Acute liver failure

Fin Stolze Larsen and Peter Nissen Bjerring

Department of Hepatology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Correspondence to Fin Stolze Larsen, MD, PhD, DMSc, Department of Hepatology, A-2121, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark
E-mail: stolze@post3.tele.dk

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Purpose of review
Acute liver failure (ALF) results in a multitude of serious complications that often lead to multi-organ failure. This brief review focuses on the pathophysiological processes in ALF and how to manage these.
Recent findings
The clinical presentation in ALF ranges from slightly altered conscious level with profound coagulopathy to coma with a catastrophic failure of multiple organs, including uncontrollable cerebral edema and brain death, which is rarely seen in decompensated cirrhosis. Interestingly, ALF patients who recover as the liver is regenerating, usually do not suffer from hepatic or extrahepatic sequelae. In contrast patients surviving acute-on-chronic liver failure will return to a state with incompensated cirrhosis, and eventually need transplantation for survival.
In the management of ALF, the use of noradrenalin in combination with continuous high-dose renal replacement therapy, terlipressin, hypertonic sodium chloride, and mannitol can ameliorate systemic vasodilation and attenuate brain edema. Furthermore, liver assist devices seem to improve extrahepatic organ dysfunction and survival.
Summary
Insight into the of pathopysiological mechanisms of ALF that lead to cardiovascular instability, brain edema and development of multiorgan failure has advanced and resulted in improved survival. The role of liver assisting is still unknown but preliminary results indicate a positive effect on survival.

Keywords
ammonia, brain edema, MODS, plasmapheresis, sepsis, transplantation

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Introduction

Massive hepatic necrosis results in a multitude of serious complications that include coagulopathy and the development of hepatic encephalopathy, the common denominators that define acute liver failure (ALF) [1]. The condition was earlier termed fulminant hepatic failure meaning 'sudden and severe' liver failure in a previously healthy person without chronic liver disease [2].

The liver synthesizes in the region of 20 000 individual proteins and a subset of these are almost exclusively synthesized in liver, such as albumin and clotting factors. Whereas most clotting factors have a half-life of 8–72 h, albumin has a half-life of 20 days and hypoalbuminemia is therefore not commonly seen initially in ALF. As part of the definition of ALF, prolonged prothrombin time is a pathognomonic factor and the result of a marked reduction of circulating clotting factors. This brief review focuses on pathophysiological processes and how to manage these in ALF patients.

Prognosis and clinical presentation

Patients with ALF remain quite different from patients with known chronic liver disease experiencing an acute deterioration ['acute-on-chronic liver failure (AoCLF)'] with regard to the time course and extent of extrahepatic complications.

The clinical condition following ALF is, indeed, life-threatening with a mortality rate previously exceeding 80%, now still as high as 40–50% depending on the cause and the kind of institution taking care of the patient [3••].

The clinical presentation is multifaceted ranging from slightly altered conscious level with profound coagulopathy to a catastrophic failure of multiple organs, including development of uncontrollable systemic inflammation and cerebral edema. This latter complication may cause high intracranial pressure (ICP) and brain death, and is in contrast very rarely seen in patients with

suddenly decompensated chronic liver disease with overt hepatic encephalopathy, that is AoCLF.

Certain patients present with a more protracted course of ALF, with development of only minimal encephalopathy and no brain edema, a condition termed subacute liver failure [1,3••]. The disease progression is usually associated with severe jaundice, renal dysfunction and moderate coagulopathy. The prognosis for such patients is far worse than for those with a more hyperacute course of the disease. As in most patients with AoCLF liver transplantation is often the only option for survival in subacute liver failure patients.

Cause

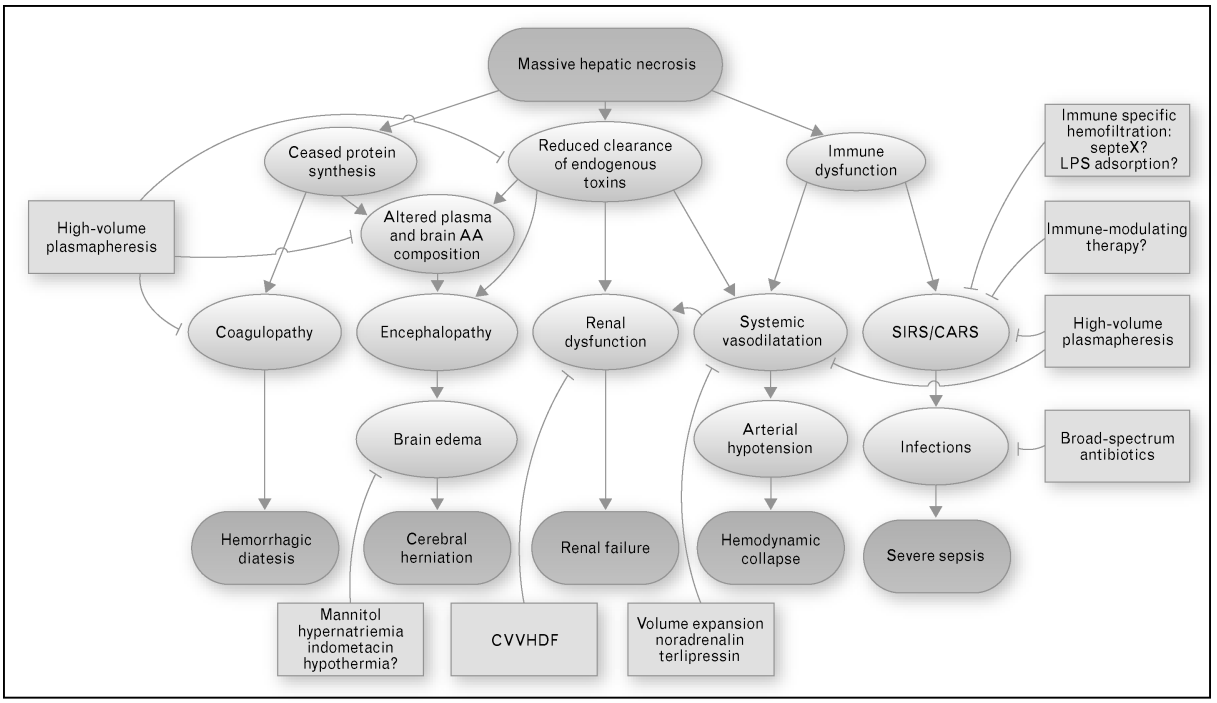
The causes of ALF encompass a wide variety of toxic, viral, metabolic, and vascular insults to the liver, and the prevalence of any single cause depends on the geographic and socioeconomic location of the patient. In areas of the developing world, where orthotopic, or living related liver transplantation is not widely available, acute viral hepatitis (principally hepatitis B and E) predominates, whereas drug-induced ALF (including acetaminophen overdose) is the principal cause in Europe and the US [3••]. Although the hepatic pathology in ALF differs according to the cause, the manifestation of the extrahepatic complications – including cerebral edema – appears very uniform, implying that therapies aimed at treating complications should be applicable to all affected patients.

Pathophysiology

Systemic vasodilation with arterial hypotension, coagulopathy, renal failure, sepsis, acute lung injury, encephalopathy and brain edema, are all frequent complications of ALF. ALF also results in reduced function of platelets and white blood cells that may lead to hemorrhagic diathesis, life-threatening infections and end-organ dysfunction. Although the genesis of hepatic dysfunction in ALF now has been described in great detail, the 'motor' mechanism responsible for development of the associated multiple organ dysfunction syndrome (MODS) is not fully understood (Fig. 1).

Acute and massive hepatic necrosis results in release of ammonia, alanine, lactate and proinflammatory cytokines from the splanchnic circulation (Fig. 1). Apart from this, release of large amounts of intracellular material, such as DNA, RNA, and cytoskeletal debris, from the failing liver may result in polymerization of proteins that physically may hamper laminar blood flow and exchange of nutrients in the microcirculation. Furthermore, alterations in the splanchnic circulation often result in low systemic blood pressure and a poor systemic microcirculation with

Figure 1 Representation of how the multiorgan dysfunction syndrome develops in acute liver failure



Suggested interventions are shown in rectangular boxes. AA, amino acid; CARS, compensatory anti-inflammatory response syndrome; CVVHDF, continuous veno-venous hemodiafiltration; LPS, lipo-polysaccharide; SIRS, systemic inflammatory response syndrome.

a build-up of lactate, a complication that may be accentuated by the lack of the lactate metabolism in the failing liver.

Patients with ALF develop acute portal hypertension due to inflammation, edema and hampered microcirculation of the failing liver. Leakage of endotoxins from the gut to the portal blood may result in elevated systemic endotoxin levels because portal blood bypasses the liver via extrahepatic collaterals. It is also assumed that endotoxins are shunted through the failing liver without being cleared due to a vastly reduced Kuppfer cell mass. Endotoxins induce the release of various proinflammatory cytokines [such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6], which also are potent stimulators of the inducible isoform of nitric oxide synthetase. Indeed, there is accumulating evidence that hyperdynamic circulation in ALF may result from cytokine activation of the endothelium, which releases excessive amounts of endothelium-derived nitric oxide [4].

Treatment

Even life-threatening liver failure with manifest MODS is entirely reversible, if the liver function is rapidly restored. Thus the overall strategy for optimizing the prognosis is to stabilize the condition until hepatic regeneration or a graft becomes available for liver transplantation. Because one-third to half of patients with severe ALF survive without transplantation (depending on cause), it is important to determine if emergency transplantation is needed for survival [5–8]. In most centers worldwide, the King's College criteria are used for this purpose. But also, nonspecific liver function tests such as lactate, phosphate and the model for end-stage liver disease (MELD) may be of value in selecting/deselecting patients for transplantation [5–8]. However, a more detailed discussion on the prognostic markers of ALF is beyond the scope of this study.

Basic handling

Though the liver may have an exceptional ability to regenerate this is rarely going to happen if vital functions are not immediately supported and the patient referred to an experienced liver failure center with a liver transplantation program. This is even the case if the patient has medical or psychosocial contraindications to liver transplantation.

Before transportation it is important to correct for hypoglycemia by an intravenous infusion of 20% glucose, and for metabolic acidosis and arterial hypotension by aggressive volume expansion with colloids, crystalloids and fresh frozen plasma (if the patient is ooze bleeding). Also, patients with stage 3 to 4 encephalopathy should be intubated and be switched to mechanical ventilation aiming at a slightly reduced partial pressure of carbon dioxide in arterial blood with sufficient oxygenation. If sedation is needed to allow controlled ventilation, propofol, midazolam and fentanyl are preferred.

Appropriate management and monitoring, regardless of the decision to proceed with liver transplantation or not, should include the placement of arterial and central venous catheters. In patients with systemic hemodynamic instability who do not respond to volume expansion or achieve adequate cardiac filling pressures, the insertion of a pulmonary artery catheter may in rare cases be needed to select and/or adjust the use of inotropic drugs. In addition to the importance of proper-volume resuscitation it has also been shown that high-volume plasma exchange improves systemic, splanchnic and cerebral hemodynamics as well as oxidative metabolism in patients with ALF [9]. In fact, high-volume plasma exchange (defined as exchange of 10 l of plasma with fresh frozen plasma every day for 3 consecutive days) in combination with continuous hemodiafiltration may not only help clear circulating necrotic components and lactate but also improves survival in such patients [10].

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. Low-dose terlipressin (0.5–1.0 mg every 4–6 h) can be used to preserve or restore cerebral perfusion and renal function [11]. Occasionally, patients may develop low cardiac output syndrome, which is associated with a poor prognosis. In these patients, the use of dopamine, dobutamine and adrenaline may be of value to increase cardiac output and arterial pressure. In such patients transthoracic echocardiogram should be obtained to exclude pericardia effusion and/or hypokinesis. In addition, plasma magnesium and calcium ions, and phosphate levels should be determined and corrected. Sudden deterioration in arterial pressure and/or systemic vascular resistance often results from the development of sepsis. In fact, sepsis should always be suspected in patients with ALF and broad spectrum antibiotics administered prophylactically.

The brain

To preserve normal intracranial compliance, treatment of severe cases of ALF is based upon the monitoring of ICP and calculation of cerebral perfusion pressure (CPP) (mean arterial pressure subtracted by ICP). In addition surrogate markers of cerebral blood flow (transcranial Doppler, near infrared spectroscopy, internal jugular vein oxygen saturation) and cerebral microdialysis may be of value in the assessment of brain viability. In the most severe cases of brain edema, ICP and brain monitoring are important in therapeutic decisions such as initiation of treatment with mannitol, hypertonic saline, higher doses of sedatives, hypothermia, indomethacin, inotropic

support and whether or not to proceed with liver transplantation. However, drift of the transducer, bending of catheters, inaccurate calibration or displacement during nursing or interventions frequently influence and change these parameters. Thus, potentially dangerous treatments may be instituted on a false basis. ICP and CPP should always be interpreted critically, always in combination with a close evaluation of clinical condition before the escalation of medical treatment is instituted, and before liver transplantation is considered to be contraindicated. It is generally recommended that the use of ICP monitoring is only used in a small subgroup of patients with a high risk of cerebral edema (patients with persistent hyperammonemia above 200 μmol/l and those with poor prognosis and signs of systemic inflammation) [12].

It is strictly important to control the plasma sodium concentration as it also affects the ICP. In cases with surges high ICP hypertonic saline and mannitol infusion are the most important treatments of cerebral edema [12]. Not only is ICP reduced, but cerebral perfusion and the cerebral metabolic rates of oxygen and lactate improve. This effect is probably the result of an increase in colloid osmotic pressure in the cerebral capillaries and a reduction in interstitial water content.

Induction of hypometabolic-induced cerebral vasoconstriction (by propofol, midazolam or barbiturates) or by hypothermia is still used for the treatment of intracranial hypertension to reduce ICP by lowering intracranial blood volume [12,13]. The prophylactic use of mild hypothermia (tp. ~33–35 C) is probably more well tolerated and effective, but a prospective randomized controlled trial is under way and the results are warranted before more firm conclusions can be drawn [14•].

Liver assist devices

As stated earlier cytokines may be important for the development of low systemic vascular resistance and blood pressure, and one strategy to maintain vascular tone is to decrease the plasma levels of endotoxins and cytokines. In fact, clearance procedures such as continuous veno-venous hemodiafiltration (CVVHD) with SepteX (Gambro, Glostrup, Denmark) filters (a high cut-off filter that removes cytokines) or lipo-polysaccharide (LPS)-specific adsorbers (Alteco Medical, Lund, Sweden), high-volume plasmapheresis and the Molecular Adsorbents Recirculating System (MARS) treatment (Gambro, Glostrup, Denmark) may help re-establish normal systemic arteriolar tone though more studies are needed [15]. Though MARS and the related Prometheus (Fresenius, Bad Homburg, Germany) have no effect on the survival in patients awaiting acute liver transplantation it remains to be established whether the use of artificial liver assist devices may influence survival in nontransplant candidates [16]. Preliminary data on the use of bioartificial liver assist devices and high-volume plasma exchange suggest, however, a beneficial effect on transplant-free survival [10,17].

Conclusion

Treatment of patients with ALF is mainly symptomatic. Recent discoveries of distinct pathophysiological mechanisms responsible for cardiovascular instability, brain edema and development of multiorgan failure indicate the following specific treatments may be helpful to improve the chance of survival:

(1) Use isotonic saline and human albumin to quickly restore normal central filling pressure and arterial pressure in patients presenting with ALF.
(2) Refer the patient to a liver failure unit with liver transplantation facilities.
(3) If associated with severe hyperammonemia or lactic acidosis CVVHDF may be needed even if renal function is preserved.
(4) If inotropic is needed the combined use of noradrenalin with a small-dose terlipressin is recommended.
(5) Administration of broad-spectrum antibiotics in all ALF patients is recommended.
(6) Consider if the patient is a candidate for emergency transplantation using current scoring systems for predicting poor prognosis.
(7) Normalize and control plasma sodium concentration and body temperature, which both delay onset of brain edema.
(8) Use of any form of advanced liver supporting system is not indicated unless studied in a randomized controlled trial. High-volume plasma exchange, however, seems to improve the transplant-free survival in patients with ALF.

References and recommended reading

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- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 208–209).

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