive immediate intervention. Early gastric decontamination with 1–2 g/kg of single-dose activated charcoal is effective if administered within the first 4 hours after ingestion (104). There are data to support administration after 4 hours with improved outcomes especially when coadministered with *N*-acetylcysteine (NAC) (105,106). Use of activated charcoal must take into consideration the

Table 10. Etiology-specific management

Recommended treatment based on etiology of Acute Liver Failure	
Etiology	**Treatment**
Acetaminophen	IV protocol 300 mg/kg total dose • 1st bag = 150 mg/kg/loading dose over 1 hr • 2nd bag = 50 mg/kg over 4 hr = 12.5 mg/kg/h • 3rd bag = 100 mg/kg over 16 hr = 6.25 mg/kg/h Extended IV protocol (Fontana 2008) • 1st bag = 50 mg/kg over 4 hr • 2nd bag = 125 mg/kg over 19 hr • Remaining bag = 100 mg/kg over 24 hr × 2 d or until INR <1.5 Oral protocol 72 hr 1,330 mg/kg total dose • Loading dose 140 mg/kg = 35/mg/kg/hr (for 4 hr) • Maintenance doses 70 mg/kg every 4 hr × 17 doses (for 68 hr) = 17.5 mg/kg/h
Drug-induced liver injury	• Discontinue offending agent • Consider NAC for early coma grade • Corticosteroids for those with hypersensitivity or autoimmune features
Hepatitis B	Nucleoside analog (e.g., Entecavir, tenofovir)
HSV or VZV hepatitis	IV Acyclovir
CMV hepatitis	IV ganciclovir
Mushroom poisoning	• IV silibinin • IV penicillin
Wilson disease	• Continuous hemofiltration • Plasma exchange
Autoimmune hepatitis	IV corticosteroids
HELLP syndrome/ AFLP	• Prompt delivery of fetus • Supportive care
Budd-Chiari syndrome	• Anticoagulation with low-molecular weight heparin • Portal decompression with TIPS • Revascularization with angioplasty or stent

AFLP, acute fatty liver of pregnancy; ALF, acute liver failure; CMV, cytomegalovirus; HELLP, hemolysis, elevated liver enzymes, low platelets; HSV, herpes simplex virus; INR, international normalized ratio; IV, intravenous; NAC, *N*-acetylcysteine; VZV, varicella zoster virus.

patient's level of consciousness and cooperation to avoid the low risk of aspiration.

NAC is the only effective antidote for APAP hepatotoxicity. The oral regimen was first approved, but subsequently, the IV form has become the preferred route of administration, given the ease of use and tolerability (107). Continuing treatment beyond the initial protocol may be based on persistent coagulopathy (INR>1.5) and encephalopathy (108,109). Fontana et al (110) have proposed an extended protocol specifically in the setting of ALF.

Administration of NAC should begin as soon as toxicity is suspected, especially if time of ingestion is unknown because there is proven benefit of late administration of NAC (111). Clinical judgment should direct therapy, and it is reasonable to proceed with treatment while awaiting diagnostic test results. Administration can be guided by the Rumack-Matthew nomogram for assessing the potential for toxicity based on the time from ingestion and serum APAP level; calculators can be readily found online (112). The nomogram is most useful for single time point ingestions and is less useful for repeated ingestion or ingestion of sustained release products. The most commonly used end point is the improvement of INR to <1.5 (110). Others have suggested using an ALT <50% of peak value (or 3 consecutive values all <1,000 IU/L), an INR <2, and/or an undetectable APAP level.

Novel therapeutic interventions are being investigated. 4-Methylpyrazole has shown some promise in inhibition of NAPQI in early clinical trials of healthy volunteers (113). Calmangafodipir has also shown early safety and tolerability in patients cotreated with NAC, but data regarding mechanism of action and benefits are lacking (114).

Key concepts

- In patients with APAP-ALI or APAP-ALF, the duration of NAC treatment should be individualized based on the patient's clinical condition and laboratory values.
- In patients with APAP overdose, we recommend single-dose activated charcoal administration if ingestion is known to have occurred within 4 hours.

Recommendation

6. In patients with suspected APAP toxicity, we recommend early administration of NAC. GRADE recommendation: strong, low quality of evidence.

Nonacetaminophen drug hepatotoxicity

In the United States and several other western countries, idiosyncratic DILI (I-DILI) has emerged as the second leading cause of ALF after APAP hepatotoxicity (12,115,116). Unlike APAP hepatotoxicity, I-DILI is not necessarily dose dependent, and the latency period from ingestion to time of onset can be highly variable depending on the offending agent. Among a consecutive cohort of adult patients with I-DILI ALF, antimicrobials were the most commonly implicated class of drugs, including antituberculosis therapies, sulfa drugs, nitrofurantoin, terbinafine, and azole antifungals (117–119). CAM, including multivitamins, herbals, and bodybuilding, dietary, and weight loss supplements, represent the second most common category of drugs associated with I-DILI ALF (12,117–119). Indeed, there has been an 8-fold increase in CAM-associated ALF over the past 25 years, increasing from 2.9% to 24.1% of cases with I-DILI ALF (119). A review of US ALFSG data showed that most patients with I-DILI are women (66%–71%) (117,118). Over the past 20 years, the presentation of patients with I-DILI has evolved. Previously, most of them had advanced coma grade ≥2 (68%) (117). Newer data suggest a reversal in this trend, with most (66.4%) presenting with lower-grade encephalopathy (118). Most patients have deep jaundice, with bilirubin levels generally >15 mg/dL. Liver aminotransferases in most (72.9%–78%) demonstrate a predominantly hepatocellular pattern of liver injury with modest alkaline phosphatase elevations. Aminotransferases levels are generally <1,000 IU/L.

While I-DILI generally has a favorable prognosis, those progressing to ALF have dismal transplant-free survival of 23.5%–38.7% at 3 weeks and an overall survival rate of 66% (117,118). Recent studies suggest that CAM-induced ALF may be more severe than prescription medication–induced ALF, with significantly higher transplantation rates (61% vs 36%, $P < 0.005$) and lower 21-day transplant-free survival (17% vs 34%, $P = 0.044$) (119,120). Because a growing proportion of the population use CAM, healthcare providers must maintain a high index of suspicion for their use in patients with unexplained ALF. Resources such as the NIH-funded database www.LiverTox.nih.gov can be useful in the evaluation of patients with DILI and include available data regarding CAM ("National Institute of Diabetes and Digestive and Kidney Diseases," 2012).

Management of nonacetaminophen drug hepatotoxicity. Once the diagnosis is made, the suspect drug should be discontinued immediately. Subsequent care is mostly supportive. There is currently no specific therapy approved for the treatment of I-DILI, and evidence-based data for the management of resulting ALF are scarce and heterogeneous. The US ALFSG demonstrated that IV NAC improved TFS in patients with nonacetaminophen and early coma grade (grades I-II); 52% in the treatment group compared with 30% in the placebo group (121). A meta-analysis and systematic review of 883 patients demonstrated that overall survival, posttransplant survival, and TFS were better in the NAC-treated group compared with those in the control group (122). Five percent of these patients had drug-induced liver failure.

Corticosteroid therapy may be effective in patients with hypersensitivity or autoimmune features (123). Drugs such as minocycline and nitrofurantoin are typical culprits (124). The efficacy of corticosteroid therapy is less certain in those patients without immune-related features. Studies are small and heterogeneous making firm recommendations difficult. Some have shown that corticosteroid use shortened the time to peak bilirubin from 17 to 12 days, but there was no difference in outcome (125). Others have compared prednisone dosing of 40 mg with <40 mg and with control patients showing improved survival in the low-dose prednisone group compared with controls (100% vs 91.7%; $P = 0.35$) (126).

Immune checkpoint inhibitor hepatitis is reported in up 20% of those receiving therapy (127). Cessation of medication is crucial. Corticosteroid therapy is indicated for persistent grade 2 or any grade 3 or 4 elevation of aminotransferases or bilirubin (128–130). To date, ALF has rarely been described. In the event of severe hepatotoxicity, LT may not be a viable option due to underlying malignancy and risk of hyperacute rejection.

Recommendation

7. In patients with non-APAP ALF, we suggest the initiation of IV NAC. GRADE recommendation: strong, moderate quality of evidence.

Drug reaction with eosinophilia and systemic symptoms

Drug reaction with eosinophilia and systemic symptoms is a rare severe drug-induced systemic illness characterized by an extensive skin rash associated with fever, eosinophilia, atypical lymphocytosis, and multiorgan dysfunction. Patients typically present 2–8 weeks after exposure to an offending agent. Hepatotoxicity most commonly manifests as cholestasis (37%) or cholestatic hepatitis (27%) (131). Drug reaction with eosinophilia and systemic symptoms may progress to ALF (132). Ichai et al (132) showed that of 16 patients, 9 developed acute liver injury, and all had spontaneous improvement. Of the 7 who developed ALF, 2 died and 5 underwent LT.

Viral hepatitis

Worldwide, AVH is the leading cause of ALF (133). Despite widespread adoption of vaccination efforts and routine screening of blood products in western countries in North America, northern Europe, and the United Kingdom, AVH continues to account for a substantial proportion of ALF. Based on recent estimates from the US ALFSG, AVH accounts for 12% of cases with ALF, with hepatitis A, B, and E accounting for 3%, 7%, and 2%, respectively (24,134). Some countries remain particularly vulnerable to AVH-induced ALF, including Japan where 40% of cases with ALF are due to HBV and India/Bangladesh where nearly half of cases with ALF are due to acute HEV. Notably, acute hepatitis C (HCV) is generally not associated with ALF. Though rare, cases of ALF due to herpes simplex (HSV) and zoster, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus have been described, most often occurring in immunocompromised individuals (133). It is suspected that AVH-induced ALF is underrecognized, and a substantial proportion of indeterminate cases of ALF may indeed be due to an unidentified viral infection.

Most patients with AVH will often have an acute-to-subacute presentation with a viral prodrome of fevers, chills, nausea, vomiting, diarrhea, generalized malaise, body aches, or flu-like illness that precedes onset of ALF signs and symptoms, including jaundice, coagulopathy, and HE. For most implicated viruses, laboratory studies typically reflect a predominantly hepatocellular pattern of liver injury with markedly elevated transaminase levels. The clinical course and prognosis vary based on the particular virus. Due to poor spontaneous survival of 25% patients with AVH, liver injury or ALF should be managed in a transplant center (134).

Hepatitis A

Acute HAV infection generally has a favorable prognosis, with only a small proportion of patients (<1% of adults) progressing to ALF. However, among patients with HAV ALF, transplant-free survival is only 70%.

The ALFSG evaluated 29 patients with HAV ALF. They proposed a prognostic model on day 1 of presentation based on serum ALT <2,600 IU/L, creatinine >2.0 mg/dL, intubation, and pressor use. The presence of at least 2 of these 4 factors provided a sensitivity of 92%, specificity of 88%, and a positive predictive value of 86% in identifying worse outcomes defined by transplant or death (133,135). In addition, 25% of the patients showed negative results for PCR, and this status correlated with significantly worse outcomes defined by a lower rate of spontaneous survival, suggesting that a robust immune response to the virus leads to worsened liver injury in genetically susceptible individuals (136). Vaccination for HAV is readily available and can even be used in postexposure prophylaxis.

Management of hepatitis A. Management of HAV ALF is largely supportive because no specific antiviral agent has been proven to be effective. In the rare situations where it is needed, early LT is associated with good outcomes (137).

Hepatitis B

Acute HBV causes ALF in approximately 1% of infected patients, and its incidence may be underestimated partly because HBV DNA and hepatitis B surface antigen may be undetectable during presentation (138). In the United States, both de novo infection among at-risk individuals (injection drug users, men who have sex with men, and sex workers) and reactivation of latent infection among immunocompromised individuals represent a significant proportion of cases with HBV ALF. HBV ALF generally has an unfavorable prognosis, likely partly due to the robust humoral immune responses implicated in its pathogenesis, which propagate ongoing liver injury despite antiviral treatment (133). Indeed, up to 75% of patients with HBV ALF will require LT or die because of their illness. A major risk factor of HBV ALF is coinfection or superinfection with hepatitis D virus. Up to 20% of HBV-HDV acute coinfection and 5% of HDV superinfection result in fulminant ALF with up to 80% mortality without transplant (139). Hepatitis B vaccination is safe, effective, and is widely available for all individuals.

Management of hepatitis B and D. It can be difficult to distinguish between primary infection and exacerbation of chronic infection in the absence of a clear history. The use of antiviral therapy in acute HVB-ALF is controversial. It is generally believed that antiviral therapy is less relevant in primary infections because the viral load (VL) is already low and the primary process of liver injury is immune mediated. Earlier studies showed a clear benefit of using lamivudine in patients with fulminant HBV, especially when initiated early (140,141). However, a later study reviewing acute HBV ALF showed no difference in outcomes between those treated with nucleoside (tide) analogs and those who were untreated (142). Antiviral therapy is justifiable in severe hepatitis due to reactivation of HBV due to the presence of high VL. If introduced early for severe reactivation HBV, lamivudine or entecavir significantly reduce VL, and tenofovir has shown improved survival (143,144). There are no data to support the specific use of tenofovir alafenamide in this setting.

There is no effective therapy for HDV superinfection beyond HBV antiviral therapy because treatment with interferon is contraindicated in ALF. The sodium taurocholate cotransporting polypeptide receptor-inhibitor Myrcludex B (bulevirtide) shows early promising results but has not been evaluated in ALF setting (145), and lonarfarnib (prenylation inhibitor) is currently undergoing phase 3 trials in non-ALF patients (145).

Hepatitis E

HEV infection accounts for up to 40% of cases of ALF in developing countries, and it is believed to be grossly underrecognized in western countries (146). Studies in the United States and Germany suggest that up to one-fifth to one-half of cases with ALF attributed to DILI were indeed due to HEV infection (147,148). Most cases are seen in the setting of pregnancy or immunocompromised patients. Pregnant women are at highest risk of mortality, with rates as high as 25% (147,148). Disseminated intravascular coagulation is a distinctive feature of HEV-ALF during pregnancy (149). There is an association of the severity of HEV infection and VL in the mother as a predictor

for vertically transmitted infection in the fetus (150). HEV recombinant vaccine was approved for us in China in 2012; however, no US FDA–approved vaccine exists in the United States.

Management of hepatitis E. Because most cases are self-limited, usually only supportive care is warranted. While there is some evidence to suggest treatment of chronic HEV infection with pegylated interferon or ribavirin (151,152), there is no proven benefit in ALF. As such, LT remains the only treatment option in HEV-ALF.

Rare viral infections. Case reports or series of patients with ALF attributed to HSV and zoster viruses, CMV, EBV, and adenovirus have been described (133). These infections are most often implicated in cases of ALF involving immunocompromised individuals. It is not always clear whether reactivation of latent viruses including EBV and CMV represents the primary liver insult or a consequence of a systemic disease process. Notably, in the setting of herpes viruses, skin manifestations are not always apparent.

Hepatitis C

HCV can cause severe hepatitis, but there is no definitive evidence that it causes ALF. Current antiviral therapies result in more than 95% cure of the infection.

Management of rare viral infections

Herpes simplex virus. Early antiviral therapy with IV acyclovir is indicated if HSV infection is suspected because this offers the best chance for a good outcome (153,154). Treatment should not wait on confirmatory serology. Unfortunately, despite rapid antiviral treatment, HSV-induced ALF carries a poor prognosis (155). Viral resistance to acyclovir is generally low but reaches up to 10% in the immunocompromised population (156). In those cases, IV foscarnet is a viable alternative. Based on the analysis of reported cases from the early 2000s, patients with HSV infection who are male, older, or immunocompromised with ALT >5,000 IU/L, platelets $<75 \times 103$/L, coagulopathy, and encephalopathy were at a higher risk of death or need for LTx (157). Ultimately, LT is a rescue therapy, and lifelong antiviral suppressive therapy is indicated due to the risk of recurrence.

Varicella zoster virus. Varicella zoster virus is a rare cause of ALF and should be suspected especially if a characteristic rash is present. As with HSV hepatitis, this should be treated promptly with IV acyclovir.

Cytomegalovirus virus. CMV is rarely implicated in the setting of immunosuppression. IV ganciclovir is recommended for the treatment of CMV hepatitis. Primary Epstein-Barr virus infection is seen in <1% of cases of ALF and is associated with a high case fatality rate (Mellinger et al, 2014). Treatment includes acyclovir or ganciclovir.

Key concept

- In patients presenting with ALF, grade 2 encephalopathy and features suggestive of HSV or zoster infection, we suggest empiric treatment with IV acyclovir until confirmatory testing with viral PCR is obtained.

Recommendation

8. In patients with ALF due to reactivation of HBV, we recommend starting antiviral therapy with entecavir-based or tenofovir-based regimen. GRADE recommendation: strong, low quality of evidence.

Mushroom poisoning

Hepatotoxicity after ingestion of amatoxin-containing mushrooms, including species from 3 different genera—*Amanita* sp., *Galerina* sp., and *Lepiota* sp.—has been well described. Approximately 50 lethal exposures are reported annually in the United States. Most cases are related to ingestion of Amanita species. Amatoxins are heat stable and insoluble in water, so toxicity occurs despite boiling, and ingestion of only 1- to 2 medium-sized mushroom caps is enough to deliver a lethal dose of amanitin. The toxins are concentrated within hepatocytes where they induce apoptosis. Patients with ALF typically progress through 3 distinct clinical phases after ingestion.

- 6–12 hours–gastroenteritis including vomiting, diarrhea, abdominal pain, and dehydration.
- 24–36 hours–a quiescent period with improvement in clinical symptoms but with laboratory evidence of evolving hepatotoxicity.
- 4–7 days–onset of progressive liver and multiorgan failure with coagulopathy, acidosis, encephalopathy, seizures, and renal failure

Confirmatory tests are not available, and a history of mushroom ingestion should be excluded in all patients presenting with ALF. While previously believed to be associated with a high risk of death without LT, more recent data suggest that most patients (23/27 patients) survive without transplantation. Factors that predicted a favorable prognosis included peak AST levels <4,000 IU/mL, peak INR <2, and serum factor V >30% (158).

In addition to classic prognostic criteria used in ALF, a mushroom-specific set of prognostic criteria has been suggested (Table 11) (159). The Escudie criteria demonstrated a 100% accuracy in predicting 28-day mortality and identified fatal cases earlier than King's College criteria (160). Based on these criteria, LT evaluation can be initiated even before the development of HE.

Management of mushroom toxicity

The poison control center should be contacted for guidance if the patient is suspected to have Aminata poisoning. Gastric lavage is recommended within 1 hour of toxin ingestion to prevent absorption. This may not be possible due to the lag time between ingestion to symptom onset and presentation to care. Contraindication to lavage includes recent surgery, gastrointestinal hemorrhage, and altered mental status (161). Activated charcoal is also recommended soon after ingestion to disrupt the enterohepatic circulation of the amatoxin (162). Recommended doses are 50 g every 4 hours or 25 g every 2 hours. This can be further reduced to 12.5 g every hour for tolerability (163). Up to 60%–80% of amatoxins are filtered through the kidneys in the first few hours of intoxication. IV hydration to maintain urinary output of 100–200 mL/hr for up to 4–5 days is recommended to sufficiently eliminate toxins and maintain hydration (161).

There is sufficient evidence to support the use of IV silibinin dihemisuccinate in acute amanita phalloides poisoning (164, 165). Within the first 24 hours, patients should receive IV silibinin dihemisuccinate at 20–50 mg/kg/d for 48–96 hours or alternatively, 5 mg/kg of IV silibinin dihemisuccinate over 1 hour, followed by 20 mg/kg/d for 6 days or until the serum transaminases normalize (164, 166). Silibinin is an α-amanitin membrane transport inhibitor and a scavenger of free radicals (167).

Table 11. Prognostic models

Prognostic model	Individual constituents	Comments regarding use
MELD score	INR, TB, creatinine	MELD >33 for APAP-induced and MELD>32 for non-APAP–induced ALF Sensitivity 74% Specificity 67%
King's College Criteria APAP-induced ALF Non-APAP–induced ALF	Arterial pH (<7.3 after resuscitation), lactate (>3 mmol/L) OR all of the following: HE (>grade 3), creatinine (>3.4 mg/dL), INR >6.5 INR (>6.5) OR three-fifths of the following etiology (indeterminant, DILI), age (>40), jaundice to encephalopathy time (>7 days), TB (>17.4 mg/dL), INR (>3.5)	Sensitivity 65% Specificity 93% Sensitivity 68% Specificity 82%
Clichy Criteria	HE and factor V (<20%) in age<30 OR factor V (<30%) in age>30	Sensitivity 56% for APAP-ALF Sensitivity 50% for non-APA ALF
Escudie Criteria (mushrooms)	• Interval between ingestion and diarrhea <8 hr or • A decrease in prothrombin index <10% of normal (approximately an INR>6 ≥ 4 d after ingestion)	One should not wait on the development of encephalopathy to determine transplant evaluation.
Swansea Criteria (ALFP)	• Vomiting • Abdominal pain • Polydipsia/polyuria • Encephalopathy • Elevated bilirubin >14 μmol/L • Hypoglycemia <4 mmol/L • Elevated urea > 340 μmol/L • Leukocytosis > 11 × 10^9 • Ascites or bright liver on ultrasound • Elevated transaminase > 42 IU/L • Elevated ammonia > 47 μmol/L • Renal impairment: Creatinine > 150 μmol/L • Coagulopathy: PT > 14 seconds or APPT > 34s • Microvesicular steatosis on liver biopsy	6 or more findings are required in the absence of another cause

ALF, acute liver failure; ALFP, acute fatty liver of pregnancy; APAP, N-acetyl-p-aminophenol; DILI, drug-induced liver injury; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

Despite this, the US ALFSG showed that only 23% of patients presenting with amanita-induced ALF received silibinin, 39% received penicillin, and 85% received NAC (168). Silibinin dihemisuccinate has not been US FDA approved in the United States, which likely accounts for the small number of patients receiving it.

IV penicillin G is also believed to block the hepatic uptake of α-amanitin. The dose consists of a continuous infusion of 1,000,000 IU/kg on day 1 and 1,500,000 IU/kg on days 2 and 3 (169). The results are inferior to those obtained with silibinin; therefore, penicillin G is considered the second-line therapy. IV NAC has been shown to be of benefit in treating amanita phalloides poisoning (170). The recommended dosing schedule is 150 mg/kg over 15 minutes, followed by 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours (163, 169). Alternate dosing similar to that used to treat acute APAP toxicity is also acceptable (121).

Because of rapid absorption and excretion, there is a low serum level of amatoxin compared with that in urine, and therefore, hemodialysis, hemoperfusion, and plasmapheresis are of little benefit, even if initiated early. There is some evidence to suggest that the Molecular Adsorbent Recirculating System may be beneficial, but more data are needed before this can be routinely recommended (171).

Ultimately, LT is an effective intervention for ALF due to amanita phalloides poisoning with excellent outcomes (172).

Key concepts

- In patients presenting with mushroom poisoning and acute liver injury, Escudie criteria can be used to predict the need for LT even before the development of encephalopathy.
- Gastric lavage and activated charcoal should be administered within the first few hours after ingestion, provided no contraindications exist.

Recommendation

9. In patients with ALF due to mushroom poisoning, we recommend initiation of IV silibinin as soon as possible. IV penicillin G may be used if IV silibinin is unavailable. GRADE recommendation: conditional, very low quality of evidence.

Wilson Disease

WD can manifest from asymptomatic liver enzyme abnormalities to acute decompensated disease (173). Most patients present between ages 5 and 35 years, and women are more likely to present with ALF (2:1 female-to-male). Patients with known WD can present with ALF on discontinuation or poor adherence to copper-chelating therapy.

Laboratory findings in WD ALF include Coombs-negative hemolytic anemia with features of acute intravascular hemolysis, rapid progression to renal failure, modest transaminase elevation, and normal or very low alkaline phosphatase (often <40 IU/L). Serum copper may be markedly elevated because of sudden release from injured liver tissue. Patients may have a low ceruloplasmin, but this finding is common in ALF even due to other etiologies. Liver biopsy is rarely needed, but if performed is often accompanied by underlying advanced fibrosis or cirrhosis. If the diagnosis remains in question, quantitative copper measurement of the liver tissue or genetic testing may be performed. However, these tests take time to result and should not delay consideration for transplantation.

Management of acute decompensated Wilson disease. The prognosis of patients with WD ALF is guarded without LT. Medical therapy alone is rarely successful at stabilizing disease. Various interventions such as plasmapheresis, albumin dialysis, plasma exchange, and continuous hemofiltration have been used for copper depletion to avoid renal injury but are only temporizing measures (174). Treatment with copper chelators (D-penicillamine and trientine) is ineffective in the setting of acute decompensated WD.

In addition to traditional prognostic criteria (King, MELD), several Wilson-specific indicators have been evaluated, including the WD prognostic index and the revised King's College score of the WD prognostic index (175). Ultimately, those with ALF should be listed for LT, which has excellent outcomes. United Network for Organ Sharing data from 1987 to 2008 demonstrated a 1-year and 5-year patient survival of 90.1% and 89% for children and 88.3% and 86% for adults, respectively (176).

Key concept

- In patients presenting with ALF due to suspected or confirmed Wilson disease, LT evaluation should be initiated during diagnosis due to the lack of effective medical therapy.

Autoimmune hepatitis

Acute severe AIH (AS-AIH) (jaundice; no cirrhosis, INR ≥1.5, and symptom onset <26 weeks) progresses to ALF in up to 3%–6% of patients (177–180). Studies suggest that Black patients with AIH are at a higher risk of ALF requiring LT compared with White patients (181,182). Human leukocyte antigen types human leukocyte antigen–DR3 and human leukocyte antigen DR7 are seen more commonly with type 2 AIH and have been associated with more severe disease presentation.

Diagnosis of AS-AIH–associated ALF can be difficult. There is overlap in the clinical and histopathologic features of true de novo AIH compared with exacerbation of chronic AIH or immune-mediated DILI (183). Patients typically have a subacute presentation, and liver tests show a predominantly hepatocellular injury pattern. Serologic evaluation may reveal elevated antinuclear antibody, antismooth muscle actin antibody, and elevated immunoglobulin G levels. Liver biopsy may show nonspecific findings. Distinguishing histological features include injury predominating in the centrilobular zone with prominent lymphoplasmacytic lobular inflammation and centrilobular confluent necrosis without significant portal inflammation (184,185). The US ALFSG proposed 2 specific patterns of massive hepatic necrosis—centrilobular hemorrhagic necrosis or confluent necrosis superimposed on chronic hepatitis—as more specific for an autoimmune etiology (179). A plasma cell infiltrate is also characteristic of AIH. It is likely that AS-AIH is underrecognized as an etiology of ALF leading to delayed treatment (186,187). According to US ALFSG data, up to 60% of patients with ALF with an indeterminate etiology probably had AIH.

The prognosis of AS-AIH ALF has improved significantly with the greater adoption of corticosteroid therapy and LT. Survival rates for AS-AIH ALF in the pretransplant era were less than 20% (188). More recent series show mortality rates of 16%–19%, and patient prognosis is largely associated with the severity of initial disease (189).

Management of autoimmune hepatitis. Corticosteroid therapy is well established in the management of chronic AIH. For those with AS-AIH without ALF, glucocorticoid therapy (prednisone or prednisolone alone, 0.5–1 mg/kg or a total of 60 mg daily in adults) can be beneficial without an increased risk of adverse outcome such as infection (189,190). Therapy should not delay evaluation for LT (186,191). Up to 48% of treated patients are likely to require LT (178).

In 128 patients with AS-AIH without ALF treated with corticosteroid therapy, De Martin et al identified lack of improvement in INR and bilirubin as predictive of a nonresponse. They concluded that the SURFASA score (created by combining the INR and bilirubin) was highly predictive (88% specificity, 84% sensitivity) of LT or death. They propose that within 3 days of initiating corticosteroids, the SURFASA score can identify nonresponders who should be referred for LT (192).

Use of corticosteroid therapy in patients with chronic AIH with exacerbation or with ALF remains less certain. Data have been mixed, showing both improved outcome and TFS or no benefit (183,193). More recent data, however, suggest that in select patients, corticosteroid therapy may improve outcome and transplant-free survival in AIH-ALF (194). Vigilant surveillance for infection should also be a part of the comprehensive care of patients with AS-AIH or AIH-induced ALF.

The role of budesonide and other immunosuppressive agents such as tacrolimus in severe acute AIH is not well supported, so they cannot be recommended for general use at this time, and patients should be immediately evaluated for LT (193,195).

Key concepts

- In patients presenting with AS-AIH, we recommend the use of IV corticosteroids.
- In patients with AS-AIH that has progressed to ALF, we recommend early evaluation for LT.

Pregnancy-related acute liver failure

Pregnancy-specific causes of ALF include hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome and acute fatty liver of pregnancy (AFLP). They may present during the third trimester of pregnancy or in the immediate postpartum period. It

is often difficult to distinguish between the 2 conditions due to overlap in clinical features and natural history.

As demonstrated by the US ALFSG, ALF associated with pregnancy is rare, occurring in only 2.2% of more than 3,100 patients. HELLP syndrome and AFLP each accounted for 25% of cases (196). The remaining half of patients in the pregnant cohort had ALF due to conditions also observed in nonpregnant individuals. These included APAP hepatotoxicity (60%), HSV (11%), AIH (9%), DILI (6%), cancers (lymphoma and adenocarcinoma, 9%), Kikuchi-Fujimoto syndrome (3%), and thyrotoxicosis (3%). The median gestational age at presentation was higher in HELLP syndrome and AFLP compared with patients with nonpregnancy-specific ALF (36 vs 30 weeks). Two-thirds of patients with HELLP syndrome and AFLP experienced preeclampsia or eclampsia, and most (approximately 90%) required emergency cesarean delivery.

In cases with HELLP syndrome/AFLP ALF, 69% had spontaneous recovery; 14% survived after LT; and 11% died at 21 days after presentation. Maternal and fetal outcomes varied by etiology. The presence of HE, elevated lactate level, and higher MELD score predicted worse survival in HELLP/AFLP ALF (197,198).

Management of pregnancy-related acute liver failure. HELLP syndrome/AFLP ALF is an obstetric emergency. Care in this setting is multidisciplinary. The cornerstone of management is prompt delivery of the fetus as soon as clinically feasible. Care is otherwise supportive for metabolic, renal, and respiratory complications. Clinical and laboratory abnormalities may persist for weeks after delivery, and care must be taken in deciding the need for LT for this potentially reversible condition. The Swansea criteria were developed to help determine the diagnosis of AFLP (199). An increased Swansea score (Table 11), HE and platelet-to-white blood cell ratio (PWR) may be helpful prognostic indicators (199,200). LT for AFLP has good survival outcomes comparable with that of other etiologies (201). Hepatic bleeding, hematoma, or rupture may occur, particularly in HELLP syndrome and may require urgent surgical intervention.

Key concepts

- In patients with pregnancy-related ALF, supportive care and multidisciplinary management is essential, and prompt delivery of the fetus is crucial.
- In patients with pregnancy-associated ALF, who fail to improve after delivery of the fetus, we suggest prompt evaluation for LT.

Budd-Chiari syndrome

BCS is one of the rarest causes of ALF, most often affecting White women in their fourth to fifth decades of life (202). It is characterized by obstruction of the hepatic venous outflow tract, usually resulting from venous thrombosis in the setting of underlying hypercoagulable states such pregnancy, oral contraceptive use, polycythemia vera, or the presence of membranous webs. Complete occlusion of the hepatic veins can lead to ALF by causing severe ischemia and massive hepatocyte necrosis. Patients with BCS-ALF present with an acute-to-subacute illness usually with abdominal pain and ascites (202). Laboratory evaluation reveals a predominantly hepatocellular liver injury pattern with marked aminotransferase elevation (AST > ALT) in the 1000s. Once BCS is diagnosed, evaluation for an underlying hypercoagulable disorder is warranted. Historically, transplant-free survival of patients with BCS-ALF has been dismal in the 37%–40% range, increasing to 80% in more recent decades (203).

Management of Budd-Chiari syndrome

The mainstay of BCS management is to initiate anticoagulation in an attempt to halt the propagation of thrombosis and restore patency of thrombosed veins. In the absence of contraindications, IV heparin should be started promptly. In an ALFSG registry review spanning 17 years, 71% of patients were anticoagulated with heparin (202). Overall survival was 42%. Those who were anticoagulated were more likely to survive, especially if anticoagulation was started shortly after admission. Other interventions included a combination of thrombolysis and angioplasty, TIPS, surgical shunting, and LT (37%). Thrombolytic therapy carries a risk of bleeding, stroke, and pulmonary embolism and is typically reserved for select patients with recent clots. Zhang et al (204) describe a series of 14 patients with acute and subacute BCS who successfully underwent catheter-directed thrombolysis, combined with angioplasty. Angioplasty is particularly effective when the underlying etiology is a membranous web obstruction (205). However, for those who fail medical therapy, angioplasty or stenting, shunt creation is necessary for an alternative outflow tract. TIPS or direct intrahepatic portocaval shunt is preferred over transabdominal surgical shunts. Data supporting TIPS placement are increasing despite the lack of randomized prospective trials (206,207). When performed, a polytetrafluoroethylene stent is preferred because it reduces stent occlusion rate (206,207).

Patients with BCS presenting with ALF who do not respond adequately to medical and therapeutic intervention should be listed for LF in a timely manner. A review of the United Network for Organ Sharing (UNOS) database showed that patients with BCS listed as status 1A category had comparable posttransplant survival with patients with nonstatus 1A BCS at 1 (82% vs 86%), 3 (82% vs 81%), and 5 years (82% vs 76%) (208,209). A large European study of 248 patients reported 1-year, 3-year, and 5-year posttransplant survival rates of 76%, 71%, and 68%, respectively (210).

Key concepts

- In patients with BCS leading to ALF, TIPS is the preferred intervention in those who fail anticoagulation.
- In patients with BCS-induced ALF, we recommend heparin as initial therapy, in the absence of contraindications to anticoagulation.
- In patients with BCS-induced ALF who do not respond to medical and therapeutic interventions, we recommend LT.

Secondary causes of acute liver failure

Ischemic liver injury. Ischemic liver injury—also called "hypoxic hepatitis" or "shock liver"—results from transiently or persistently decreased hepatic perfusion (211). Ischemic liver injury often occurs in the setting of congestive heart failure, sepsis, traumatic injury, or major surgery. A documented episode of hypotension is not always identified. Patients with ischemia-related ALF often have an acute-to-subacute presentation with laboratory evaluation revealing a severe hepatocellular pattern of injury with marked AST elevation >10,000 IU/L. Bilirubin levels are typically normal initially, often worsening along with rising INR despite improvement in transaminase levels. Patients often have rapid clinical improvement with restoration of normal hemodynamic status, and prognosis is largely dictated by the underlying condition.

Management of ischemic liver injury. The treatment of ischemic hepatitis is largely supportive and aimed at correcting the underlying cause and restoring hemodynamic stability. Vasopressor use may be necessary to maintain a satisfactory MAP. Two case reports suggest that NAC is helpful in treating ischemic hepatitis caused by vascular obstruction or heat stroke (212,213). In a report from the ALFSG of 55 patients with ALF due to ischemic hepatitis, 8 of 9 spontaneous survivors were treated with NAC (214). This is yet to be supported in larger numbers. LT is not usually indicated or necessary for ischemic hepatitis.

Malignant infiltration. Although the liver is a common site of cancer metastases, malignant infiltration of the liver accounts for only a minority of cases with ALF. In the US ALFSG registry, 27 of 1910 cases (1.4%) were attributed to malignancy, including lymphoma or leukemia (33%), breast cancer (30%), and colon cancer (7%) (215). In this cohort, the median age was 47 years, and most of them were female (67%) and White (67%). Patients often present with abdominal pain, jaundice, HE, and hepatomegaly. Laboratory evaluation reveals a mixed hepatocellular and cholestatic liver injury pattern with markedly elevated transaminase levels (approximately 40× ULN), prolonged INR, and thrombocytopenia. Less than half had evidence of liver masses on abdominal imaging, and the diagnosis typically relied on liver or bone marrow biopsy. Prognosis is dismal for patients with ALF due to malignant infiltration of the liver, with 85% of patients dying within 3 weeks of study enrollment.

Management of malignant infiltration. A high degree of suspicion is required in this setting, especially if malignancy is previously undiagnosed. Malignancy-directed treatment may be indicated (216,217). LT is generally not performed because of tumor infiltration and poor patient outcome. In the US ALFSG, there were only 2 reported cases of LT with one surviving beyond 5 years (215).

Coronavirus 2019–related disease. Patients with coronavirus disease (COVID-19) frequently have elevated liver enzymes reflecting hepatic injury (218). The pattern of liver injury is typically hepatocellular rather than cholestatic (219). Liver injury is multifactorial, including direct viral cytotoxicity, immune-mediated damage, ischemic liver injury, thrombotic complications, endotheliitis, and DILI (220). Management is supportive. Although liver injury during COVID-19 is generally considered to be mild in severity, patients may develop severe hepatic dysfunction in the context of multiorgan failure. LT is generally not possible due to multiple comorbidities.

The optimal timing of LT in patients presenting with ALF and testing positive for COVID-19 remains unknown. The American Society of Transplantation recommends that a candidate has complete symptom resolution (and ideally a negative COVID-19 PCR test) before proceeding with transplant surgery. In case of asymptomatic patients with ALF who otherwise would benefit from LT consideration, a multidisciplinary approach should be taken to consider risks and benefits of proceeding with transplant (221).

Indeterminate etiology. In some instances of ALF, a clear etiology cannot be determined. Of the 2,718 patients in the US ALFSG, 5.5% were eventually adjudicated to have an indeterminate cause of liver failure (14). On review, nearly half (142, 46.9%) of the previously assigned indeterminate cases were found to have an etiology, with APAP (45) and AIH (24) representing most of the reassigned cases. The remainder were caused by DILI, viruses such as HEV, and miscellaneous etiologies (14,147,148,186,187). In these instances, a liver biopsy may be warranted. Steroid therapy was not found to improve survival in indeterminate cases (193). Consideration can be given to using NAC, given evidence showing increased transplant-free survival in patients with nonacetaminophen-associated ALF with low-grade encephalopathy (stage 1–2) (121,222). Otherwise, patients should be considered for LT because spontaneous survival is otherwise poor (110).

LIVER TRANSPLANTATION

In the era preceding LT, mortality in patients with ALF approached 80% (223). With advances in LT and critical care, the patient and graft survival rates have improved dramatically over the past 20 years, although remain lower than those of patients living with cirrhosis (224,225). One-year and 5-year post-LT patient survival are approximately 80% and 75%, respectively. Most deaths occur within months after transplantation. Otherwise, long-term survival is excellent.

Prognostic models

Identifying patients with a low chance of spontaneous recovery is of utmost importance. This is particularly important for a provider who makes an initial assessment of the patient, frequently outside of the liver transplant center. Several predictive models of patient mortality in ALF have been described (Table 11). Development of encephalopathy in the setting of acute liver injury should trigger transfer to a transplant center; patients with APAP-induced ALF are particularly at risk of rapid clinical progression compared with non-APAP cases.

The KCC is the most used prognostic model for predicting transplant-free survival (226). The KCC has a reported sensitivity and specificity in non-APAP–induced ALF of 68% and 82% and 65% and 93% for APAP-induced ALF, respectively. The addition of lactate to the model improved KCC performance characteristics to a sensitivity of 91% (227). Several meta-analyses indicate that the KCC has good specificity but limited sensitivity, thus raising concerns that it may be a poor predictor of death without transplantation (28,228).

The MELD score has been evaluated in ALF in multiple studies (229–231). Meta-analysis of 23 studies comprising 2,153 patients compared performance characteristics of MELD vs KCC. It was noted that MELD thresholds were not standardized ranging from 25 to 37 depending on the study. Pooled data showed that the KCC had lower sensitivity for mortality than MELD (59% vs 74%), but a slightly higher specificity (79% vs 67%) (49).

Clichy criteria, widely used in France, have not gained popularity in the United States. The score is based on age, Factor V levels, and presence of grade 3–4 HE and was shown to have low specificity (56% for APAP-induced ALF and 50% for nonacetaminophen-induced ALF); thus, it has not been widely used.

Using the ALF Study group population, another model predicting transplant-free survival was developed that incorporates the grade of HE, ALF etiology, use of vasopressors, bilirubin, and INR that showed a c-statistical value of 0.84; however, prospective validation of this model is needed (11).

Key concept

- Identifying patients with ALF at risk of poor outcomes is important and should trigger transfer to a transplant center early in presentation.

Recommendation

10. In patients with ALF, we recommend using either the KCC or MELD score for prognostication. Patients meeting the KCC criteria or presenting with MELD >25 are at high risk of poor outcomes. GRADE recommendation: conditional, low quality of evidence.

Transplant evaluation

At the transplant center, the transplant team (hepatology, surgery, and psychiatry/social work) should be engaged promptly to guide the evaluation and management of the patient (Figure 1). The team then considers the patient's candidacy for transplant, based on both medical and psychosocial consideration.

Literature review did not reveal studies specifically addressing alcohol use disorder recurrence in patients with ALF. There is great heterogeneity in center-specific protocols in psychosocial assessment and alcohol abstinence requirements. Within the constraints of urgency of the situation, all efforts must be made to gather as much collateral information as possible from patients' family and friends to make an informed decision regarding the risk of alcohol-related liver disease after transplantation.

Brain death in patients with ALF, determined by previously validated measures outside of ALF setting, is the only absolute contraindication for LT (232). Multiorgan dysfunction, sepsis, ARDS, pancreatitis, and cancer are all relative contraindications. Decisions regarding proceeding with transplantation should be made in the setting of multidisciplinary discussion with the transplant team.

Key concept

- Multidisciplinary discussion involving the transplant team to determine individual transplant candidacy should be undertaken at the transplant center.

Graft considerations (living donor and ABO-incompatible grafts)

Although most patients listed as status 1A receive a timely organ offer, a recent analysis of the UNOS database shows that 18.2% of patients died or became too sick for transplantation (233). This led to the consideration of living donor grafts and ABO-incompatible deceased organ grafts.

Concerns regarding offering living donor LT (LDLT) revolve around limited time available for donor evaluation, obtaining informed consent from the donor to minimize coercion and safety of the donor procedure. A systematic review of the literature revealed only 3 studies with 2,533 adult patients with ALF, of whom 155 underwent LDLT (234). Comparison of LDLT with DDLT in ALF showed no significant differences in survival at 1, 3, and 5 years (235). The UNOS database review since 2011 revealed only 3 patients, confirming that this is not a widely practiced approach.

ABO-incompatible (ABO-I) transplantation has been described both with living and deceased donors with mostly observational retrospective studies. Two observational studies of ABO-I grafts for ALF from China (n = 22, patients with severe hepatitis B) and Norway (n = 33) showed inferior graft, patient survival, and an increased risk of antibody-mediated rejection (235,236). An earlier study, also from China, showed noninferior 3-year patient and graft survival in 33 patients with ALF who received ABO-I, with only 2 patients developing rejection. There was significant heterogeneity in immunosuppressive regimens reported across these studies, which may contribute to poorer outcomes in ABO-I cohorts. In addition, these data are based on patients undergoing transplants in the 2000 era. Medical supportive care for ALF has since improved, and development of ABO-I protocols, which include rituximab, may render these findings not relevant for the current patient population.

Key concepts

- In patients with ALF, listed as status 1A priority, LDLT may be considered in centers with LDLT experience when DDLT is not readily available.
- In patients with ALF, listed as status 1A priority, we suggest consideration of ABO-I grafts in a rapidly declining patent.

Experimental procedures

Two-staged liver transplantation. Two-staged LT, which involves hepatectomy, formation of portocaval shunt and prolonged anhepatic state while the patient awaits an organ has been

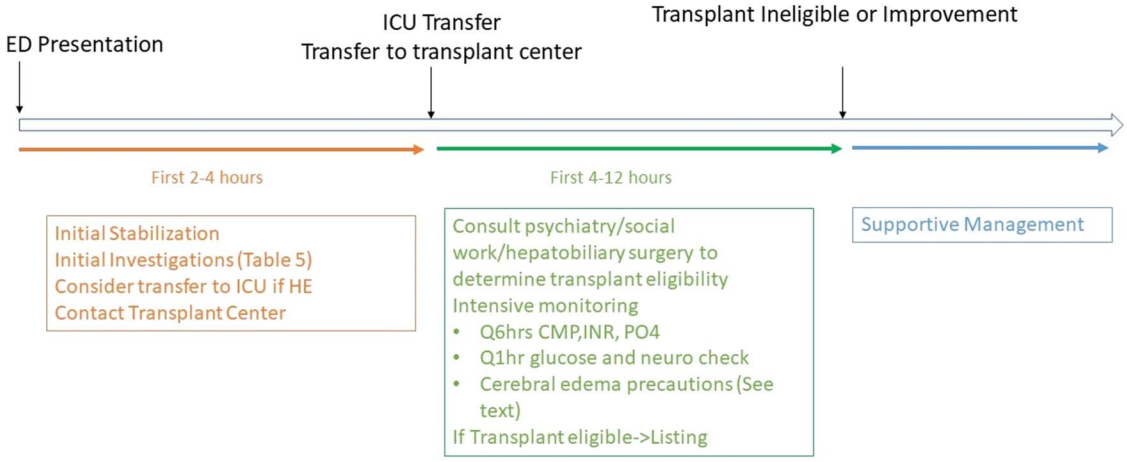

Figure 1. Timeline of acute liver failure presentation and investigations. ED, emergency department; HE, hepatic encephalopathy; ICU, intensive care unit; INR, international normalized ratio.

described (237–242). Due to paucity of evidence, this procedure is not routinely recommended in patients with ALF.

Auxiliary orthotopic liver graft. Auxiliary orthotopic partial LT refers to the surgical practice of adding an auxiliary partial or whole liver graft alongside the recipient's native liver to support the patient while allowing the native liver to regenerate. Although predominantly used in children, several reports of APPOLT in the adult ALF population exist both with living and deceased donor grafts (243–245). Reported outcomes with this technique are mixed.

CONCLUSION

ALF is a medical emergency and is potentially reversible if recognized and treated early. ALF must be differentiated from ACLF and decompensated cirrhosis because management is vastly different. ALF affects multiple organs and carries high short-term mortality, making timely transfer to the transplant center a priority early on in patient management. Patients at high risk of death have excellent prognosis after lifesaving LT.

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CONFLICTS OF INTEREST

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