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Research Article

OVERVIEW; PUBLIC HEALTH APPROACH TOWARD ACUTE LIVER FAILURE AND ITS MANAGEMENT

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Abstract:

The purpose of this review was to assess the most recent information about the treatment of acute liver failure (ALF) and to explain the diagnostic strategies that will identify the appropriate treatment for ALF. We evaluate the most recent studies on approaches to acute liver failure, as well as those papers that were published prior to March, 2022. The Midline (PubMed) and Embase databases were searched for papers pertinent to our topic of interest, and then evidence was carefully gathered from each study in order to conduct this review as an up-to-date assessment of all ALF therapy options. Severe liver failure is associated with quickly progressing multiorgan failure and catastrophic complications; nevertheless, emergency liver transplantation has improved patient outcomes. A practice-based evidence base is growing for supportive therapy, and a better knowledge of the pathophysiology of the illness, particularly as it relates to hepatic encephalopathy, will likely lead to additional increases in survival rates in the near future. According to additional research, liver transplantation is the only option with a survival benefit. Liver assist devices and hepatocyte transplantation are still experimental, and additional progress is required. Controlling hepatitis A, B, E, and drug-induced liver injury will reduce the incidence and mortality of ALF.

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INTRODUCTION:

Acute liver failure (ALF) is the clinical manifestation of severe and sudden hepatic damage and has numerous causes. It produces hepatic encephalopathy, coagulopathy, and, frequently, progressive multiorgan failure after a sudden loss of hepatic metabolic and immunological function. This uncommon critical health issue primarily affects young adults and is associated with high mortality and resource expenditures. In many nations, it is the most common reason for emergency liver transplantation. In the past decade, there have been significant shifts in the understanding of the disease's etiology and development, and the evidence basis for treatment has advanced (1,2). Severe liver failure is quite rare. Reports from the industrialized world indicate an annual incidence of one to six incidents per million persons. 16 - 18 Data for other regions are scant, but rates are expected to be high in areas where infectious hepatitis is prevalent and where medicinal interventions that inhibit the progression of hepatic injury and the onset of extrahepatic organ dysfunction are not easily available (3,4,5). From 1998 to 2008, the most prevalent causes of ALF in the United States were acetaminophen (46%), followed by undetermined causes (14%), other medications (12%), hepatitis B (7.7%), and autoimmune causes (5.9%). (6). Ischemia, Wilson illness, Budd-Chiari syndrome, and pregnancy were uncommon causes (7). Despite the fact that European countries have comparable data, viral hepatitis (often hepatitis B and A) is the leading cause of ALF worldwide. In underdeveloped areas, drug-induced hepatitis is substantially less prevalent, however antituberculosis treatment deserves special mention as the most common cause of drug-induced ALF in South Asia (8). ALF caused by hepatitis B is also on the rise in Europe and the United States due to immigration, with some researchers attributing 5 to 10% of new ALF cases to hepatitis B infection (9). Although only 1% of individuals with severe liver disease B advance to ALF, the incidence approaches 20% in situations of co-infection with hepatitis D. (7). Aged individuals and those infected with the hepatitis C virus also have a higher incidence of acute liver failure in patients with severe liver disease B infection (10).

Regardless of the origin, ALF is a rare illness, with 2,000 to 2,300 cases reported annually in the United States (13). In 2009, severe hepatic necrosis accounted for 4.2% (243/5,748) of all liver transplants done on adult patients in the United States (12). Despite improvements in liver transplantation and intensive

care unit (ICU) management, the mortality rate associated with acute liver failure (ALF) still ranges from 60 to 80 percent, which is far worse than many 1-year survival rates (80 to 90 percent) for liver transplant due to chronic liver disease (13,14). Early diagnosis and treatment, as well as the possibility of a liver transplant, are the most important factors in improving survival rates.

METHODOLOGY:

We review the most up-to-date studies on the management of acute liver failure, but we also include some published studies. Up to March 2022, the Midline (PubMed) and Embase databases were searched for relevant articles to our concern subject, and then evidence was carefully extracted from each study in order to perform this review as an up-to-date study on all ALF treatment approaches.

DISCUSSION:**❖ Diagnosis of Acute Liver Failure (ALF):**

Exposures to drugs and viral infections are at the top of the list of questions to ask patients and their families while obtaining a thorough medical history. The use of over-the-counter or natural supplements must be thoroughly explored, as patients generally disregard them as drugs. Bodybuilding supplements such as hydroxycut have been widely documented as potential hepatotoxins, although many others, such as green tea, have only been associated in case studies (15,16). Mushroom consumption must also be specifically addressed, as *Amanita phalloides* ingestion may result in ALF (17). Additionally, sexual encounters, tattoos, travel, alcohol consumption, and recreational drug use must be evaluated.

Laboratory verification of ALF is rather simple. A prolonged prothrombin time of 4 to 6 seconds or more (global normalized ratio [INR] greater than 1.5) in conjunction with any degree of encephalopathy confirms the diagnosis of ALF and necessitates hospitalization. A complete blood count, total metabolic panel with serum chemistries and liver-associated enzymes, arterial blood gases, and lactate should also be acquired early on. A serum acetaminophen level is necessary, but early treatment with n-acetylcysteine (NAC) may be beneficial even in nonacetaminophen-associated ALF (18). **Table 1** displays the complete array of laboratory tests for the initial evaluation of ALF (19).

Table 1: Laboratory Tests to Perform in the Initial Evaluation of Acute Liver Failure ⁽¹⁹⁾

Type of Tests	Specific Laboratory Tests
Serum chemistries	<ul style="list-style-type: none"> Basic metabolic panel <ul style="list-style-type: none"> - Sodium, potassium, bicarbonate, calcium, magnesium, phosphate, glucose, blood urea nitrogen, creatinine Amylase, lipase Serum lactate
Hepatic panel	<ul style="list-style-type: none"> AST, ALT, albumin, total bilirubin, alkaline phosphatase
Hematology	<ul style="list-style-type: none"> Complete blood count <ul style="list-style-type: none"> - Coagulation - PTT PT/INR, fibrinogen
Arterial blood	<ul style="list-style-type: none"> Blood gas Ammonia
Toxicology	<ul style="list-style-type: none"> Blood alcohol level Acetaminophen level Urine toxicology screen
viral hepatitis serologies	<ul style="list-style-type: none"> Anti-HAV IgM Hep B surface Ag, anti-hep B core Ab IgM Hep D Ab, hep D RNA Anti-HCV, \pmhepatitis C RNA PCR \pmAnti-HEV IgM Anti-VZV IgM Anti-HSV IgM
Autoimmune markers	<ul style="list-style-type: none"> Antinuclear antibody Antismooth muscle antibody Serum IgG levels
Urine	<ul style="list-style-type: none"> Pregnancy test Urinalysis
Other	<ul style="list-style-type: none"> Serum ceruloplasmin > 24-hour urine copper

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; VZV=varicella zoster virus.

To risk-stratify individuals with ALF, various criteria and scoring systems based on test data and medical observations have been created. King's College in London developed a system that classifies patients as acetaminophen ALF or nonacetaminophen ALF. This system is currently in widespread use. This rating method (**Table 2**) (19) is typically highly accurate for forecasting a poor prognosis, and, in conjunction with medical judgment, is advantageous for ensuring rapid transfer to a liver transplant.

Table 2: King's College Criteria for Poor Prognosis in ALF ⁽¹⁹⁾

Acetaminophen-induced ALF	No acetaminophen-induced ALF
Arterial pH <7.30 after fluid resuscitation	Prothrombin time >100 sec (INR >6.5)
Or all of the following: <ul style="list-style-type: none"> Prothrombin time >100 sec (INR >6.5) Serum creatinine >3.4 mg/dL Grade 3 or 4 hepatic encephalopathy 	Or any 3 of the following: <ul style="list-style-type: none"> Non-A, non-B viral hepatitis, drug-induced or indeterminate etiology of ALF Time from jaundice encephalopathy >7 days Age <10 years or >40 years Prothrombin time >50 sec (INR >3.5) Serum bilirubin >17.4 mg/dL

ALF= acute liver failure;

INR= international normalized ratio.

❖ Optimal Treatment of ALF:

Intensive care support, therapy of the specific etiology if detected early, and diagnosis of the need for a liver transplant comprise the management (20,21). Coma care, fluid management, hemodynamics, metabolic parameters, and infection control require special consideration. Coagulation parameters, a complete blood count, a metabolic panel, and arterial blood gases should be examined often (22). Early restoration of intravascular volume and systemic circulation can prevent the failure of multiple organs (20). In individuals who remain hypotensive despite adequate volume replacement, vasopressors must be used (23). Patients with coma grades III or IV must be intubated and sedated to facilitate general care and prevent aspiration pneumonia (24). ALF is a state of immunosuppression that increases the risk of sepsis. High infection control standards should be implemented. To detect infection early, sputum, blood, and urine cultures should be performed frequently. Antibiotics having a broad spectrum of activity may be delivered prophylactically to patients with coagulopathy, grade III or grade IV encephalopathy, or multiorgan failure (20). In ALF, bleeding is infrequent. The administration of coagulation factors should be avoided except in cases of bleeding or before invasive procedures (20).

Management of ALF's underlying causes: Depending on the cause, certain treatments may be successful. This medication should be initiated early in the evolution of the disease, and careful monitoring of disease progression is required to minimize liver transplantation delays or failure (20,21). Early administration of N-acetyl cysteine reduces liver damage and accelerates recovery in patients with acetaminophen-induced acute liver failure (ALF) (24). A multicenter, double-blind, randomized, controlled trial demonstrated that N-acetyl cysteine is effective in the treatment of nonacetaminophen ALF (25). ALF may be treated with corticosteroids due to autoimmune

liver disease (26). Patients who do not respond within two weeks must be considered for transplantation. Antiviral therapy has been shown to improve outcomes in hepatitis B (27) and herpes simplex-associated acute lymphoblastic leukemia (ALF), but no randomized controlled trials are available. In patients with *Amanita phalloides* ingestion, early treatment of activated charcoal may improve survival by preventing amatoxin absorption (28). Other therapies include silibinin and penicillin G administration (28). ALF owing to Wilson disease often requires a liver transplant, but plasma exchange with fresh frozen plasma replacement may improve survival (29). ALF associated with pregnancy must be treated with quick delivery of the fetus (30).

Treatment of neurological problems resulting from ALF: 25-35% of individuals with grade III encephalopathy and around 75% of those with grade IV encephalopathy had cerebral edema (31). Cerebral edema in ALF results from a combination of vasogenic and cytotoxic edema (32,33). Excessive ammonia and glutamine modify cerebral osmolality, increase free radical generation, disrupt glucose metabolism, and induce calcium-mediated mitochondrial damage, resulting in astrocyte enlargement (32,33). Alterations in cerebral blood flow and cytokine activation can exacerbate cerebral edema (33). All patients with encephalopathy should be treated by elevating the head of the bed 30 degrees, maintaining a neutral neck posture, intubating the patient, reducing unpleasant stimuli, and controlling arterial blood pressure (32,33). It is important to prevent hypercapnia, hyponatremia, frequent movement, neck vein compression, fluid overload, fever, hypoxia, coughing, sneezing, seizures, and regular endotracheal suctioning (32,33). Propofol may be used for sedation and fentanyl for pain management (32). Measures to reduce arterial ammonia, such as lactulose, gut decontamination, and ornithine aspartate, have failed to reduce ALF, and lactulose

may exacerbate abdominal distension and bloating (20). Treating seizures with phenytoin or short-acting benzodiazepines is recommended (20,32). There is no function for the preventative phenytoin.

The objective of therapy in ALF is to maintain intracerebral pressure (ICP) below 20 mm Hg and cerebral perfusion pressure (CPP) below 20 mm Hg and cerebral perfusion pressure (CPP) above 60 mm Hg (34). ICP monitoring may be demonstrated in a subgroup of patients (34). Nonetheless, a retrospective examination of the effect of ICP monitoring revealed no difference in the outcomes of the two groups. In the presence of severe coagulopathy, it may be hazardous, according to the findings of the research (35). A recent systematic review of the use of therapeutic hypothermia in ALF patients indicated that there were insufficient data on the safety and efficacy of moderate hypothermia for the treatment of intracranial hypertension in ALF patients (36). Acutely reducing ICP with hyperventilation to obtain a PaCO₂ between 30 and 35 mm Hg should not be performed for extended periods (37). Intravenous indomethacin and barbiturates should only be used as a last resort after all other therapies have failed to lower intracranial pressure (ICP).

High blood concentrations of nitric oxide and cGMP in ALF result in an elevated cardiac output, low mean arterial pressure, and decreased systemic vascular resistance (25). This situation is exacerbated by volume depletion owing to inadequate oral intake, extravasation of fluid into the third space, and, in rare cases, gastrointestinal bleeding. The initial treatment for hemodynamic instability is resuscitation with fluids (38). Patients who do not respond to fluid resuscitation must be administered norepinephrine to attain a mean arterial pressure of 75 mm Hg (38). Vasopressin or its analog, terlipressin, may be utilized as an adjuvant to augment the effects of norepinephrine (38). Patients who do not react to fluid resuscitation and vasopressors should be evaluated for and treated for adrenal deficit.

CONCLUSION:

Severe liver failure is associated with quickly progressing multiorgan failure and catastrophic complications; nevertheless, emergency liver transplantation has improved patient outcomes. A practice-based evidence base is growing for supportive therapy, and a better knowledge of the pathophysiology of the illness, particularly as it relates to hepatic encephalopathy, will likely lead to additional increases in survival rates in the near future. According to additional research, liver transplantation is the only option with a survival benefit. Liver assist

devices and hepatocyte transplantation are still experimental, and additional progress is required. Controlling hepatitis, A, B, E, and drug-induced liver injury will reduce the incidence and mortality of ALF.

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