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Acute Liver Failure

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Abstract

Acute liver failure (ALF) is a progressive life-threatening condition characterized by hepatic dysfunction with coagulopathy and hepatic encephalopathy (HE) that evolves over a few days or weeks. Besides development of HE, ALF results in development of multi-organ failure (MOF), and is still associated with a ~40% mortality risk depending on the etiology and severity of liver injury. The prognosis for ALF patients has improved significantly over the last 3 decades due to advances in medical critical care management, including early treatment of hyperammonemia, renal insufficiency and the use of high-volume plasma exchange (HVP). Liver transplantation is the ultimate treatment option. In this short review we mainly focus on the basic medical management of patients with ALF and on the value of liver support by HVP in the waiting time for spontaneous recovery of the liver or to ensure vital organ stability before liver transplantation.

Keywords: Fulminant hepatic failure; Ammonia; Sepsis; Hepatic encephalopathy; Artificial liver support; Shock; Critical care

Definition

The most widely accepted definition of ALF includes evidence of coagulation abnormality, usually an International Normalized Ratio (INR) ≥ 1.5, and any degree of HE in a patient without preexisting chronic liver disease and with an illness of <26 weeks' duration [1-5]. For Wilson's disease and vertically acquired hepatitis the disease must have been recognized for less than 26 weeks [5].

A number of other terms have been used for this condition, including fulminant hepatic failure and fulminant hepatitis or necrosis [6,7]. Terms used signifying length of illness, such as "hyperacute" (<7 days), "acute" (7-21 days) and "subacute" (>21 days and <26 weeks) [5] are widely used but are not particularly helpful since they have less prognostic value distinct from the cause of the illness.

Clinical Characterization of Patients with ALF

In addition to the development of HE in patients with severe hepatic damage, the condition is often characterized by manifestations of severe cardiovascular dysfunction, brain edema, hypoglycemia, and MOF [2,4].

The pathophysiology for development of MOF in ALF is not fully understood. Earlier studies on the pathophysiology of ALF have focused on hyperammonemia and the accumulation of various metabolites and toxins of varying size, distribution volume, lipophilicity, and protein binding [8-11]. In recent years the importance of infections and systemic inflammation for the outcome of ALF has been demonstrated and has been shown to be associated with progression in the severity of HE, risk of brain edema and an increased mortality [12,13]. The focus has now been set on the consequences of the overwhelming hepatocyte death that results in a release of damage associated molecular patterns (DAMPs) into the systemic circulation, e.g., DNA, histones, HMGB-1 and trigger Toll-like receptor (TLR) dependent activation of innate immune cells, which seems to result in hepatic and systemic pro-inflammatory responses and ultimately MOF [4].

Prognostic Scoring Systems

One of the key issues in the management of patients with ALF is to predict the outcome, as a help in deciding the treatment strategy and intensity, i.e., maximum supportive therapy while waiting for the liver to regenerate or deciding to list the patient for liver transplantation. Over the years different scoring systems have been developed to predict the prognosis of such patients (Table 1).

The King's College prognostic criteria are the most widely used criteria, and have been developed specifically to predict which patients will benefit from emergency liver transplantation [1,5,11,14]. There are criteria for acetaminophen-induced, as well as non-acetaminophen-induced ALF, and both set of criteria are based on a combination of clinical and biochemical measurements [15] (Table 1).

The Model of End Stage Liver Disease (MELD) may predict survival in patients with ALF. A MELD score <30 in patients with acetaminophen related liver injury had a high probability of survival [14-16]. However, we have previously reported that the discriminative power of MELD score is not superior to that of INR alone or of the King's College Hospital criteria [11,14].

The CLIF-SOFA score was developed for patients with acute-on-chronic liver failure to predict short-term mortality [17] whereas the value of the score is not sufficiently investigated in patients with ALF [4]. Yet, it is potentially more valuable to record the score on a daily basis, as this may offer a more dynamic picture of how the patient is responding to therapy.

King's College of poor prognostics score	
Acetaminophen-induced ALF	Arterial pH <7.3 (regardless of HE) OR all 3 of the following 1. INR >6.5 2. S-creatinine >3.4 mg/dL 3. Grade III-IV HE
Non-acetaminophen-induced ALF	Prothrombin time >6.5 (INR), OR Any three of the following variables: 1. Age <10 or >40 years 2. Etiology: non-A, non-B hepatitis, idiosyncratic drug reaction 3. Duration of jaundice before encephalopathy >7 days 4. Prothrombin time >3.5 (INR) 5. S-bilirubin >17.5 mg/dL
Model of end stage liver disease - MELD	3.78 × $\log_e$ S-bilirubin (mg/dL)+11.20 × $\log_e$ INR+9.57 × $\log_e$ S-creatinine (mg/dL)+6.43 (constant for liver disease etiology) If the patient has been dialyzed twice within the last 7 days, the value for serum creatinine should be 4.0. Any value less than one is given if 1 (i.e., if bilirubin is 0.8 a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any below 1 would yield a negative result)
CLIF-SOFA score	**Grade I:** Single kidney failure (S-creatinine >2.0 mg/dL or use of renal replacement therapy) OR liver failure (S-bilirubin >12.0 mg/dL), coagulopathy (INR >2,5 and/or platelet count <20 × 10^9), circulatory failure (use of catecholamine's or terlipressin to maintain arterial pressure), respiratory failure (PaO/FiO_2 ≤ 200 mg/dL or SpO_2/FiO_2 ≤ 214 mg/dL), S-creatinine 1.5 mg/dl to 1.9 mg/dl and/or mild to moderate HE OR brain failure (grade III or IV hepatic encephalopathy) with S- creatinine 1.5 mg/dl to 1.9 mg/dl **Grade II:** Two organ failures **Grade III:** Three or more organ failures
HE: Hepatic Encephalophalopathy; INR: International Normalized Ratio; S: Serum	

Table 1: Criteria in scoring systems.

Basic Work-Up

Although the liver may have an exceptional ability to regenerate this is rarely going to happen if vital functions are not immediately supported. Therefore the patient should be referred to an experienced liver failure center with a liver transplantation program with no delay.

Prior to transportation of the patient it is important to correct for hypoglycemia by intravenous infusion of 20% glucose, metabolic acidosis and arterial hypotension by volume expansion with isotonic saline, human albumin and fresh frozen plasma (if the patient is oozing). Patients with stage 3 to 4 encephalopathy should be sedated, tracheal intubated and switched to mechanical ventilation [1,2].

Early identification of the etiology of ALF may in some cases improve the chance of survival due to the possibility of specific treatment such as N-acetyl cysteine (NAC) infusions due to acetaminophen intoxication, antiviral treatment, corticosteroid treatment and other specific treatment regimes, e.g. in mushroom poisoning [1,2].

Screening for etiology includes thorough recording of patient history (symptoms, travelling, behavioral risk, autoimmune disease, use of medicine or exposure to other potential toxic substances), and besides routine biochemistry screening for viral etiology, autoimmune disease, toxins and metabolic liver diseases should be performed (etiologies are presented in Table 2).

In addition ultrasonography, computed tomography and echocardiography should be considered to exclude Budd-Chiari syndrome and portal vein thrombosis and to ensure adequate central blood volume and exclude heart failure [1].

Viral etiologies	Drug-induced toxic hepatitis	Other causes
Viral etiologies Hepatitis A Hepatitis B Hepatitis E Epstein Barr virus Cytomegalovirus Parvovirus B19 Herpes Simplex virus Varicella Zoster virus	Acetaminophen Antibiotics and a wide spectrum of other prescription drugs Over-the-counter drugs Herbal substances Toxic types of mushrooms Anabolic steroids Inhalation substances and more	Autoimmune hepatitis Hypoxia and hypovolemia Portal vein thrombosis Budd-Chiari Malignant disease Wilson's disease

Table 2: The causes of acute liver injury.

Liver biopsy is in most cases of ALF contraindicated due to an increased risk of bleeding. Even though transjugular liver biopsies can be obtained rather safely the diagnostic and prognostic value of a liver biopsy is of less value if not acute Wilson's disease, autoimmune hepatitis or malignant infiltrative diseases including lymphoma are highly suspected [1,2].

Critical Care Medical Treatment

Arterial hypotension and central volume depletion

Due to a decrease in the systemic vascular resistance the preload of the heart decreases and the arterial pressure drops. If arterial hypotension remains fluid resistant the use of vasopressors is relevant [1]. Noradrenaline is the agent of choice if volume expansion is insufficient, and the dose should be increased until a satisfactory effect on arterial pressure is seen to secure vital organ perfusion [1,2]. Low-

dose terlipressin (0.5 mg to 1.0 mg every 4 h to 6 h) can be used to preserve or restore cerebral perfusion and renal function if needed, especially in cases with high requirements of noradrenaline infusion [18]. The use of low dose terlipressin may also be helpful in patients with severe acidosis to allow initiation of continuous renal replacement therapy (CRRT) [18]. Occasionally, patients may develop low cardiac output syndrome, which is associated with a poor prognosis. In these patients, the use of dobutamine may be of value to increase cardiac output and arterial pressure [1,2]. In such cases it is also relevant to determine whether the patient suffers from adrenal dysfunction [1].

Acute kidney failure (AKI)

In many cases of ALF the patient will develop kidney failure, either due to causes independent of the liver condition per se (as pre-renal hypotension caused by dehydration, drug toxicity or SIRS). Yet, more than half patients with ALF with need support by CRRT [4].

The brain

Severe HE is a poor prognostic sign. HE develops as the blood ammonia concentration increases and ammonia passes over the blood brain barrier [8]. Treatment with Lactulose and L-ornithine-L-aspartate is not effective to improve survival in patients with ALF and HE [1,19]. Rifaximin has been shown to be effective in patients with cirrhosis and recurrent episodes of encephalopathy [20], but efficacy of this drug in ALF remains unknown.

Early intervention with CRRT to lower the circulating ammonia concentration and correct metabolic acidosis seems important [1,2,21]. If intracranial hypertension develops; treatment with hypertonic saline or Mannitol is indicated [22] and is essential to ensure brain viability [1]. In refractory cases with intracranial hypertension the active induction of mild hypothermia [23] or intravenous administration of indomethacin can be considered [24].

Systemic inflammation and infections

Patients with ALF are at high risk of developing infections, sepsis and septic shock. The severe pro-inflammatory immune response seen in the early stage of ALF in part explains the later development of immune "paresis" and the susceptibility to (re-)infections and development of MOF [25]. Appropriate cultures should be obtained prior to the institution of antimicrobial therapy at any suspicion of infection. Emperic antibiotic therapy should seriously be considered.

Mechanical ventilatory support is primarily needed to provide airway protection when the level of consciousness diminishes to HE stage 3 or 4. This will also allow for deep sedation and institution of hypothermia in patients who develop brain edema and high intracranial pressure. Furthermore, about 21% of patients with ALF will develop acute respiratory distress syndrome [26]. In other patients in a critical condition with development of ARDS and sepsis, permissive hypoventilation i.e., hypercapnia may be allowed. However in about 20% to 25% of patients with ALF cerebral edema may develop. Accordingly permissive hypercapnia may potentially raise intracranial pressure by an increase in cerebral blood flow and the risk of cerebral herniation.

SIRS and High-Volume Plasma Exchange

In case of MOF a variety of metabolites and toxins are released and circulate within the bloodstream. Furthermore, different intracellular components are released as a result of hepatocyte death. These processes play a role in development of SIRS, which together with MOF is associated with a high mortality. Also the decreased production of coagulation factors and other substances synthesized in the liver seem to play a role in MOF [1,2,4]. One specific treatment, i.e. HVP is effective by removing plasma cytokines and adhesion molecules and replaces plasma factors [4].

HVP is a highly specialized treatment offered in referral centers, and a plasma volume corresponding to 15% of the body weight is exchanged with fresh frozen plasma. This has a significant impact on survival as documented in a recent multi-center trial [4]. The study showed an in-hospital survival of 58.7% in the patients treated with HPV vs. 47.8% in the group treated with standard medical treatment. The treatment caused a decrease in INR, bilirubin, ALT and arterial ammonia. Furthermore, the treatment caused positive hemodynamic changes with increased blood pressure and thus a decreased need of vasopressors. Fewer patients in the HPV group needed renal replacement therapy. Accordingly the SIRS and CLIF-SOFA scores improved [4].

A model for how HVP dampens tissue innate immune responses has been proposed [4]. Hepatocyte death in ALF triggers release of DAMPs that activate innate immune cells in the liver and the circulation, and subsequently leads to tissue inflammation and SIRS. HVP leads to a reduction of circulatory DAMPs and to an attenuation of the pro-inflammatory profile of innate immune cells, conferring reduced tissue destructive capabilities [4].

Liver Specific Interventions

The coagulopathy (increase of INR) in ALF is a result of hepatocyte necrosis. The administration of K-vitamin rarely has an effect. However, often not knowing the pre-ALF status, an intravenous K-vitamin supplement initially is recommended in ALF. N-acetylcysteine infusion should be used not only in cases of acetaminophen intoxication but should be considered in all patients with non-acetaminophen drug-induced toxic ALF due to a potential cytoprotective effect, and seems especially important in the early phase, i.e. before development of severe HE [27].

Liver transplantation is the ultimate rescuing treatment of ALF. The timing for transplantation is of vital importance, as diagnostic and treatment attempts should not inappropriately delay listing for liver transplantation, and at the same time, all other possible modalities should be offered early and intensively in the attempt to achieve survival without transplantation. On the other hand, extending therapy for too long may bring the patient to a stage where too many other organ failures contraindicate transplantation [1,2].

Conclusion

Acute liver failure is a life-threatening condition in patients without known liver disease, which often is complicated by development of MOF. Due to the complexity and severity of the condition, the patients should without delay be referred to and treated in specialized hepatology referral centers. The intensive care treatment of patients with ALF has improved significantly over the last 3 decades with a significant increase in survival. High-volume plasma exchange diminishes the inflammatory response in patients with ALF and should be considered in the early, pro-inflammatory stage of ALF to increase the probability of liver transplant-free survival.

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