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Acute liver failure: A review for emergency physicians

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ABSTRACT

Introduction: Acute liver failure (ALF) remains a high-risk clinical presentation, and many patients require emergency department (ED) management for complications and stabilization.
Objective: This narrative review provides an evidence-based summary of the current data for the emergency medicine evaluation and management of ALF.
Discussion: While ALF remains a rare clinical presentation, surveillance data suggest an overall incidence between 1 and 6 cases per million people every year, accounting for 6% of liver-related deaths and 7% of orthotopic liver transplants (OLT) in the U.S. The definition of ALF includes neurologic dysfunction, an international normalized ratio ≥ 1.5, no prior evidence of liver disease, and a disease course of ≤26 weeks, and can be further divided into hyperacute, acute, and subacute presentations. There are many underlying etiologies, including acetaminophen toxicity, drug induced liver injury, and hepatitis. Emergency physicians will be faced with several complications, including encephalopathy, coagulopathy, infectious processes, renal injury, and hemodynamic instability. Critical patients should be evaluated in the resuscitation bay, and consultation with the transplant team for appropriate patients improves patient outcomes. This review provides several guiding principles for management of acute complications. Using a pathophysiological-guided approach to the management of ALF associated complications is essential to optimizing patient care.
Conclusions: ALF remains a rare clinical presentation, but has significant morbidity and mortality. Physicians must rapidly diagnose these patients while evaluating for other diseases and complications. Early consultation with a transplantation center is imperative, as is identifying the underlying etiology and initiating symptomatic care.
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1. Introduction

Although acute liver failure (ALF) is a rare clinical presentation in the emergency department (ED), it carries high morbidity and mortality. ALF occurs most often in younger patients without preexisting liver disease, presenting unique challenges in clinical management. Across the developing world, the underlying etiology is primarily viral, with hepatitis B and E infections recognized as the leading causes in many countries. In the U.S. and much of Europe, the incidence of virally associated liver failure has declined substantially, with the large majority of cases now arising secondary to drug-induced liver injury, frequently from acetaminophen or idiosyncratic drug reactions [1,2]. While data from developing countries are sparse, surveillance reports from the developed world suggest an overall incidence between 1 and 6 cases per million people every year, close to 2000 cases per year [1,2]. ALF accounts for 6% of liver-related deaths and 7% of orthotopic liver transplants (OLT) in the U.S. each year [3,4]. The rarity of ALF, as well as its severity and heterogeneity in presentation, has resulted in a limited evidence base to guide management [5]. However, survival rates have improved in recent years due to advances in critical care management and the advent of emergent liver transplantation [6]. This review outlines the etiologies and clinical manifestations of acute liver failure and discuss current approaches to patient care in the ED.

2. Discussion

2.1. Definition of acute liver failure

While there are >40 definitions of acute liver failure in use, many of the modern definitions recognize distinct disease phenotypes and seek to differentiate ALF based on the interval between the onset of symptoms and the development of encephalopathy [7–9]. Presently, the most widely accepted definition comes from the American Association for the Study of Liver Diseases (AASLD) (Table 1) [10].

Quantifying the time course of the disease provides clues to the underlying etiology, complications, and prognosis with supportive medical care alone. One of the most common classification systems, developed by O'Grady and colleagues, remains the most common description of

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Table 1
Definition of acute liver failure from the American Association for the Study of Liver Diseases (AASLD).

Definition of acute liver failure
International normalized ratio (INR) ≥ 1.5
Neurologic dysfunction with any degree of hepatic encephalopathy
No prior evidence of liver disease
Disease course of ≤26 weeks

acute liver failure in adults [11]. This classification recognizes the prognostic importance of encephalopathy and altered consciousness after initial hepatic injury and subdivides the clinical presentation into three groups: hyperacute, acute, and subacute, as determined by the interval between development of jaundice and onset of encephalopathy (Table 2) [11]. Hyperacute presentations, which develop in <1 week, are most commonly caused by acetaminophen toxicity or a viral infection. More slowly evolving, or subacute, cases may be confused with chronic liver disease and are often the result of idiosyncratic drug-induced liver injury or idiopathic in nature. Patients who present subacutely, despite having less marked presentations, have a consistently worse outcome with medical treatment alone compared to those in whom the illness develops more rapidly [12].

2.2. Etiologies of acute liver failure

ALF is the clinical manifestation of sudden and severe hepatic injury and has a variety of underlying etiologies, including drug toxicity, viral infections, autoimmune and genetic disorders, thrombosis, malignancy, heat injury, and ischemia. Metabolic disorders like Wilson disease (WD), HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, acute fatty liver of pregnancy, Reye's syndrome, galactosemia, hereditary fructose intolerance, hemochromatosis, α1-antitrypsin deficiency, and tyrosinemia may also cause ALF (Table 3) [14]. Overall, ALF is much less common in the developed world compared to the developing world, where viral infections (hepatitis A, B, and E) predominate. Public health measures, notably vaccination and improved sanitation, are among the factors leading to the reduced incidence of these infections in the U.S. and Western Europe, where drug-induced liver injury, particularly acetaminophen, is the most common etiology of ALF. After abrupt loss of hepatic metabolic and immunological function, ALF can result in hepatic encephalopathy, coagulopathy, and in many cases, progressive multiorgan failure and death, unless emergent liver transplantation occurs [13].

2.2.1. Viruses

Viral Hepatitis is the most common cause of ALF worldwide, with the largest burden of disease in developing countries. Hepatitis A, B (±D), and E infections have been widely implicated, as well as other less common viral etiologies, including herpes simplex virus, Epstein-Barr virus, cytomegalovirus, and parvoviruses. Globally, hepatitis A and E infections are responsible for the majority of ALF, with reported case fatality rates exceeding 50% throughout the developing world [15,16]. Hepatitis A and E viruses are transmitted through the fecal-oral route, usually due to consumption of contaminated food or water. While hepatitis A infection occurs in roughly 1.5 million people a year worldwide, <1% of these patients develop ALF [16]. Hepatitis A infection produces a more severe course in adults as compared to children, resulting in a hyperacute or acute pattern of liver failure. However, a subacute pattern of liver failure may develop in elderly patients. Hepatitis E infection has a mortality rate of <1%, with elderly patients experiencing poorer outcomes. Hepatitis E virus infection remains an important cause of viral hepatitis in pregnant women and was originally thought to be associated with high rates of mortality, which is not borne out in recent literature [17]. However, hepatitis E infection leads to ALF in more than half of all neonates infected through vertical transmission [17].

ALF may also occur due to hepatitis B infection, common in some Asian and Mediterranean countries [18]. It is transmitted through exposure to blood or other bodily fluids of infected persons. While <1% of patients infected with hepatitis B will develop ALF, the mortality of hepatitis B-induced ALF remains higher than in those with hepatitis A or E infection. Particularly poor survival is seen in those patients without established chronic liver disease after reactivation of previously stable subclinical hepatitis B, as seen in patients with treatment-induced immunosuppression for cancer. It is important to note that reactivation can occur spontaneously, but it is most commonly seen when the patient is immunocompromised. Hepatitis C virus is not believed to cause ALF in the absence of a coexisting etiology, but rare cases of ALF

Table 2
Classification, clinical features, and prognosis of acute liver failure subtypes [13].

Classification, clinical features, and prognosis of acute liver failure subtypes			
Clinical feature	Hyperacute	Acute	Subacute
Time from jaundice to encephalopathy	0–1 week	1–4 weeks	4–12 weeks
Severity of coagulopathy	Severe	Moderate	Mild
Severity of jaundice	Mild	Moderate	Severe
Degree of intracranial hypertension	Moderate	Moderate	Mild
Survival without emergency transplantation	Good	Moderate	Poor
Typical etiology	Acetaminophen Hepatitis A &E	Hepatitis B	Drug induced

Table 3
Etiologies of acute liver failure. NSAID = nonsteroidal anti-inflammatory drug, CMV = cytomegalovirus, EBV = Epstein-Barr virus, HELLP = hemolysis, elevated liver enzymes, low platelet count.

Etiologies of Acute Liver Failure
Drug-induced Liver Injury
Acetaminophen
Antibiotics: amoxicillin-clavulanate, ciprofloxacin, nitrofurantoin, minocycline, dapsone, doxycycline, trimethoprim-sulfamethoxazole, efavirenz, didanosine, abacavir, ketoconazole
Anti-epileptics: valproic acid, phenytoin, carbamazepine
Anti-tuberculosis drugs: isoniazid, rifampin-isoniazid, pyrazinamide
Anti-hypertensives: methyldopa, hydralazine, labetalol, nicotinic acid (slow release)
NSAIDs: diclofenac, ibuprofen, indomethacin, naproxen
Herbs and supplements: ma huang, kava kava, herbalife, Green Tea Extract, Ginseng, Black Cohosh, anabolic steroids
Anesthetics: halothane
Miscellaneous: propylthiouracil, amitriptyline, statins, amiodarone, methotrexate
Viral Hepatitis
Hepatitis A, B (+/- D), C, and E
CMV, EBV, Herpes virus, Parvovirus, Varicella zoster virus
Pregnancy-related Liver Disease
Acute fatty liver of pregnancy
HELLP syndrome
Preeclampsia-associated liver disease
Acute hepatic rupture
Ischemic Hepatitis
Systemic hypotension
Budd-Chiari syndrome
Hepatic artery thrombosis
Congestive hepatopathy
Reversible Etiologies
Autoimmune hepatitis
Leptospirosis, hepatic amoebiasis, malaria, rickettsial disease
Genetic
Wilson Disease
Galactosemia
Hereditary fructose intolerance
Hemochromatosis
α1-antitrypsin deficiency
Tyrosinemia
Miscellaneous
Malignancy
Mushroom poisoning
Heat injury
Reye's syndrome

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from hepatitis C have been reported [19]. Other rare viral causes of ALF include herpes simplex virus, varicella zoster, cytomegalovirus, Epstein–Barr virus, and parvoviruses.

2.2.2. Drug-induced liver injury

Drug-induced liver injury is responsible for approximately 50% of cases of ALF in the U.S. and Western Europe [20,21]. Hepatic injury may be dose-dependent and predictable, as is the case with acetaminophen-induced hepatotoxicity, which remains the most common cause of ALF in the U.S. However, drug-induced liver injury may be unpredictable and independent of dose in some circumstances [1,4,22]. Acetaminophen-induced hepatic injury is secondary to the increased production of *N*-acetyl-p-benzoquinoneimine, a toxic metabolite. Although acute liver failure after acetaminophen ingestion can occur after consumption of a single large dose, typically at least 10 g/day, the mortality risk is greatest with substantial drug ingestion staggered over hours or days [23,24]. Acetaminophen toxicity is dose related; however, patients with history of alcohol abuse, malnourishment, and those patients on concomitant cytochrome P450 enzyme inducing drugs are at a substantially increased risk of developing ALF at lower acetaminophen doses [25]. ALF due to acetaminophen toxicity is associated with delayed presentation because of unintentional rather than deliberate self-poisoning [26]. While the list of hepatotoxic drugs is long, idiosyncratic drug-induced liver injury is rare, even among patients who are exposed to potentially hepatotoxic medication. Furthermore, few patients with drug-induced liver injury progress to encephalopathy and ALF [27]. Factors including older age, elevations in blood aminotransferase and bilirubin levels, coagulopathy, and a history of cirrhosis are associated with increased mortality risk [27].

2.2.3. Other causes

Acute ischemic hepatic injury, colloquially known as “shock liver”, primarily occurs in critically ill patients with primary cardiac, circulatory, or respiratory failure [28]. This may be caused by severe sepsis associated with signs of cardiac failure and major, transient elevations in blood aminotransferase levels, requiring supportive management as opposed to specific interventions targeted at the liver injury [29]. Other causes of ALF include neoplastic infiltration, autoimmune hepatitis, acute Budd–Chiari syndrome, heatstroke, metabolic diseases such as α-1 antitrypsin disease, and toxic mushroom ingestion, with *Amanita phalloides* being the most common mushroom to cause hepatotoxicity [20,30]. ALF may be seen in certain systemic infections such as leptospirosis, rickettsial infections, hepatic amoebiasis, dengue, malaria, and typhoid [31-33]. Pregnancy-specific liver diseases may result in ALF and are associated with significant morbidity and mortality for mother and fetus [34]. Preeclampsia-associated liver diseases, acute fatty liver of pregnancy, and HELLP syndrome can lead to ALF [35-37].

2.3. Clinical features of acute liver failure

The manifestation, timing, and severity of ALF's clinical features vary according to its underlying etiology, and a high index of suspicion is required to make an early diagnosis. The initial manifestation of ALF may range from non-specific constitutional symptoms including malaise, anorexia, fatigue, nausea, vomiting, and abdominal pain to severe hypotension, sepsis, seizures, and hepatic encephalopathy (Fig. 1) [38,39]. The clinical course of ALF follows that of multiple organ failure. The loss of hepatocyte function results in liver necrosis, as well as a release of toxins and cytokines leading to severe systemic inflammation and secondary bacterial infections from decreased immunity [40-42]. Direct hepatic necrosis causes severe and rapid loss of metabolic function, resulting in decreased gluconeogenesis, clearance of lactate and ammonia, and synthetic capacity, which present clinically as hypoglycemia, lactic acidemia, hyperammonemia, and coagulopathy, respectively [43]. The release of cytokines, inflammatory mediators, and subsequent systemic inflammatory response leads to a variety of clinical manifestations, including circulatory dysfunction, pancreatitis, immunosuppression, bone marrow suppression, acute lung injury, and acute respiratory distress syndrome [44-47].

Coagulopathy is a hallmark clinical manifestation of ALF, as all clotting factors with the exception of von Willebrand factor and factor VIII are synthesized in the liver, and many have a half-life measured in hours. The primary mechanism for abnormal coagulation tests in ALF is the decreased production of clotting factors II, V, VII, IX, and X. Furthermore, intravascular coagulation and fibrinolysis consumes platelets and coagulation factors, exacerbating coagulopathy. Thrombocytopenia and platelet dysfunction secondary to uremia are common in patients with ALF, reported in >60% of patients [10].

ALF results in circulatory dysfunction, initially due to poor oral intake and increased fluid loss leading to hypovolemia [48]. Following liver necrosis and release of cytokines, a systemic inflammatory state begins, characterized by vasodilation and increased cardiac output resembling septic shock [49-51]. This in turn leads to hypoperfusion of vital organs, exacerbating multiorgan failure. Likewise, acute renal failure and hepatorenal syndrome are important complications of ALF and are primarily a result of the hemodynamic alterations in ALF [52-54]. Initially renal injury is prerenal in etiology secondary to hypovolemia, but acute tubular necrosis rapidly develops due to ongoing ischemia of renal tubules [55,56]. Additionally, direct renal toxicity may be seen, as in the case of acetaminophen toxicity, *Amanita* poisoning, or an idiosyncratic reaction to trimethoprim-sulfamethoxazole [57,58]. Significant renal dysfunction may occur in >50% of patients with ALF and is more common in the elderly and in patients with acetaminophen-induced hepatotoxicity [59].

Hypoglycemia and electrolyte abnormalities remain important complications of ALF. The main mechanisms contributing to hypoglycemia in ALF include impaired gluconeogenesis and decreased insulin uptake by dysfunctional hepatocytes [14]. This increased level of insulin in the peripheral circulation results in severe hypoglycemia. Electrolyte abnormalities including hyponatremia, hypokalemia, hypophosphatemia, and acid-base imbalances are common. Hyponatremia is commonly caused by hypervolemia [43,48]. Central nervous system induced hyperventilation precipitates a respiratory alkalosis, in turn causing the kidneys to exchange hydrogen ions for potassium, resulting in hypokalemia. Fortunately, these electrolyte abnormalities rarely result in cardiac arrhythmias [13].

Encephalopathy in ALF remains a key neurological manifestation and is necessary to make a diagnosis of ALF. Encephalopathy comprises a number of clinical manifestations of differing severity, ranging from drowsiness, slowed mentation, cognitive impairment, confusion, and euphoria to deep coma [60]. Hepatic encephalopathy is classified based on severity, ranging from grade 1 to grade 4 [61]. Grade 1 is defined as altered behavior with euphoria, anxiety, and decreased attention span, while grade 2 is distinguished by disorientation, lethargy, or asterixis. Grade 3 presents with marked disorientation, incoherent speech, and somnolence. Grade 4 is defined as a patient becoming comatose or unresponsive to verbal or pain stimuli. Severity of ALF corresponds to the grade of encephalopathy upon presentation, with higher grades of encephalopathy portending a worse prognosis [62].

While the pathogenesis of hepatic encephalopathy is not fully understood, it is believed that inflammatory mediators and circulatory neurotoxins, such as ammonia, alter cerebral blood flow and blood-brain barrier permeability [63,64]. Acute liver failure leads to both systemic inflammation and local inflammation in the brain, resulting in the release of cytokines and neurotoxins, which cause astrocyte swelling, cerebral edema, and encephalopathy. Additionally, ammonia, a byproduct of nitrogen compound catabolism, is toxic at high serum concentrations. The body utilizes the urea cycle to excrete ammonia, which occurs primarily in the liver [62]. The urea cycle converts toxic ammonia to metabolically inert urea, while also metabolizing other nitrogenous wastes to nontoxic substances. Within the brain, astrocytes metabolize

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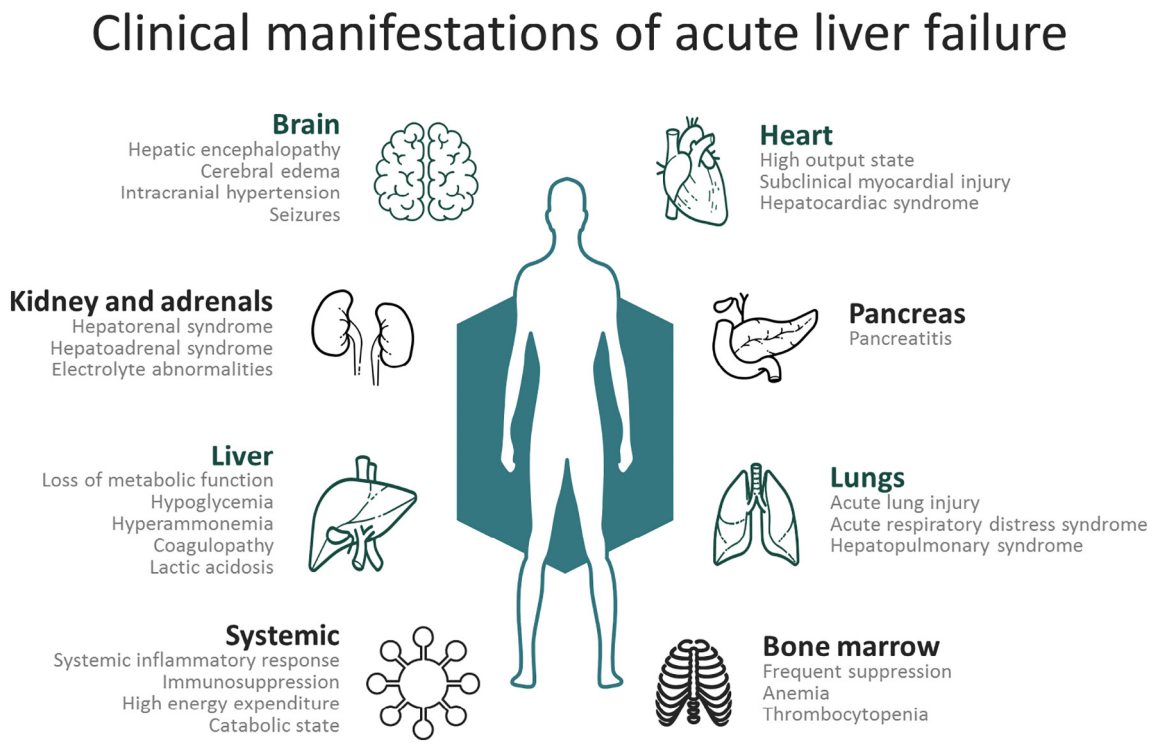

Fig. 1. Clinical manifestations of acute liver failure [13].

ammonia to a minor extent by utilizing glutamate, which is then converted to glutamine [63]. In ALF, increased levels of ammonia and other toxic nitrogenous compounds in the serum result in increased exposure to ammonia by the brain, thereby increasing production of glutamine in the astrocytes [64]. As glutamine is osmotically active, water moves into the astrocytes causing cerebral edema and encephalopathy. Similarly, seizures may occasionally be seen in patients with ALF, leading to cerebral hypoxia, exacerbating cerebral edema and intracranial hypertension (ICH) [64].

Hemodynamic instability and systemic hypotension associated with ALF further contribute to encephalopathy. Cerebral edema is seen in 75–80% of patients with ALF and grade 4 hepatic encephalopathy [65]. This edema can be life threatening, as it can progress to ICH, accounting for 20–25% of deaths in ALF [38]. Signs suggestive of ICH include systolic hypertension, bradycardia, and irregular respirations. Untreated, this may progress to muscle hypertonicity, decerebrate posturing, loss of pupillary reflex, and eventually respiratory failure. A high index of suspicion for the presence of intracranial hypertension is necessary, as it can develop before other clinical signs of ALF and may result in cerebellar herniation prior to any intervention [66].

2.4. Considerations in history and physical examination

The diagnosis of ALF is established through focused history and examination, including chronology of events prior to presentation, and supportive laboratory studies. Specific historical information is important to help better decide the potential cause of the patients' presentation to the ED and necessary investigations. Assessment of risk factors and potential exposures, including current medications, drug ingestions, alcohol or substance abuse, pregnancy status, family history, and recent travel, is helpful in discovering the underlying etiology. Further qualifying any exposure to specific hepatotoxins, such as the *Amanita phalloides* mushroom, is imperative, as this information may change management strategies and therapy. Key historical risk factors for ALF include age > 40 years, female gender, poor nutritional status, pregnancy, chronic hepatitis, and the use of multiple acetaminophen-containing medications for chronic pain [67-70]. Clarification of the time course of the illness, specifically the interval from the onset of jaundice to the development of encephalopathy, allows the clinician to further classification ALF into categories based on hyperacute, acute, or subacute presentations, which has diagnostic and prognostic value [11,12].

The underlying etiology of ALF is not only established through history and laboratory testing, but also by the exclusion of alternative causes, including acute presentations of chronic liver diseases. Chronic liver diseases, including hepatitis B and autoimmune hepatitis, routinely present as an acute exacerbation with clinical features indistinguishable from ALF, known as “acute-on-chronic” hepatic failure [71-75]. All components of the physical examination are important in evaluation. For instance, jaundice, a Cruveilhier-Baumgarten murmur (a venous hum in patients with portal hypertension), scleral icterus, fetor hepaticus, and Kayser-Fleischer rings may be subtle signs prompting further evaluation of ALF [38,69]. Abdominal examination may reveal hepatomegaly due to acute viral hepatitis, congestive heart failure (CHF) with secondary hepatic congestion, Budd-Chiari syndrome, or infiltrative malignancies. Physical examination findings may provide evidence suggesting the presence of an underlying chronic liver disease, including splenomegaly, caput medusa, gynecomastia, spider angiomata, palmar erythema, and ascites [69]. A detailed neurologic examination, especially in the patient presenting with hepatic encephalopathy, is necessary to evaluate for signs of cerebral edema and increased ICH (Fig. 1) [60,66]. Evaluation for any signs and symptoms of a concomitant infectious process, as well as a psychiatric screening for depression and suicidal ideation, may provide significant clinical value [76].

2.5. Diagnostic considerations

2.5.1. Laboratory testing

Laboratory and imaging studies should be pursued to confirm the diagnosis of ALF, evaluate for end organ dysfunction, and provide accurate prognostication of the patient's clinical condition (Table 4). It is beneficial to evaluate for electrolyte and metabolic abnormalities with a basic metabolic panel, venous blood gas, and lactate level. Additionally, hepatic abnormalities should be investigated by obtaining liver enzymes,

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Table 4
Initial Investigations in Acute Liver Failure. Ab= antibody; Ag= antigen; ALT= alanine aminotransaminase; AST= aspartate aminotransferase; HAV= hepatitis A virus; HCV= hepatitis C virus; HEV= hepatitis E virus; HSV= herpes simplex virus; Ig= immunoglobulin; INR= international normalized ratio; PCR= polymerase chain reaction; PT= prothrombin time; PTT= partial thromboplastin time; TEG= thromboelastogram; VZV= varicella zoster virus. CT= computed tomography; US= ultrasound.

Initial Investigations in Acute Liver Failure	
Serum Chemistries	**Viral Hepatitis Serologies**
Basic metabolic panel: sodium, potassium, bicarbonate, calcium, magnesium, phosphate, glucose, blood urea nitrogen, creatinine	Anti-HAV IgM Hep B surface Ag, anti-hep B core Ab IgM
Amylase, lipase	Hep D Ab, hep D RNA
Serum lactate	Anti-HCv, ±hepatitis C RNA PCR ±Anti-HEV IgM Anti-VZV IgM Anti-HSV IgM
Hepatic panel	**Autoimmune Markers**
AST, ALT, Albumin, total bilirubin, alkaline phosphatase	Antinuclear antibody Anti-smooth muscle antibody Serum IgG levels
Arterial Blood	**Urine**
Blood gas	Pregnancy test
Serum ammonia	Urinalysis and urine culture
Toxicologic	**Miscellaneous**
Blood alcohol level	Serum ceruloplasmin
Acetaminophen level	Blood cultures
Urine toxicology screen	Electrocardiogram
Serum salicylate level	
Hematologic	**Imaging**
Complete blood count	CT Brain without contrast
Blood type and screen	Abdominal US
Coagulation studies: PT/INR, Fibrinogen, PTT, TEG, D-Dimer	Chest x-ray Echocardiogram Transcranial Doppler

alkaline phosphatase, direct/indirect bilirubin, ammonia, albumin, and coagulation studies, including fibrinogen. A pregnancy test should be obtained in any woman of child bearing age at risk for HELLP syndrome, and a blood type and screen sent in cases of suspected gastrointestinal bleed from severe coagulopathy. A complete blood count may reveal leukocytosis, anemia, and thrombocytopenia, while blood cultures may be useful in the febrile patient. The clinician should have a low threshold for obtaining toxicologic studies, including acetaminophen level and any possible co-ingestants. The AASLD recommends obtaining acetaminophen levels in all patients with ALF, regardless of any history of acetaminophen ingestion [10]. Acetaminophen levels in the blood vary depending on the time of consumption, and a low acetaminophen level does not exclude acetaminophen-induced hepatotoxicity [77]. The time of ingestion may be remote, unknown, or occurring over days, and as such, measuring acetaminophen levels in patients with liver tests suggesting liver failure may not yield meaningful diagnostic information. Other tests should be guided by the physical examination, including serum ceruloplasmin and copper in suspected presentations of Wilson disease, viral hepatology serologies, autoimmune hepatitis markers, serum ammonia, and viral hepatitis PCR studies. However, these studies may be obtained in the in-hospital setting.

2.5.2. Imaging

Imaging, while not necessary to establish a diagnosis of ALF, may be useful in the correct clinical context. Abdominal ultrasound may provide information regarding hepatic venous disease or underlying Budd-Chiari syndrome, while a chest x-ray is useful to evaluate for aspiration pneumonia in the vomiting patient [78]. In the patient with encephalopathy, a head computed tomography (CT) or bedside transcranial Doppler may provide information regarding cerebral edema and ICH [79]. One should have a low threshold for non-contrast CT to evaluate for cerebral edema prior to non-invasive monitoring. A bedside echocardiogram can evaluate for CHF causing hepatic congestion and aid in determining fluid status and responsiveness [80].

2.6. Acute liver failure management

The most important aspect of management involves the timely diagnosis of ALF. Diagnosis is the most important management step for the clinician, as a delay can lead to substantial morbidity and mortality. While there is no proven therapy for ALF, understanding the progression of ALF, from loss of hepatocytes to the development of multiorgan failure, helps the clinician in disease-specific complication management. Generally speaking, the management of ALF should involve the following tests [81].

1. Identification of the etiology of ALF whenever possible and initiation of specific treatment.
2. Supportive and symptomatic management of ALF, with timely transfer to the critical care unit.
3. Early consultation with liver transplant specialists and transfer of patients to a liver transplant center when necessary.

2.6.1. Identification and treatment of underlying etiology

2.6.1.1. Acetaminophen toxicity. Identification of the underlying cause of ALF is necessary, as treatment varies. The most prevalent cause of ALF in the U.S. is acetaminophen toxicity, with an effective antidote available, *N*-acetylcysteine (NAC). Hepatotoxicity is not usually seen in the immediate period following acetaminophen ingestion, and the treatment of acetaminophen toxicity differs from the treatment of patients with ALF [13,22,24]. The Rumack-Mathew nomogram helps predict the development of hepatotoxicity in patients with acetaminophen toxicity and should be used to determine the need for NAC [82]. In confirmed cases of acetaminophen toxicity, acetaminophen levels should be plotted on the nomogram based on in order to determine the risk of development of hepatotoxicity, and NAC should be immediately started, as it is most efficacious when given within 8 h of ingestion [83]. However, it may still be effective up to 48 h post-ingestion [84]. NAC has a favorable side-effect profile (predominately nausea and vomiting, while rash, urticaria, and bronchospasm rarely occur) [85]. NAC should be administered in all patients with suspected or confirmed acetaminophen toxicity even if they present beyond 8 h of presentation [10]. Dosing is demonstrated in Table 5 [10]. Studies suggest oral NAC is as effective as IV NAC and comparatively much cheaper [86]. However, IV NAC is more commonly used due to the fact that the majority of patients with acetaminophen-induced hepatotoxicity suffer from significant nausea, vomiting, or altered mental status, making oral NAC impractical. Furthermore, the administration of activated charcoal, at a dose of 1 g/kg body weight orally, may be useful up to 4 h after ingestion, and acts by decontamination of the GI tract [10]. Administration of activated charcoal prior to NAC does not affect the efficacy of NAC. Thus, it is recommended to give activated charcoal prior to NAC if acetaminophen ingestion is within 4 h of presentation [10].

Table 5
N-acetylcysteine dosing by route.

N-acetylcysteine dosing		
Preparation	Loading dose	Maintenance dose
Intravenous	150 mg/kg in 5% dextrose solution over 15 min	50 mg/kg given over 4 h, followed by 100 mg/kg over 16 h
Oral	140 mg/kg by mouth or as a 5% diluted solution through nasogastric tube	70 mg/kg every 4 h for a total of 17 doses

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2.6.1.2. Other causes. Drug-induced hepatotoxicity is a diagnosis of exclusion; any drug identified as the possible cause of ALF should be immediately stopped. While the efficacy of NAC in drug-induced liver failure has not been clearly demonstrated, NAC administration is recommend, with equivalent dosing as acetaminophen toxicity [10]. In cases of suspected or confirmed mushroom poisoning induced ALF, activated charcoal and gastric lavage via nasogastric tube may be helpful during initial hours post-ingestion [87]. Three drugs have been proposed for the treatment of ALF secondary to mushroom poisoning: penicillin G, silibinin [88] (known as silymarin or milk thistle), and NAC [10]. These medications must be given separately, as no combination medication exists at this time. The dose of intravenous penicillin G for mushroom induced ALF in the U.S is 300,000 units to 1 million units/kg/day [89]. In Europe, silibinin at doses of 30 to 40 mg/kg/day either intravenously or orally for a period of 3–4 days has been used, although at this time, it is not routinely available in the U.S. as a licensed drug, but rather as a supplement (milk thistle) [90]. NAC at the same dosage as for acetaminophen-induced hepatotoxicity may be administered in mushroom poisoning, although large-scale studies are lacking [91]. Finally, an underlying etiology of viral hepatitis may affect management of the patient with ALF. Hepatitis A- and hepatitis E-induced ALF have no specific treatment and should receive supportive care [92]. Acute hepatitis B-induced ALF patients benefit from antiviral agents, including Lamivudine, and their use is recommended by the AASLD [93,94]. Patients with documented or suspected herpes virus or varicella zoster virus infection should be given intravenous acyclovir, 5 to 10 mg/kg IV every 8 h for at least 7 days [10]. Patients with fulminant Wilson disease are thought to require transplant for patient survival, and treatment with penicillamine is not recommended in the setting of significant hepatic dysfunction. Rather, hemofiltration via albumin dialysis or plasma exchange is recommended [10]. Autoimmune hepatitis is another potentially reversible cause of ALF, as a small but significant subset of these patients will respond to treatment with either prednisone alone at a dose of 60 mg/d or a combination of prednisone 30 mg/d and azathioprine 50 mg/d as initial treatment, whereas most others will eventually require liver transplantation [10]. Pregnancy-related ALF usually resolves with delivery in the majority of patients, though a minority eventually require liver transplantation [35,36].

2.6.2. Supportive and symptomatic management of ALF

2.6.2.1. Encephalopathy. Since there is no proven therapy for ALF, understanding the progression of ALF, as well as the development of multiorgan failure, helps the clinician in disease-specific complication management. One of the most prevalent complications of ALF is hepatic encephalopathy. Treatment goals include preventing the onset of encephalopathy if possible, slowing the progression to severe encephalopathy, and minimizing the development of cerebral edema and ICH, which can cause cerebral herniation and death. Neurologic care centers on the maintenance of stable cerebral perfusion, and the control of circulating ammonia and its cerebral metabolism. While the drug L-ornithine-L-aspartate enhances ammonia detoxification to glutamine in muscle, the drug failed to lower serum ammonia levels, reduce the severity of encephalopathy, or improve survival rates among ALF patients in a large randomized controlled trial [95]. Lactulose, however, is an accepted treatment for acute hepatic encephalopathy, with an initial dose of 45 ml by mouth, followed by a repeated dose every hour until the patient has a bowel movement. For patients at significant risk for aspiration, lactulose may be given as an enema (dosing is 300 ml in 700 ml of water, retained for 1 h) every 2 h as needed until mental function improves [96]. Medications commonly used in chronic liver disease may be inappropriate in ALF, neomycin, rifaximin, and other nonabsorbable antibiotics in particular. ICH requires aggressive management, aiming for a goal intracranial pressure (ICP) of <20–25 mm Hg while maintaining the patient's cerebral perfusion pressure (CPP) above 50–60 mm Hg. There are a variety of treatments available to achieving adequate hemodynamic stability, thus increasing the CPP, including fluid resuscitation, intravascular volume expansion, and vasopressors. Hypertonic saline (at a dose of 20 ml of 30% sodium chloride or 200 ml of 3% sodium chloride, keeping serum sodium at 145-155 mmol per liter) or mannitol (at a dose of 2 ml of 20% solution per kilogram of body weight) is effective in decreasing cerebral edema, and hyperventilation can be used for a short duration [97]. However their ability to decrease cerebral edema is transient. Recommended management for hepatic encephalopathy includes intubation, sedation, head-of-bed elevation to at least 30°, and efforts to minimize interventions and stimuli that result in increased ICP [10]. Prophylactic doses of antiseizure medications, such as phenytoin, have not been shown to improve outcomes [98].

Patients with ALF will hyperventilate spontaneously, decreasing the partial pressure of carbon dioxide in their arterial blood, resulting in cerebral vasoconstriction and decreased intracranial pressure. Thus, spontaneous hyperventilation in ALF should be preserved, as it aids in restoring cerebral autoregulation. However, this effect is transient. Studies have not shown survival benefit for hyperventilation in ALF, and there is no known benefit of prophylactic hyperventilation [99]. Hyperventilation is only recommended in life-threatening ICH when all other therapies have failed [10]. Mechanical ventilation is often necessary in the setting of substantial volume resuscitation or significant encephalopathy. Acute respiratory distress syndrome is common in ALF patients, and protective ventilation strategies designed to minimize lung injury are imperative [100]. Unfortunately, the most effective method of neurologic monitoring to guide therapy in patients with high-grade encephalopathy is not clear, although indicators of increased risk of ICH are known. These risk factors include a serum ammonia concentration of >200 μmol per liter or a sustained level of at least 150 μmol per liter despite treatment, an age of 35 years or less, and concurrent renal or cardiovascular organ failure [101-103].

2.6.2.2. Coagulopathy. Coagulopathy remains an important complication of ALF. In the absence of bleeding, routine correction of thrombocytopenia or elevated INR by infusion of plasma is not indicated in ALF [10]. However, patients with ALF have been shown to be deficient in vitamin K, and the AASLD recommends administration of vitamin K (5 to 10 mg subcutaneously) [10,104]. Additionally, though fresh frozen plasma (FFP) and four-factor Prothrombin Complex Concentrate (PCC) may play a role in reversal of coagulopathy, they are not indicated in the absence of bleeding [105]. If the patient has clinically significant bleeding or needs to have an invasive procedure with a high risk of bleeding such as placement of an ICP monitor, then coagulopathy should be corrected, initially with plasma [10]. If the INR is markedly high, or the patient requires a large volume of plasma, recombinant activated factor VII may be used [106]. Thrombocytopenic patients with platelet count < 50,000 cells/mm^3 who have clinically significant bleeding should receive platelet transfusions. In the absence of bleeding, platelet transfusion is not recommended [106]. For patients requiring invasive procedures, the need for platelet transfusion depends on the extent of thrombocytopenia and the bleeding risk. For low risk procedures, platelet transfusion may be initiated at platelet counts < 30,000 cells/mm^3. For high-risk procedures, it is reasonable to maintain the platelet count > 50,000 cells/mm^3 in order to minimize bleeding [107,108]. In the setting of ALF and coagulopathy, gastrointestinal bleeding is a concern, and patients should receive prophylaxis with proton-pump inhibitors, sucralfate, or H2 blockers to prevent bleeding from stress ulcers [10].

2.6.2.3. Infection. Infection complicates many cases of ALF, leading to substantial morbidity and mortality, as infection can worsen encephalopathy and may preclude liver transplantation. In critically ill patients with ALF, particularly those presenting with severe hepatic encephalopathy,

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Table 6
King's College Criteria.

King's College Criteria
The presence of one of the following should prompt a referral/transfer to a liver transplantation center
Acidosis (admission arterial pH < 7.30) **OR** Hepatic encephalopathy (grade III or IV), AND coagulopathy (PT > 100 s), AND acute kidney injury (creatinine > 3.4 mg/dl), **OR** Hyperlactatemia (4-hour lactate > 3.5 mmol/l, or 12-hour lactate >3.0 mmol/l), **OR** Hyperphosphatemia (48–96 h phosphate > 3.7 mg/dl) in patients with acetaminophen-induced fulminant hepatic failure.

broad spectrum antibiotics, most commonly a third-generation cephalosporin and vancomycin, should be given [10,109]. Gram-positive cocci, including staphylococci and streptococci, as well as enteric gram-negative bacteria, are the most common organisms isolated in ALF patients [109]. Fungal infections are also frequently reported in the literature, most commonly *Candidiasis*, and the decision to begin fluconazole in ALF patients may be deferred to the intensive care team [109]. A reasonable approach for the emergency clinician is to obtain pan cultures of patients and to consider empiric antibiotics, with antifungal coverage, in high-risk individuals with severe encephalopathy, renal failure, or on mechanical ventilation.

2.6.2.4. Renal dysfunction. Acute renal failure plays an important role in the prognostication of ALF. Management of renal dysfunction begins with identifying the underlying etiology, which is difficult given the multifactorial nature of renal failure in the ALF patient. Prerenal failure is managed by maintaining hemodynamic stability, correcting hypovolemia, and using vasopressors as needed [109,110]. Additionally, the clinician should avoid all nephrotoxic medications, including antibiotics such as aminoglycosides and nonsteroidal anti-inflammatory agents. Acute renal failure secondary to hepatorenal syndrome usually only improves when liver function is recovered or in the case of liver transplantation [111]. Early initiation of dialysis should be considered when clinically indicated. In patients requiring renal-replacement therapy, continuous rather than intermittent forms are preferred, as they achieve greater metabolic and hemodynamic stability [112]. Additionally, renal-replacement therapy may be used to treat refractory hyperammonemia and other biochemical or acid–base disturbances. Any associated electrolyte abnormalities, as well as hypoglycemia, should be treated promptly, often necessitating a continuous infusion of glucose. Frequent monitoring of blood glucose is critical, as hepatic encephalopathy commonly masks symptoms of hypoglycemia [111].

2.6.2.5. Cardiovascular dysfunction. Circulatory disturbances in ALF are characterized by decreased systemic vascular resistance and elevated cardiac output, similar to that seen in septic shock. Appropriate management includes IV fluid resuscitation and vasopressors guided by the use of invasive hemodynamic monitoring. Additionally, adrenal insufficiency is commonly seen in ALF [113]. Thus, the presence of persistent hypotension despite adequate volume resuscitation and the use of vasopressors requires consideration of this. Empiric treatment for adrenal insufficiency with IV steroids is indicated, especially if clinical suspicion is high. Commonly recommended corticosteroid therapy includes IV hydrocortisone 200–300 mg/day in four divided doses for a week before tapering slowly in patients with vasopressor-dependent septic shock [114].

Table 7
MELD score calculation.

MELD score calculation
Candidates who are at least 12 years old receive an initial MELD(i) score equal to $MELD(i) = 0.957 \times \ln(Cr) + 0.378 \times \ln(bilirubin) + 1.120 \times \ln(INR) + 0.643$
Then, round to the tenth decimal place and multiply by 10. Maximum MELD = 40. If MELD(i) > 11, perform additional MELD calculation as follows $MELD = MELD(i) + 1.32 \times (137 - Na) - [0.033 \times MELD(i) \times (137 - Na)]$

Table 8
MELD score and associated mortality.

MELD score	Mortality at 3 months
≤9	1.9%
10–19	6.0%
20–29	19.6%
30–39	52.6%
≥40	71.3%

2.6.2.6. Liver transplantation. Despite the most aggressive medical management, many patients with ALF deteriorate to a point where transplantation remains their only option for survival. When presented with a patient in ALF, an early decision should be made about whether or not the patient is a candidate for liver transplantation, and consultation with the transplantation service is necessary. If the patient is a candidate, early transfer to a transplant center is recommended to initiate simultaneous evaluation for a liver transplant by the transplant team and advanced ALF management [10,115].

2.7. Prognosis and disposition

There are many prognostic tools for ALF, but the two most common are the King's College criteria (Table 6) [116] and the Model for End-Stage Liver Disease (MELD) score (Tables 7 and 8) [117]. While the King's College Criteria remain the most widely accepted prognostic tool for patients presenting with ALF, due to its high specificity for mortality, the sensitivity and negative predictive value remain low [118]. Thus, not fulfilling the criteria does not ensure patient survival. The King's College Criteria has a sensitivity of 68–69% with a specificity of 82–92% [119], although it has only been validated in adults and may not reliably prognosticate ALF in pediatric populations [120].

The MELD score is a well-established and validated predictive model of short-term mortality in patients with liver failure. Adopted by the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplantation Network (OPTN) organization, it is currently the preferred method for the allocation of donor organs in patients awaiting liver transplantation in the U.S. [117,121] Recently, several retrospective studies have shown the MELD score to have comparable predictive value to the King's College Criteria in terms of predicting mortality associated with ALF [122–124]. Based on findings from a large meta-analysis, the MELD score could play a role in predicting hospital mortality in patients with ALF, as well as need for emergent liver transplantation (Table 6) [124].

Disposition is dependent on a variety of factors, including underlying etiology of ALF, clinical stability, and severity of disease, possibly necessitating emergent liver transplantation. It is vital to use prognostic criteria in the evaluation of ALF patients and contact a liver transplant hospital early, as transplantation may be the only treatment which can provide long-term benefit. Many of these patients in fulminant liver failure will require intensive care unit admission at the very least, and most likely transfer to a transplant center [13,125–128].

3. Conclusions

Although comprising a minority of visits to the emergency department, ALF represents one of the most challenging clinical scenarios in terms of the level and complexity of care required, as well as time-sensitive nature of the treatment decisions. Effective care of the ALF patient begins with early diagnosis and triage to the appropriate level of care in order to maximize the chance of recovery and/or extend the window of opportunity for a potential transplant.

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Conflicts of interest

None.

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