

Advances in the management of acute liver failure

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Abstract

Acute liver failure (ALF) is an uncommon but dramatic clinical syndrome characterized by hepatic encephalopathy and a bleeding tendency due to abrupt loss of liver function caused by massive or submassive liver necrosis in a patient with a previously healthy liver. The causes of ALF encompass a wide variety of toxic, viral, metabolic, vascular and autoimmune insults to the liver, and identifying the correct cause can be difficult or even impossible. Many patients with ALF develop a cascade of serious complications involving almost every organ system, and death is mostly due to multi-organ failure, hemorrhage, infection, and intracranial hypertension. Fortunately, the outcome of ALF has been improved in the last 3 decades through the specific treatment for the disease of certain etiology, and the advanced intensive care management. For most severely affected patients who fail to recover after treatment, rapid evaluation for transfer to a transplantation center and consideration for liver transplantation is mandatory so that transplantation can be applied before contraindications

develop. This review focuses on the recent advances in the understanding of various contributing etiologies, the administration of etiology-specific treatment to alleviate the liver injury, and the management of complications (*e.g.*, encephalopathy, coagulopathy, cardiovascular instability, respiratory failure, renal failure, sepsis and metabolic disturbance) in patients with ALF. Assessment of the need for liver transplantation is also presented.

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Key words: Acute liver failure; Cerebral edema; Liver transplantation

Core tip: Acute liver failure (ALF) is a dramatic clinical syndrome of abrupt loss of liver function in a patient with a previously healthy liver. The causes of ALF encompass a wide variety of toxic, viral, metabolic, vascular and autoimmune insults to the liver. ALF patients develop serious complications, and death is mostly due to sepsis, followed by multiple organ failure, and intracranial hypertension. However, disease outcome has been improved through etiological treatment and advanced intensive care management. For most severely affected patients who fail to recover after treatment, liver transplantation may be life-saving.

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INTRODUCTION

Acute liver failure (ALF) is an uncommon but dramatic clinical syndrome characterized by sudden and massive hepatic necrosis that results in jaundice, coagulopathy [international normalized ratio (INR) \geq 1.5], and hepatic

encephalopathy (any degree of altered mentation) in the absence of pre-existing liver disease^[1]. A timely diagnosis of ALF is critical because of its feature of rapid deterioration, and delayed diagnosis can be disastrous. The most prominent causes include drug-induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion; many cases have no discernible cause^[2]. The mortality rate of ALF is as high as 40%-50%, depending on the cause and improper therapeutic management. The immediate cause of death in 35% of ALF patients is brain herniation due to elevated intracranial pressure (ICP), and most other deaths are the result of severe refractory hypotension resulting from supervening sepsis culminating in multiorgan failure^[3]. Orthotopic liver transplantation (OLT) has emerged as the only therapeutic intervention with proven benefit for patients with advanced ALF^[4].

ETIOLOGY AND SPECIFIC THERAPIES

The causes of ALF encompass a wide variety of toxic, viral, metabolic, and vascular insults to the liver, and the etiology of ALF varies with geography. In Africa and Asia, viral hepatitis dominates the causes of ALF^[5]. By contrast, in Europe and North America, toxic etiologies predominate^[6]. In many cases, the cause of ALF cannot be established and remains indeterminate. Determination of etiology is important because specific therapies can be given once the diagnosis is established. In addition, knowing the cause could provide a reasonably valid guide to predicting outcome^[7].

Toxins

Acetaminophen (APAP) overdose accounts for 46% of ALF cases in some areas, and APAP-induced ALF is currently more commonly seen after unintentional than intentional overdose^[8]. The development of liver failure from APAP is dose dependent; hepatic failure is more likely with ingested dosages > 150 mg/kg. Various risk factors increase the probability of acute liver damage even at therapeutic doses of APAP. The factors include alcoholic addiction, malnutrition (resulting in glutathione depletion), and concurrent use of narcotic analgesics compounded with APAP. The liver damage leads to a characteristic pattern of pericentral necrosis due to cytochrome P450-mediated oxidative metabolism of APAP to the highly reactive, intermediate metabolite, *N*-acetyl-p-benzoquinone imine (NAPQI)^[9]. Accumulation of NAPQI leads to cell death and hence hepatocellular necrosis. *n*-Acetylcysteine (NAC) is established as a proven beneficial agent for APAP-induced hepatotoxicity^[10]. It acts by replenishing glutathione that detoxifies NAPQI. In addition, excessive NAC also provides substrates for hepatic ATP synthesis, thus supporting mitochondrial energy metabolism. The latter pathway may be particularly important in delayed administration of NAC.

Mushroom poisoning, most commonly from *Amanita* genus mushrooms, should be suspected in patients with

a history of severe gastrointestinal symptoms (nausea, vomiting, diarrhea and abdominal cramping), which occur within hours to a day after mushroom ingestion^[11]. Amanitin toxin, recycled *via* the enterohepatic circulation, interrupts hepatocyte mRNA synthesis resulting in dose-dependent hepatotoxicity. The mortality of ALF secondary to mushroom poisoning approaches 10%-30%. Penicillin G and silybinin may ameliorate the hepatic injury, however, patients should be listed for hepatic transplantation, because this procedure is often the only life-saving option^[12].

Drugs other than APAP rarely cause dose-related liver injury^[13]. Many of these injuries are idiosyncratic, and they often occur within the first 6 mo after intake of the drug. In this setting, it is necessary to discontinue all but the most essential medications. Medications commonly associated with acute liver injury include antimicrobials, neurological and psychiatric drugs, and nonsteroidal anti-inflammatory drugs (Table 1)^[14].

Virus

Patients with viral hepatitis that develop hepatic failure are largely suffering from hepatitis B, and less frequently hepatitis A. Hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy may experience reactivation of hepatitis B virus (HBV) replication, which may lead to ALF. Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy^[15-17]. High viral load at baseline is the most important risk factor for HBV reactivation. Patients with baseline HBV DNA < 2000 IU/mL level should continue treatment for 6 mo after completion of chemotherapy or immunosuppressive therapy. Patients with a high baseline HBV DNA (> 2000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients. Lamivudine or telbivudine can be used if the anticipated duration of treatment is short (< 12 mo) and baseline serum HBV DNA is not detectable. Tenofovir or entecavir is preferred if longer duration of treatment is anticipated^[17]. In addition, all transplant recipients positive for hepatitis B surface antigen should receive antiviral therapy, preferably using tenofovir or entecavir^[15].

In an endemic area such as Russia, Pakistan, Mexico, or India, hepatitis E remains an important cause of hepatic failure, particularly in the context of pregnancy, and it carries a high mortality in this setting^[18]. Moreover, vertical transmission of hepatitis E from women with acute infection results in ALF in more than half of neonates. So far, ALF due to acute hepatitis C infection is uncommon and occurs in < 1% of patients. Few data suggest that hepatitis G virus plays a major pathogenic role in ALF^[19]. Herpes viruses occasionally cause ALF, usually among immunosuppressed and pregnant patients^[20]. Epstein-Barr virus, adenoviruses, cytomegalovirus, varicella zoster virus, parvovirus B19, yellow fever virus and hemorrhagic fever virus are also implicated as causes of ALF. For ALF caused by herpes viruses or varicella zoster,

Table 1 Drugs which may cause idiosyncratic liver injury leading to acute liver failure

Classification	Drugs
Anti-infective agents	Amoxicillin/clavulanate erythromycin, roxithromycin, telithromycin, doxycycline, minocycline nitrofurantoin, ciprofloxacin, levofloxacin, moxifloxacin trimethoprim-sulfamethoxazole, sulfasalazine, isoniazid, rifampin, pyrazinamide, ethambutol, dapson, fluconazole, itraconazole, terbinafine, ketoconazole, chloroquine Didanosine, fialuridine, efavirenz, abacavir, nevirapine-lamivudine
Cardiovascular agents	Amiodarone, labetalol, diltiazem, methyldopa, valsartan, lisinopril, angiotensin converting enzyme inhibitor Asparaginase, flutamide
Hypolipidemic agents	Atorvastatin, cerivastatin, simvastatin, pravastatin, fluvastatin, ezetimibe
Hypoglycemic Agents	Metformin, troglitazone
Anti-allergic agents	Zafirlukast, loratadine, diphenhydramine
Herbal products/dietary supplements	Kava, Herbalife, Comfrey, Senecio, Greater Celandine, Polygonum multiflorum, ginseng, Teucrium polium, usnic acid, ma huang, Chaso, Onshido, Hydroxycut, LipoKinetix
Neurological and psychiatric drugs	Halothane, isoflurane, butorphanol opiates, amphetamines, marijuana, cocaine Phenytoin, valproic acid, carbamazepine, felbamate, lamotrigine, vigabatrin amitriptyline, imipramine, sertraline, paroxetine, venlafaxine, pemoline, bupropion Chlorpromazine, quetiapine, clonazepam tolcapone
Nonsteroidal anti-inflammatory drugs	Diclofenac, bromfenac, etodolac, naproxen, ibuprofen, indometacin
Miscellaneous	Propylthiouracil, retinol, infliximab, allopurinol, cyclosporine, disulfiram, iron sulfate, anabolic steroids, carbon tetrachloride, phenprocoumon, nicotinic acid
Antineoplastic agents	Methotrexate, cytoxan, etoposide, dactinomycin, azathioprine, tamoxifen

acyclovir (5-10 mg/kg *iv* every 8 h) is the recommended treatment^[21].

Metabolic causes

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, α 1-antitrypsin deficiency and tyrosinemia may also cause ALF.

WD accounts for 6%-12% of all patients with ALF who are referred for emergency liver transplantation. ALF due to WD occurs predominantly in young women (female:male ratio 4:1)^[22]. Diagnostic tests for WD should include ceruloplasmin, serum and urinary copper levels, total bilirubin/alkaline phosphatase ratio, slit lamp examination for Kayser-Fleischer rings, and hepatic copper levels when liver biopsy is feasible^[23]. High bilirubin (> 20 mg/dL) and low alkaline phosphatase levels (including

undetectable levels) due to profound hemolytic anemia help with its rapid recognition. Liver transplantation is the only effective option for those with WD who present with ALF. One-year survival following liver transplantation ranges from 79% to 87%, and those who survive this early period continue to survive in the long term^[23].

The hepatic damage of HELLP syndrome is proposed to result from disordered placentation, leading to either the circulation of antiangiogenic factors and endothelial dysfunction, or cytokine production causing the characteristic periportal hemorrhage and fibrin deposition observed by Sánchez-Bueno *et al*^[24]. Acute fatty liver degeneration of pregnancy is a sudden catastrophic illness occurring most frequently in the third trimester, when mitochondrial dysfunction due to maternal and fetal fatty acid β -oxidation defects resulting in microvesicular fatty acid accumulation in hepatocytes^[25]. There is an overlap of these two clinical syndromes, and they play a major role in the pathogenesis of pre-eclampsia, with hypertension, and proteinuria. Early recognition of these syndromes and prompt delivery are critical in achieving good outcomes. Failure to recover from the illness should be promptly listed for liver transplantation^[26].

Vascular causes

The Budd-Chiari syndrome (acute hepatic vein thrombosis) is an uncommon cause of ALF^[27]. Right upper quadrant pain, striking hepatomegaly, and fluid retention characterize the initial clinical picture and may help distinguish this syndrome from other forms of ALF in which the liver is small and not tender. Therapeutic strategies have included anticoagulation, use of transjugular intrahepatic portocaval shunting, or transplantation. It is important to rule out underlying cancer prior to transplantation for these patients. Liver ischemic injury can also cause ALF and could be seen in the setting of sepsis, cardiac arrest, heart failure, or hypotension induced by long-acting niacin or cocaine^[28]. Aminotransferase levels will be markedly elevated and respond rapidly to stabilization of the circulatory problem. Cardiovascular support is the treatment of choice in this setting.

Miscellaneous causes

Some rare causes of ALF include heat shock, protracted seizures, autoimmune hepatitis, and malignant infiltration^[29,30]. ALF occurs in a small fraction of autoimmune hepatitis patients-probably < 20%. These cases are usually recognized prior to hospitalization as having autoimmune disease that proceeds to rapid deterioration. The clinical picture is in the form of a subacute presentation, with intermediate elevation of enzyme levels and high bilirubin concentrations. Presence of autoantibodies and a compatible picture on biopsy help to confirm the diagnosis, but they may not be notable. Some autoimmune hepatitis patients may respond well to steroid therapy, and others may still require transplantation. The most common forms of malignant infiltration implicated in ALF are lymphoma, breast cancer, and melanoma^[31].

Others include small cell lung cancer and prostate cancer. Diagnosis should be made by imaging and biopsy, and treatment appropriate for the underlying malignant condition is indicated.

Indeterminate causes

About 15%-20% of ALF occurs with an indeterminate cause, which includes unrecognized idiosyncratic drug toxicity, non-A-E viral hepatitis, and possibly unrecognized metabolic and genetic diseases. The reasons for this misdiagnosis may include failure to obtain an adequate history as mentioned, failure to perform the definitive diagnostic tests, or simply due to some other elusive diagnoses. As has been noted, about 20% of ALF of indeterminate cause is related to obscure APAP toxicity through detection of APAP-protein adducts, the byproducts of the toxic reaction^[32]. However, the adduct assay is not available for routine use at this time.

CLINICAL MANIFESTATIONS

The clinical presentation of ALF is multifaceted, ranging from slightly altered conscious level with profound coagulopathy to a catastrophic failure of multiple organs. The initial clinical features of ALF may be nonspecific and may include anorexia, fatigue, abdominal pain and fever. As the metabolic and detoxification function of liver becomes impaired, the signs of ALF emerge, including jaundice, encephalopathy, coagulopathy, haemodynamic instability, acute lung injury/acute respiratory distress syndrome (ARDS), renal failure, sepsis, and metabolic disturbance.

Depending on the interval between development of jaundice and onset of encephalopathy, clinical manifestation could be stratified into three groups such as hyperacute (< 7 d), acute (7-28 d) and subacute (4-26 wk)^[33]. This classification is popular but not particularly helpful because it does not have prognostic significance that is distinct for identifying the cause of the illness. Hyperacute failure, most commonly caused by APAP hepatotoxicity, is characterized by high aminotransferase level and low bilirubin level^[34]. Hepatic encephalopathy develops rapidly in this setting, sometimes preceding jaundice. Subacute liver failure due to idiosyncratic drug toxicity presents as minimal encephalopathy with no cerebral edema^[35]. This condition is usually associated with severe jaundice, renal dysfunction, and moderate coagulopathy.

ICU TREATMENT

NAC is a proven effective therapy for APAP hepatotoxicity. It is also beneficial in non-APAP ALF patients showing early (grades I / II) hepatic encephalopathy^[36]. NAC can increase non-transplant survival among these patients. Thus, administration of NAC should be initiated immediately when ALF is established. Except for NAC, there is no other proven therapy for ALF. Management consisting of intensive care support should be initiated to address

the various organ dysfunctions associated with ALF.

Cerebral edema and intracranial hypertension

Cerebral edema leading to intracranial hypertension (ICH) is one of the major causes of morbidity and mortality in patients with ALF. The pathogenesis of cerebral edema and ICH in ALF appears to be multifactorial. Ammonia is converted in the astrocytes to osmotically active glutamine, producing osmotic cerebral edema^[37]. Other factors such as impaired cerebral blood flow (CBF) autoregulation, systemic inflammatory response and ischemic injury have also been proposed as the cause of ICH. Some risk factors for the development of cerebral edema in patients with ALF include high-grade encephalopathy (grade III or IV), high serum ammonia concentrations (> 200 $\mu\text{mol/L}$), and requirement for vasopressor support or renal replacement therapy.

Cerebral edema presents clinically as hepatic encephalopathy due to ICH. Basic interventions for the management of cerebral edema should be applied universally in patients with high-grade hepatic encephalopathy. These interventions include elevation of the head of the bed to 30°, maintenance of a neutral neck position, endotracheal intubation, minimizing painful stimuli, and control of arterial hypertension^[38]. Propofol is a reasonable choice for adequate sedation because it may protect from ICH. For treatment of pain, fentanyl is preferred as the first-line agent. Factors that increase ICP need to be avoided and include hypercapnia, hyponatremia, frequent movements, neck vein compression, fluid overload, fever, hypoxia, coughing, sneezing, seizures, and endotracheal suctioning.

ICP monitoring is recommended in ALF patients with high-grade hepatic encephalopathy, in centers with expertise in ICP monitoring as well as in patients awaiting and undergoing liver transplantation^[39]. ICP monitoring can detect elevations in ICP to direct interventions, which may preserve brain perfusion and prevent cranial herniation. Generally, the goal of therapy in ALF is to maintain ICP < 20 mmHg and cerebral perfusion pressure (CPP) > 60 mmHg. Prolonged ICP > 40 mmHg and CPP < 50 mmHg are associated with a poor outcome. CPP < 40 mmHg for > 2 h indicates reduced neurological blood flow to maintain intact brain function and should contraindicate liver transplantation because of poor post-transplantation prognosis. However, patients with refractory ICP elevation > 35 mmHg and CPP < 50 mmHg who made a full neurological recovery contradicted previous findings.

In patients with persistently elevated ICP, osmotic therapy can be considered. Mannitol reduces ICP by osmotically drawing water from the brain parenchyma into the intravascular space^[40]. ICP > 20 mmHg necessitates intravenous administration of mannitol (0.5-1 g/kg) provided serum osmolality is < 320 mOsm/L. However, mannitol fails to normalize ICP once a level > 60 mmHg is reached. Thus, its best use is for mild to moderate ICH. Alternately, hypertonic saline mitigates ICH through both osmotic and nonosmotic effects^[41]. Hypertonic saline to

target serum sodium levels 145-155 mmol/L are suggested to avoid complications associated with extreme hyponatremia, such as seizure and changes in mentation.

Hypothermia also has some benefit in reducing ICP, because it lowers brain energy metabolism, reduces arterial ammonia concentration and extraction of ammonia by the brain, normalizes CBF autoregulation, and reverses systemic inflammatory reactions^[42]. In addition to its neurological effect, hypothermia results in significant improvement of cardiovascular hemodynamics, as manifested by increased mean arterial pressure (MAP) and systemic vascular resistance, and reduction in noradrenaline requirements. Therapeutic hypothermia (cooling to a core temperature of 34 °C-35 °C) is probably well tolerated and effective, but randomized, controlled trials are needed to confirm the benefits of hypothermia before it is applied routinely.

Barbiturates are centrally acting hypnotics that reduce brain oxygen utilization and are effective in lowering ICP^[43]. However, untoward side effects such as arterial hypotension, negative inotropic effects, and immunosuppressant effects make barbiturates a poor first-choice treatment for ICH. Hyperventilation can induce hypocapnia that causes cerebral vasoconstriction, which in turn reduces CBF, thus leading to a decrease in ICP^[44]. Although hyperventilation effectively reduces ICP, there is a concern that the resultant vasoconstriction could exacerbate cerebral ischemia and even cause hypoxia. It is believed that hyperventilation to maintain PaCO₂ between 30 and 35 mmHg may reduce ICP acutely, but it should not be used over a prolonged period.

The use of hepatectomy in patients awaiting liver transplantation is based upon the concept that the necrotic liver is the source of unknown humoral substances that contribute to increased ICP^[45]. Removal of the liver in an ALF patient resulted in improved ICP possibly through a reduction in CBF, nitric oxide (NO) and liver-derived proinflammatory cytokines.

Hemodynamic failure

ALF is characterized by a hyperdynamic circulation with high cardiac output, low MAP, and low systemic vascular resistance^[46]. Increased NO production and cyclic GMP may be involved in these hemodynamic disturbances. Because the patients have such markedly deranged circulation, it is important to use monitoring devices that are able to provide information about changes in MAP, filling status, cardiac output, and oxygenation status. Due to poor oral intake, transudation of fluid into the extravascular space, and possibly gastrointestinal bleeding, most patients are volume depleted and require initial fluid resuscitation. The initial treatment of hypotension should involve intravenous infusion of normal saline and a volume challenge is recommended^[47].

After adequate fluid replacement and treatment of infection and sepsis, vasopressors may also be required to maintain adequate MAP and CPP. ALF patients have lost CBF autoregulation and an increase in MAP results in an

increase in CPP. The MAP should be maintained in a narrow range to achieve a CPP of 60-80 mmHg to prevent cerebral hypoperfusion on the one hand and further cerebral hyperemia on the other hand. Noradrenaline, with fewer β -adrenergic side effects, could increase hepatic blood flow in parallel with minimizing tachycardia and is often the preferred vasopressor^[48]. In patients who do not respond to a volume challenge and norepinephrine, vasopressin or terlipressin may potentiate the effects of norepinephrine. Patients with uncorrectable hypotension after volume repletion and vasopressor administration should be evaluated for adrenal insufficiency, which occurs frequently in this setting^[49]. Adrenal insufficiency could be corrected with a stress dose of hydrocortisone 200-300 mg/d in divided doses.

Respiratory failure

Acute lung injury/ARDS is not uncommon in patients who have ALF and severe multiple organ dysfunction; particularly a requirement for vasopressors and concurrent ICH^[50]. The hypoxemia caused by acute lung injury and ARDS should be managed with low tidal volume ventilation to minimize risks of pulmonary volume trauma and barotrauma. Upregulation of respiratory rate is needed to ensure adequate minute ventilation, avoiding marked hypercapnia. It is desirable to maintain the lowest level of positive end-expiratory pressure that achieves adequate oxygenation because high levels may exacerbate cerebral edema and hepatic congestion. Recruitment, a transient increase in mean airway pressure to expand the lungs, is also beneficial in improving oxygenation.

Acute renal failure

The incidence of acute renal failure in ALF is as high as 50%-80%. Acute renal failure resembling hepatorenal syndrome is multifactorial in the setting of ALF^[51]. Direct drug nephrotoxicity and acute tubular necrosis due to ischemia from hypotension are among the most important associated disease entities. In addition, development of abdominal compartment syndrome, due to ascites, intra-abdominal hemorrhage or severe abdominal and gut wall edema, is a common cause of renal impairment in ALF. Management includes avoidance of nephrotoxic agents, treatment of infection, maintenance of adequate renal perfusion, and renal replacement therapy. Early targeted volume replacement and vasoactive agent administration are essential to avoid arterial hypotension and ensure adequate renal perfusion. Worsening renal failure needs to be addressed with renal replacement therapy. Continuous renal replacement therapy is recommended, because most patients with ALF tolerate intermittent hemodialysis poorly because of circulatory instability, precipitous fluid shifts, and a rise in ICP^[52].

Infection

ALF patients have enhanced susceptibility to infection because of the presence of indwelling lines and catheters, dysfunction of monocytes, and impaired complement

system and neutrophil and Kupffer cell function^[53]. Bacterial infections have been documented in 80% of cases; most commonly pneumonia, urinary tract infections, intravenous catheter-induced bacteremia, and spontaneous bacteremia. Infectious organisms are mainly Gram-negative enteric bacilli, Gram-positive cocci and *Candida* species. Infection inhibits hepatic regeneration, and it is associated with progression of hepatic encephalopathy and renal failure, reduces successful rate of transplantation, and increases mortality in ALF. Thus, close surveillance for infection should be maintained in all ALF patients, with frequent chest radiographs and cultures of blood, urine and sputum. Empirical antibiotics should be administered when surveillance cultures are positive. To patients who develop progression to grade 3 or 4 hepatic encephalopathy and elements of systemic inflammatory response syndrome, antibiotic treatment is also recommended^[54].

Bleeding

Deficiencies of fibrinolytic proteins, anticoagulant proteins (protein C/S or antithrombin III) and procoagulation factors (II, V, VII, IX and X) are often present in ALF; in part due to failure of synthesis as well as consumption of these factors. Data have also shown quantitative and qualitative platelet dysfunction in ALF. Hemostatic changes thus incorporate coagulopathy [confirmed with prolonged prothrombin time (PT) and partial thromboplastin time] as well as a tendency to develop thrombotic events such as disseminated intravascular coagulation. However, there are abnormalities in both the coagulation and the fibrinolytic pathways, and data suggest that the defects are balanced; that is, there is a relative preservation of hemostasis^[55]. Clinically significant bleeding occurs rarely (about 5% of cases) and the perceived bleeding risk based upon INR may be overstated.

Bleeding generally occurs from superficial mucosal lesions, especially gastric erosions. Administration of histamine-2 receptor antagonists or proton pump inhibitors has been shown to decrease the risk of gastric mucosal bleeding in patients with ALF. In general, infusion of fresh frozen plasma is indicated only for control of active bleeding or during invasive procedures such as insertion of ICP monitor, to maintain an INR < 1.5^[56]. When fresh frozen plasma fails to normalize PT/INR adequately, the use of recombinant factor VIIa can be considered. Cryoprecipitate is recommended in patients who have significant hypofibrinogenemia (< 1 g/L). Platelet transfusion is indicated only to aid in controlling active bleeding or during invasive procedures if the count is < 50 × 10⁹/L or prophylactically if < 15 × 10⁹/L^[57]. Finally, vitamin K (5-10 mg subcutaneously) should be considered in all patients with ALF, because its deficiency can occur in > 25% of patients.

Metabolic concerns

Patients are prone to develop hypoglycemia because hepatocyte necrosis causes glycogen depletion and defective

glycogenolysis and gluconeogenesis. Rapid development of hypoglycemia, which can confound the hepatic encephalopathy, should be managed with continuous intravenous glucose infusion^[58]. Hyperglycemia should also be avoided because it may contribute to poor ICP control. Low systemic blood pressure and poor systemic microcirculation result in a build-up of lactate; a complication that may be accentuated by the lack of the lactate metabolism in the failing liver. Correction of hyperlactatemia is important because it can affect circulatory function and aggravate cerebral hyperemia. Serum phosphate, potassium and magnesium are frequently low, requiring repeated supplementation. Severe restrictions of protein should be avoided; normal protein intake of about 1 g/kg per day is reasonable in most cases^[59]. Owing to the hypercatabolic state of ALF, nutrition is vital and enteral feedings should be initiated early. If enteral feeding is contraindicated, parenteral nutrition is a reasonable alternative.

LIVER SUPPORT DEVICES

Extracorporeal supportive devices have been advocated to replace the liver function in ALF patients; however, the complexity of liver metabolic, synthetic, detoxifying, and excretory functions makes the extracorporeal hepatic support extremely difficult. Currently available liver support systems comprise nonbiological systems and bioartificial systems. As the most common techniques of nonbiological systems, molecular adsorbent recirculatory system and Prometheus therapy are useful methods of detoxification for patients with ALF^[60]. Unfortunately, no survival benefit could be demonstrated compared with standard medical therapy.

Bioartificial liver (BAL) systems rely on the use of liver cells (human or nonhuman) to perform detoxification and secretion of hepatocyte-derived factors. The selection of the ideal cell source and the design of more sophisticated bioreactors are the main issues in this field of research. Preliminary data on the use of BAL devices suggest some improvement in encephalopathy, but no real improvement could be demonstrated in overall survival.

LIVER TRANSPLANTATION

OLT remains the only definitive treatment for patients with ALF proven to have irreversible liver injury. Rapid evaluation for transfer to a transplantation center and consideration for liver transplantation is mandatory so that transplantation can be applied before contraindications develop. Towards this end, multiple prognostic indicators and scoring systems have been devised to predict outcome in ALF. The King's College criteria are widely used to assess of the severity of ALF and the potential variability of the prognosis, with a sensitivity of 68%-69% and a specificity of 82%-92% (Table 2). Recently, the addition of arterial lactate levels in patients with APAP-induced ALF has been proposed to improve sensitivity of the criteria and identifies patients in need

Table 2 King's College criteria for selecting recipients of emergency liver transplants

Acetaminophen-induced ALF	Non-acetaminophen-induced ALF
Strongly recommended list for OLT if: Arterial lactate > 3.5 mmol/L after early fluid resuscitation	List for transplantation if: INR > 6.5 and encephalopathy present irrespective of grade
List for transplantation if: Arterial pH < 7.3 or arterial lactate > 3.0 mmol/L after adequate fluid resuscitation	Or if any 3 of the following features (encephalopathy irrespective of grade) are present: Age < 10 yr or > 40 yr ¹ Interval from jaundice to encephalopathy > 7 d ¹
List for transplantation if all 3 of the following occur within a 24-h period: Grade 3 or 4 hepatic encephalopathy INR > 6.5 Creatinine > 300 µmol/L	INR ≥ 3.5 Serum bilirubin ≥ 300 µmol/L Unfavorable etiology, such as seronegative hepatitis, idiosyncratic drug reaction or Wilson disease

¹These criteria have not been found to be predictive of outcome in recent analyses. ALF: Acute liver failure; OLT: Orthotopic liver transplantation; INR: International normalized ratio.

for OLT earlier^[61]. The Clichy/Villejuif criteria are widely used in Northern Europe for ALF patients with severe encephalopathy, and assess outlook with consideration of coagulation factor V concentrations and patient age. The criteria include grade 3 and 4 hepatic encephalopathy and factor V levels < 20% in patients < 30 years of age or < 30% in patients aged > 30 years. Other systems such as Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Model for End-Stage Liver Disease (MELD) score have also been used to determine the prognosis in ALF. The MELD score is calculated by the formula: MELD = 3.8 [Ln serum bilirubin (mg/dL)] + 11.2 (Ln INR) + 9.6 [Ln serum creatinine (mg/dL) + 6.4]. The sensitivity of APACHE II score and MELD score is too low to determine outcome, but the specificity is acceptable. This means that they are more applicable for predicting death rather than spontaneous survival.

In general, key factors involved in determining outcome of ALF are the etiology, degree of encephalopathy, degree of hepatocyte damage, and risk of extrahepatic complications. First, the etiologic diagnosis *per se* appears to be the strongest driver of outcome. ALF cases due to APAP toxicity, hepatitis A, ischemia, and pregnancy may have a better prognosis^[62]. Approximately 90% of APAP-induced ALF cases recover with supportive measures, whereas ALF cases due to idiosyncratic drug injury, acute hepatitis B, autoimmune hepatitis, mushroom poisoning, WD, Budd-Chiari syndrome and indeterminate causes carry a much poorer prognosis in the absence of OLT. Up to 80% of patients who develop liver failure due to idiosyncratic drug injury might die without transplantation. Second, grade 3 or 4 encephalopathy is considered to show irreversible liver damage; spontaneous recovery is rare, and in most cases the patient is transferred to a transplantation centre and undergoes OLT as soon as possible^[63]. Moreover, the degree of hepatocyte damage,

reflected as coagulopathy or jaundice, is viewed as inverse correlation with survival. Finally, extrahepatic complications, such as comorbid cardiovascular, respiratory and systemic conditions have a negative affect on patient outcomes. In addition, studies have also identified serum phosphate, blood NH₃ levels, high body mass index, genetic polymorphism, and surrogate markers of cell death as additional predictive or diagnostic factors^[64]. Hypophosphatemia is an indication of increased hepatic ATP production during liver regeneration and serve as a good prognostic indicator especially in APAP-induced ALF. Genetic polymorphisms in keratins 8 and 18, the sole keratins expressed by hepatocytes, confer susceptibility to ALF and are also prognostic.

Before OLT, contraindications to transplantation such as substance abuse, suicidal predilection, psychiatric disorders, uncontrollable sepsis and other organ system involvement (irreversible brain damage, extrahepatic malignancy, cardiovascular failure requiring > 1 µg/kg per minute norepinephrine infusion, and ARDS requiring FiO₂ > 60% and PEEP > 12 cm H₂O) must be excluded. Once listed for OLT, patients waited an average of 3.5 d. However, 66% of patients were transplanted, and of the remainder, 22% died prior to transplantation and 12% recovered spontaneously. The 1-year survival of cadaveric liver transplant in ALF patients is lower than that in chronic liver failure patients; in part because of the extreme emergency conditions often encountered. After the first year, this trend has reversed and ALF patients have a better long-term survival. In addition to whole-organ deceased donor liver transplantation, live donor and auxiliary liver transplantation have been attempted but still remain controversial^[65].

CONCLUSION

The management of ALF challenges our best skills because of its rapid progression and frequently poor outcomes. Early identification of ALF and the administration of etiology-specific treatment are crucial to improve the outcome. Extrahepatic organ failure should be well managed with advanced intensive care management. Better-targeted use of OLT techniques becomes important to save the patients who fail to recover spontaneously. A better understanding of the pathophysiology of ALF will probably lead to further improvement in survival rates.

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