Acute Liver Failure

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Definition

The term "acute liver failure" (ALF) describes the clinical consequence of a sudden injury to the liver, resulting in massive hepatocyte dysfunction and/or necrosis. Clinical hallmarks of ALF include liver dysfunction as measured by biochemical values, coagulopathy, encephalopathy, and multi-organ dysfunction (Table 24.1) [1]. More recent definitions employ the time interval between the development of jaundice and encephalopathy to further stratify this disease entity into hyperacute, acute, and subacute phenotypes (Table 24.2) [2–4]. Typically, hyperacute and acute cases (which occur secondary to viral infection or acetaminophen toxicity) have improved outcomes when compared to subacute scenarios [5]. Although many causes of ALF may also be implicated in chronic liver disease and subsequent cirrhosis, the patient must be free of chronic liver dysfunction to cinch the diagnosis of ALF.

Causes

Viral

Infection with hepatitis A, B, and E viruses (HAV, HBV, and HEV, respectively) is the most common causes of both ALF and liver transplantation in developing countries. ALF secondary to viral hepatitis is much less predominant in the Western world as a result of vaccination and modern sanitation. Transmission of HAV and HEV occurs via a fecal-oral route, while HBV is transmitted through exposure to contaminated blood and bodily fluids [6, 7]. ALF secondary to HAV and HEV infections usually follows a hyperacute timeline [8, 9]. Acute infection with HBV results in ALF in less than 4% of patients; however, outcomes are inferior to cases caused by HAV and HEV [1]. Furthermore, reactivation of subclinical HBV infection, often seen in cases of immunosuppression, results in especially high mortality [1, 5]. Identification of these at-risk patients and viral prophylaxis is recommended for this population [10–12]. Although much less common, ALF secondary to viral infection with *Herpes simplex virus* (HSV), parvovirus, *Cytomegalovirus* (CMV), Epstein-Barr virus, and varicella zoster virus has been well documented [13].

Drug-Induced

The most common cause of ALF in the Western world is drug-induced liver injury, with acetaminophen as the most frequent culprit drug [14, 15]. ALF secondary to acetaminophen toxicity tends to be hyperacute, with rapid progression to multi-organ failure [16]. Acetaminophen toxicity occurs in dose-dependent fashion, requiring massive doses (15–20 g). As a result, ALF secondary to acetaminophen is often the result of a suicide attempt, although indeliberate toxicity is also seen, especially in patients with underlying liver disease. Even in patients utilizing medications known as hepatotoxins, ALF due to drugs other than acetaminophen is rare and often a diagnosis of exclusion.

Post-hepatectomy

Post-hepatectomy liver failure (PHLF) is a well-established cause of ALF and is the result of inadequate liver remnant function following major hepatectomy. It is widely accepted that a future liver remnant of at least 25% is required to avoid PHLF in healthy patients [17]. This number rises to 40% in patients with underlying liver disease or with prior extensive chemotherapy exposure [18]. Strategies) to mitigate this risk include associating liver partition and portal vein ligation for

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Table 24.1 Clinical manifestations of organ system dysfunction secondary to acute liver failure

Organ system	Clinical features
Neurologic	Hepatic encephalopathy Cerebral edema Intracranial hypertension
Cardiovascular	Hypotension
Respiratory	Late respiratory failure
Coagulation	Impaired procoagulant and anticoagulant pathways
Renal	Acute kidney injury
Metabolic	Hypoglycemia Increased metabolic demand
Immunologic	Functional immunosuppression

Table 24.2 Classification of acute liver failure based on time from jaundice to encephalopathy

	Time from jaundice to encephalopathy
O'Grady system	
Hyperacute	0–1 week
Acute	1–4 weeks
Subacute	4–12 weeks
Bernuau system	
Fulminant	0–2 weeks
Subfulminant	2–12 weeks
Japanese system	
Fulminant	
Acute	0–10 days
Subacute	10 days–8 weeks
Late-onset	8–24 weeks

staged hepatectomy (ALPPS) [19], percutaneous portal vein embolization (PVE) [20], parenchymal-sparing resections, and two-stage hepatectomies. Several clinical indices have been developed in an attempt to predict PHLF. The 50–50 criterion employs prothrombin time <50% and total bilirubin >50 umol/L on postoperative day 5 as an indicator of PHLF [21]. The International Study Group of Liver Surgery adopted a more generalized definition of PHLF describing increasing INR and serum bilirubin above locally accepted cutoff values on or after postoperative day 5 [22]. The model for end-stage liver disease (MELD) has also been used to try and anticipate PHLF with promising predictive sensitivity [23]. Despite these multiple indices for identifying patients at risk for PHLF, treatment options still remain limited.

Other Causes

Acute liver injury as the result of profound ischemia is an important condition often seen in critically ill surgical patients. Hypoxic hepatitis may progress to ALF if the magnitude of hepatocellular necrosis is severe enough [24]. Wilson's disease, Budd-Chiari syndrome, autoimmune hepatitis, and toxic mushroom ingestion remain quite rare causes of ALF. A significant number of ALF have no identifiable cause and remain a diagnostic challenge [5].

Management

Patients suspected of having ALF should be managed in an intensive care setting, ideally under the multidisciplinary care of intensivists, liver surgeons, and hepatologists. The expansive role that the liver plays in maintaining homeostasis is evident in patients with ALF as a wide variety of organ systems are affected. A thorough knowledge of the secondary complications associated with ALF will allow the intensivist to identify and treat potential life-threatening conditions early. These are summarized in Table 24.1.

Neurologic

The development of encephalopathy is central to the diagnosis of ALF and is often associated with cerebral edema in hyperacute cases. Although the pathogenesis of cerebral edema and encephalopathy is incompletely understood, impaired ammonia detoxification clearly plays an important part. In patients with grades 3–4 encephalopathy, ammonia levels >120 umol/L on admission have been shown to be associated with higher rates of mortality [25]. Pharmacologic treatments used for elevated ammonia in chronic liver disease are not generally recommended in ALF [26]. Cerebral edema and elevated intracranial pressure (ICP) are the leading cause of death from ALF and thus must be a central focus for the treating physician. Steps to prevent or decrease cerebral edema should include correction of hyponatremia, avoiding hypoxia and hypercapnia often requiring endotracheal intubation in cases of severe hepatic encephalopathy, and pharmacologic sedation. Severe cerebral edema may lead to life-threatening elevations in ICP. Elevated ICP may be diagnosed with CT, MRI, and transcranial Doppler when combined with clinical findings [26]. Patients with severe hepatic encephalopathy (grades 3–4) can also be considered for direct ICP monitoring to guide and assess response to therapy as persistently elevated ICP and decreased cerebral perfusion pressure (CPP) result in poor outcomes following liver transplantation [27]. A randomized, controlled trial (RCT) evaluating the effect of hypertonic saline on intracranial hypertension demonstrated a reduced incidence and severity of elevated ICP when hypertonic saline was administered to patients with grades 3–4 encephalopathy due to ALF [28]. Some animal studies and clinical studies have shown promising

results for mild hypothermia to prevent intracranial hypertension in ALF [29]. However, a multicentered RCT in ALF patients with high-grade hepatic encephalopathy failed to demonstrate neither any reduction of intracranial hypertension as measured by direct ICP monitoring nor any reduction in mortality [30]. Thus, it cannot be recommended to induce hypothermia in ALF patients, even in cases of suspected intracranial hypertension.

Cardiovascular

Cardiovascular derangements are frequent in ALF and are often multifactorial in origin. Initial management does not differ from standard critical care algorithms. Intravascular volume is restored using isotonic crystalloids. Pulse pressure variation has been shown to be an effective modality at assessing fluid responsiveness in ALF patients [31]. If hypotension persists despite adequate fluid resuscitation, vasopressors may be required to maintain adequate mean arterial pressure (MAP). In patients with intracranial hypertension, vasopressors may be required to maintain a MAP allowing for CPP >60 mm Hg. Patients with refractory hypotension may have relative adrenal insufficiency and may benefit from hydrocortisone replacement therapy [32].

Respiratory

Respiratory dysfunction is uncommon in the early stages of ALF. Despite this, endotracheal intubation is often required given the severity of hepatic encephalopathy in these critically ill patients [5]. Furthermore, ventilator manipulation allows for deep sedation as well the prevention of hypercapnia, which is a vital maneuver in preventing cerebral edema and intracranial hypertension as discussed above.

Coagulopathy

Elevated INR is a hallmark of ALF, and as such, many patients are aggressively transfused with fresh frozen plasma, vitamin K, and other coagulation factors. There is a paucity of data to support correction of laboratory markers of coagulation in ALF patients without evidence of active bleeding. Furthermore, it should be noted that the synthesis of anticoagulant factors produced in the liver is also impaired in ALF. As a result, the true coagulation profile of the patient may be closer to equilibrium than laboratory values suggest [33, 34]. As a result, in the absence of active bleeding, transfusion of coagulation factors should be avoided.

Renal

Renal dysfunction is observed in the majority of patients with ALF and is thought to be the result of a general systemic inflammatory response [35]. Renal replacement therapy is often required in the ALF patient to maintain fluid balance, prevent acid-base disturbances, and help to clear serum ammonia. Continuous renal replacement therapy is the preferred modality of intermittent hemodialysis as it provides greater hemodynamic stability [36] and can provide effective ammonia clearance [37]. The renal dysfunction identified with ALF is usually self-limiting and in most cases resolves once liver function has been reestablished (either through regeneration or transplantation) [38, 39].

Metabolic

Metabolic derangements in ALF are multifactorial and require attention and prompt correction to ensure favorable clinical outcomes. Impaired hepatic glucose regulation, along with increased metabolic demands, often results in profound hypoglycemia. Infusion of high-concentration intravenous dextrose is often required to maintain adequate blood glucose levels [40]. Patients with severe hepatic encephalopathy will require nasoenteric feeding access to deliver nutrition, while parenteral should be avoided. Caloric and protein goals are 25–40 kcal/kg/day and 0.8–1.2 g/kg/day, respectively, to prevent protein catabolism and preserve immune function [5, 40]. Protein restriction should be avoided in the absence of worsening hyperammonemia attributed to protein intake [41].

Infectious

Patients with ALF are felt to be at higher risk of systemic infection secondary to functional immunosuppression [5], and as a result, the majority of centers caring for ALF patients administer prophylactic antibiotics [42]. The US Acute Liver Failure Study Group identified systemic infection as a significantly contributor to hepatic encephalopathy exacerbation [43]. However, the same group recently demonstrated no significant reduction in bloodstream infection or 21-day mortality with the use of prophylactic antibiotics in ALF [44]. Given the paucity of reliable data given in the antibiotic use and ALF, we reserve antibiotic administration to patients with positive admission or surveillance cultures and clinical manifestations of infection such as fever or worsening leukocytosis, grades 3–4 encephalopathy, actively listed for liver transplantation.

Disease-Specific

When the etiology of ALF is identifiable, cause-specific interventions may be of benefit, although robust RCT data for many of the following treatments is not available. The most widely studied disease-specific treatment is the administration of N-acetylcysteine (NAC). Intravenous NAC has been shown to decrease overall mortality in ALF caused by acetaminophen toxicity [45]. Furthermore, NAC administration early in the course of non-acetaminophen ALF provided a transplant-free survival benefits in patients with grades 1–2 hepatic encephalopathy [46]. As a result, NAC should be administered early in acetaminophen-induced ALF and in non-acetaminophen cases of ALF with grades 1–2 hepatic encephalopathy.

Lamivudine administration may improve HBV-associated ALF outcomes [47–49] although RCT data is scarce. Similarly, acyclovir and ganciclovir have been used as treatment adjuncts in HSV and CMV causes of ALF, respectively, although no reliable data exists. Autoimmune ALF has been treated with steroid administration in some centers, although there is no literature demonstrating improved outcomes. In fact, some authors have suggested infectious complications which may be exacerbated with steroid administration [50].

Liver Transplantation

All patients suspected of ALF should be evaluated early for liver transplantation. The decision to proceed with liver transplantation for ALF is a difficult one, as liver grafts are in considerably short supply. Thus, identifying which patients will regain adequate hepatic reserve, and which will not, is of paramount importance to ensure efficient usage of such a valuable resource. The King's College Criteria were developed as a predictive tool to identify patients at risk for high mortality without urgent liver transplantation. They include patients with acetaminophen-induced ALF who have either an arterial pH < 7.30 after adequate volume resuscitation or an INR >6.5 and serum creatinine >3.4 mg/dL with grades 3–4 encephalopathy. Patients with non-acetaminophen ALF must demonstrate either an INR >6.5 or any 3 of age <10 or >40, INR >3.5, bilirubin >17.6 mg/dL, encephalopathy developing 7 or more days after jaundice, and etiology other than HAV/HBV hepatitis (Table 24.3) [51]. The MELD score uses serum bilirubin, INR, serum creatinine, and the need for renal replacement therapy to develop a predictive score. A MELD score above 30 is widely accepted as criteria to pursue liver transplantation. Furthermore, the MELD score has been suggested as being a superior predictive tool when compared to the King's College Criteria [52].

Live-donor liver transplant (LDLT) has been suggested as a potential solution to the shortage of deceased-donor liver grafts. Unfortunately, due to the rigorous preoperative workup, potential danger to the donor, and technically demanding nature of LDLT, few centers have pursued this modality for ALF. Those specialized centers that have reported LDLT for ALF have enjoyed favorable results however [53–56].

Table 24.3 King's College Criteria for identification of acute liver failure patients requiring transplantation

Acetaminophen ALF
Arterial pH <7.3 after adequate fluid resuscitation
Or all of the following:
INR >6.5
Serum creatinine >3.4 mg/dL
Grades 3–4 encephalopathy
Non-acetaminophen ALF
INR >6.5
Or any 3 of the following:
Age <10 or >40
INR >3.5
Bilirubin >17.6 mg/dL
Encephalopathy developing 7 or more days after jaundice
Etiology other than HAV/HBV hepatitis

Liver Support Systems

Although still not in wide clinical use, liver support systems (LSS) offer an appealing possibility of short-term stabilization of ALF patients when liver transplantation is not available or contraindicated [57].

Albumin dialysis systems remove albumin-bound molecules as well as water-soluble substances and are the most studied systems. The molecular adsorbent reticulating system (MARS) plus standard medical treatment was evaluated in an RCT versus standard medical therapy alone and was found to impart no survival benefit in ALF patients [58]. The Prometheus system has shown no significant survival benefit in patients with acute-on-chronic liver failure and has yet to be evaluated by an RCT [59].

High-volume plasma (HVP) exchange involves 8–12 L of plasma with fresh frozen plasma daily [57]. A multicenter RCT comparing HVP plus standard medical treatment to standard medical therapy alone demonstrated a significant survival advantage in the HVP group [60]. Importantly, this studies recruitment period was 13 years, during which period critical care of ALF has markedly improved. To this day, HVP is not routinely employed for ALF.

The HepatAssist system filters patient plasma through a small pore membrane where it comes in contact with cultured porcine hepatocytes before being returned to the patient. A recent RCT of HepatAssist plus standard medical treatment versus standard medical treatment alone

demonstrated no 30-day survival advantage in patients with ALF or primary non-function (PNF) following liver transplantation. This study initially included all patients, even those treated with liver transplantation within the 30-day study period. When the patients undergoing liver transplant and the PNF patients were controlled for, the HepatAssist group has a significant survival advantage over the control group [61]. Despite these results, the HepatAssist has yet to be used outside of an experimental setting.

References

1. Bernal W, et al. Acute liver failure. Lancet. 2010;376(9736):190–201.
2. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis. 1986;6(2):97–106.
3. Mochida S, et al. Re-evaluation of the Guideline published by the Acute Liver Failure Study Group of Japan in 1996 to determine the indications of liver transplantation in patients with fulminant hepatitis. Hepatol Res. 2008;38(10):970–9.
4. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993;342(8866):273–5.
5. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369(26):2525–34.
6. Dalton HR, et al. Hepatitis E: an emerging infection in developed countries. Lancet Infect Dis. 2008;8(11):698–709.
7. Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. JAMA. 2005;294(2):194–201.
8. Taylor RM, et al. Fulminant hepatitis A virus infection in the United States: incidence, prognosis, and outcomes. Hepatology. 2006;44(6):1589–97.
9. Patra S, et al. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med. 2007;147(1):28–33.
10. Katz LH, et al. Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis. J Viral Hepat. 2008;15(2):89–102.
11. Mindikoglu AL, Regev A, Schiff ER. Hepatitis B virus reactivation after cytotoxic chemotherapy: the disease and its prevention. Clin Gastroenterol Hepatol. 2006;4(9):1076–81.
12. Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. Nat Rev Clin Oncol. 2012;9(3):156–66.
13. Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. Liver Transpl. 2008;14(Suppl 2):S67–79.
14. Katarey D, Verma S. Drug-induced liver injury. Clin Med (Lond). 2016;16(Suppl 6):s104–9.
15. Reuben A, et al. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52(6):2065–76.
16. Bernal W, et al. Outcome after wait-listing for emergency liver transplantation in acute liver failure: a single centre experience. J Hepatol. 2009;50(2):306–13.
17. Schindl MJ, et al. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut. 2005;54(2):289–96.
18. van den Broek MA, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int. 2008;28(6):767–80.
19. Schnitzbauer AA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255(3):405–14.
20. de Graaf W, et al. Increase in future remnant liver function after preoperative portal vein embolization. Br J Surg. 2011;98(6):825–34.
21. Balzan S, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg. 2005;242(6):824–8, discussion 828–9.
22. Rahbari NN, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149(5):713–24.
23. Rahbari NN, et al. The predictive value of postoperative clinical risk scores for outcome after hepatic resection: a validation analysis in 807 patients. Ann Surg Oncol. 2011;18(13):3640–9.
24. Waseem N, Chen PH. Hypoxic hepatitis: a review and clinical update. J Clin Transl Hepatol. 2016;4(3):263–8.
25. Niranjan-Azadi AM, et al. Ammonia level and mortality in acute liver failure: a single-center experience. Ann Transplant. 2016;21:479–83.
26. Kodali S, McGuire BM. Diagnosis and management of hepatic encephalopathy in fulminant hepatic failure. Clin Liver Dis. 2015;19(3):565–76.
27. Wang DW, Yin YM, Yao YM. Advances in the management of acute liver failure. World J Gastroenterol. 2013;19(41):7069–77.
28. Murphy N, et al. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology. 2004;39(2):464–70.
29. Vaquero J, Rose C, Butterworth RF. Keeping cool in acute liver failure: rationale for the use of mild hypothermia. J Hepatol. 2005;43(6):1067–77.
30. Bernal W, et al. A multicentre randomized controlled trial of moderate hypothermia to prevent intracranial hypertension in acute liver failure. J Hepatol. 2016;65(2):273–9.
31. Audimoolam VK, et al. Predicting fluid responsiveness in acute liver failure: a prospective study. Anesth Analg. 2017;124(2):480–6.
32. Maheshwari R, Subramanian RM. On the brink of death: managing acute liver failure. Am J Gastroenterol. 2016;112(2):200–6.
33. Barton CA. Treatment of coagulopathy related to hepatic insufficiency. Crit Care Med. 2016;44(10):1927–33.
34. Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. J Hepatol. 2002;37(2):280–7.
35. Leithead JA, et al. The systemic inflammatory response syndrome is predictive of renal dysfunction in patients with non-paracetamol-induced acute liver failure. Gut. 2009;58(3):443–9.
36. Davenport A. Continuous renal replacement therapies in patients with liver disease. Semin Dial. 2009;22(2):169–72.
37. Slack AJ, et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int. 2014;34(1):42–8.
38. Moore K. Renal failure in acute liver failure. Eur J Gastroenterol Hepatol. 1999;11(9):967–75.
39. O'Riordan A, et al. Acute kidney injury in patients admitted to a liver intensive therapy unit with paracetamol-induced hepatotoxicity. Nephrol Dial Transplant. 2011;26(11):3501–8.
40. Ramos Figueira ER, et al. Nutritional support for fulminant hepatitis. Nutr Hosp. 2015;32(6):2427–32.
41. Montejo González JC, et al. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: update. Consensus SEMICYUC-SENPE: liver failure and liver transplantation. Nutr Hosp. 2011;26(Suppl 2):27–31.
42. Rabinowich L, et al. Clinical management of acute liver failure: results of an international multi-center survey. World J Gastroenterol. 2016;22(33):7595–603.
43. Vaquero J, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology. 2003;125(3):755–64.

44. Karvellas CJ, et al. Effects of antimicrobial prophylaxis and blood stream infections in patients with acute liver failure: a retrospective cohort study. Clin Gastroenterol Hepatol. 2014;12(11):1942–9.e1.
45. Keays R, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ. 1991;303(6809):1026–9.
46. Lee WM, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009;137(3):856–64, 864.e1
47. Kumar M, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. Hepatology. 2007;45(1):97–101.
48. Miyake Y, et al. Lamivudine treatment improves the prognosis of fulminant hepatitis B. Intern Med. 2008;47(14):1293–9.
49. Tillmann HL, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. J Viral Hepat. 2006;13(4):256–63.
50. Ichai P, et al. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl. 2007;13(7):996–1003.
51. O'Grady JG, et al. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97(2):439–45.
52. Flamm SL, et al. American Gastroenterological Association Institute guidelines for the diagnosis and management of acute liver failure. Gastroenterology. 2017;152(3):644–7.
53. Goldaracena N, et al. Live donor liver transplantation: a valid alternative for critically ill patients suffering from acute liver failure. Am J Transplant. 2015;15(6):1591–7.
54. Kaido T, et al. Liver transplantation in adults with acute liver failure: a single center experience over a period of 15 years. Hepato-Gastroenterology. 2015;62(140):937–41.
55. Kirnap M, et al. Liver transplant for fulminant hepatic failure: a single-center experience. Exp Clin Transplant. 2015;13(4):339–43.
56. Park SJ, et al. Emergency adult-to-adult living-donor liver transplantation for acute liver failure in a hepatitis B virus endemic area. Hepatology. 2010;51(3):903–11.
57. Gonzalez HC, Jafri SM, Gordon SC. Management of acute hepatotoxicity including medical agents and liver support systems. Clin Liver Dis. 2017;21(1):163–80.
58. Saliba F, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. Ann Intern Med. 2013;159(8):522–31.
59. Rifai K, et al. Prometheus--a new extracorporeal system for the treatment of liver failure. J Hepatol. 2003;39(6):984–90.
60. Larsen FS, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol. 2016;64(1):69–78.
61. Demetriou AA, et al. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. Ann Surg. 2004;239(5):660–7; discussion 667–70.