

## Review Article

# Management of Acute Liver Failure and Acute on Chronic Liver Failure: Liver Transplantation and Beyond

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Acute liver failure and acute on chronic liver failure are disease entities with high mortality rate. Urgent referral to the nearest liver transplant center may be lifesaving in the majority of instances. Over the course of several decades, the liver disease burden has continued to expand. This had led to shortage of organ pool. Widespread efforts have been taken over the past few decades to standardize the organ allocation and procurement so that the graft is available to the sickest individual. Efforts are underway to utilize extended criteria donors to match the growing need for organs. Extracorporeal liver support devices were introduced to temporarily provide liver recovery until a donor liver is available. To date the mortality benefit of such devices is unproven. Hepatocyte transplantation has emerged as a safer alternative to liver transplantation. In addition, high flow plasma exchange has recently been proven to treat acute liver failure with mortality benefit. This review aims to summarize the recent advances in the field of Hepatology and transplant Hepatology.

**Keywords:** Extracorporeal liver support devices; Hepatocyte transplant; Liver transplantation; Organ allocation; Acute liver failure

**Introduction**

Acute Liver Failure (ALF) is characterized by an abrupt decrease in liver function as measured by an INR  $\geq 1.5$  in a patient without preexisting liver disease with accompanying evidence of hepatic necrosis on histopathology [1]. Hallmark features of ALF are clinical jaundice and hepatic encephalopathy, while ascites may or may not be present. ALF may be categorized as hyperacute ( $< 1$  week), acute (1 to 4 weeks) and subacute (4-26 weeks) [1]. The leading causes in developed countries include drug induced liver injury, followed by viral etiologies. Patients may develop a sudden onset of cerebral edema and multi-system organ failure due to the accumulation of nitrogenous toxins and release of cytokines, eventually leading to death. It is thought that a high level of ammonia is converted to glutamine which results in osmolar swelling of brain cells. A new defined entity, Acute on Chronic Liver Failure (ACLF) is defined as an acute decompensation that occurs in a patient with known cirrhosis or chronic liver disease [2,3]. ACLF includes a subset of cirrhotic patients with high mortality and evidence of new organ failure as a result of complications such as bacterial infection, encephalopathy, or gastrointestinal bleeding [2,3].

Effective management of ALF and ACLF patients is cause specific and requires an experienced multidisciplinary team. Preferably, patients with ALF should be managed in the Intensive Care Unit (ICU). The presence and degree of hepatic encephalopathy is the first step in the decision process to admit the patient to the ICU. Lactulose remains the cornerstone therapy for hepatic encephalopathy. Rifaximin is considered an adjunctive therapy, and has been shown to prevent recurrence, maintain remission, and reduce hospitalization. Efforts should be made to avoid precipitating factors such as electrolyte imbalance, infection, constipation, and bleeding [4]. Intracranial pressure monitoring may be achieved where available and elevated

intracranial pressure should be treated accordingly with mannitol. Treatment of ALF should begin before etiology is confirmed, particularly in cases of toxicity. The number of liver-directed therapies in ALF is relatively limited, and it is important to recognize and administer the correct therapy [5]. For example, acetaminophen overdose should be immediately treated with N-acetylcysteine, while supportive care is recommended in cases secondary to hepatitis A and E, and administration of corticosteroids is cornerstone therapy for autoimmune hepatitis. Prompt liver transplantation is considered in cases secondary to Wilson disease, mushroom poisoning, hepatic vein thrombosis without underlying malignancy and in HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome when delivery of a fetus fails to correct hepatic failure [6].

Since the 1960s, Liver Transplantation (LT) has emerged as a cornerstone intervention to cure acute and chronic liver disease [7-9]. In ALF the hepatocytes may regenerate after removal of acute insult hence, avoiding the need for LT. Hepatocyte self regeneration has become the premise to providing Extracorporeal Liver Support Devices (ECLD) in the interim to bridge patients to LT or self-recovery (Table 1). ECLD may also provide benefit in instances where LT is contraindicated.

The discovery of cyclosporine and later FK-506 (tacrolimus) provided a major breakthrough in the year 1994. These medications further improved post liver transplant survival [10-13]. The importance of LT is further highlighted by the fact that chronic liver disease contributed to approximately 38,000 deaths in the year 2014. Of these figures, 19,000 deaths were related to alcoholic liver disease [14]. As of July 2016, approximately 14,993 patients awaited LT in the United States. Only 6,768 deceased liver transplantations were carried out in 2015 [15]. Waiting list mortality has continued to increase at a steady rate from 11.1 per 100 waitlist year (2009) to 12.3

**Table 1:** Summary of Extracorporeal Liver Support Devices.

Type of Device	Characteristics
<b>Primitive Extracorporeal Artificial Liver Support</b>	
Hemodialysis	• Removes water soluble molecules via exchange diffusion
	• Heparin administration during dialysis may worsen coagulopathy
	• Potential for sudden hemodynamic derangement
Total Body Washout	• Removal of blood followed by albumin infusion, followed by blood transfusion
Peritoneal dialysis	• Removes water soluble molecules via exchange diffusion. No need for heparin administration during dialysis.
	• Avoid sudden hemodynamic change during dialysis
Hemofiltration/Hemodiafiltration	• Removes water soluble molecules via highly permeable membrane
Plasmapheresis/plasma exchange	• Removal of toxins via plasma filters
Charcoal hemoperfusion	• Removal of lipid soluble toxins via immersion in charcoal based cartridge.
<b>Albumin based Artificial Liver Support</b>	
MARS®	• Utilize filter (MARS Flux dialyzer) which is non-permeable to albumin.
	• Remove albumin bound toxins via albumin based (600ml 20% albumin) dialysate.
	• Removes water soluble toxins via low flux HD
	• Removes lipid soluble toxins via charcoal and anion exchange resin based column
SPAD® (Single-Pass Albumin Dialysis)	• Utilize continuous renal replacement dialysis with addition of 4.4% albumin in the dialysate
Prometheus®	• Utilize fractional plasma separation with albumin permeable filter
	• Lipid soluble toxins removed by charcoal based adsorption.
	• Removes water soluble toxins via high flux HD
<b>Non-Albumin based Artificial Liver Support</b>	
High Volume Plasmapheresis	• Removes cytokines, and adhesion molecules to decrease innate immune response
	• Replace plasma factors
<b>Bioartificial Liver Support System</b>	
ELAD®	• Blood is filtered via human hepatocytes derived from hepatoblastoma (C3a hepatocytes line)
MELS® (Modular extracorporeal liver support)	• Blood filtered via human hepatocytes derived from donor discarded livers
Hepat Assist®	• Blood is filtered via porcine hepatocytes and charcoal column

per 100 waitlist year (2014), a trend that is alarming [16].

In the United States, organ procurement and allocation has now been standardized by the Organ Procurement and Transplantation Network (OPTN). Established in 1984, the OPTN works under the umbrella of the United Network for Organ Sharing (UNOS) to monitor patient listing and organ allocation [17]. The “Final rule” implemented by Congress in year 2000 regulates the functioning of OPTN. Based on this rule the organ is allocated on the basis of urgency, and not based on region or waiting time [18]. In addition, the Model for End-Stage Liver Disease (MELD) score was universally adopted in 2002 as a severity measure of liver disease and to assess LT candidacy. The MELD score was originally validated to predict 90 day mortality in patients undergoing TIPS, and has been found to be superior to the traditional Child-Turcotte-Pugh (CTP) score in predicting waiting list morality [19,20]. While the MELD score may be a ubiquitous measure and considered for allocation for chronic liver disease, the King College Criteria is a more specific predictor of prognosis and triage in patients with ALF (Specificity 82%) [21]. Patients presenting with ALF are considered priority exceptions to MELD and assigned status 1A.

Patients with a MELD score of > 15 or symptoms of decompensated cirrhosis (ascites, variceal hemorrhage, hepatic encephalopathy) are currently referred to liver transplant centers, and are listed on UNOS [22]. The guidelines for ALF differ when immediate referral is made upon initial presentation [1,22]. Deceased donor graft are retrieved, persevered and transported by Organ Procurement Organization (OPO) to the nearest transplant center. When the organ is available, it is matched to an appropriate recipient with highest MELD score in the UNOS database within the local area. In 2013, the “Share 35” rule was implemented by UNOS. Based on this rule, patients with MELD > 35 were prioritized. Therefore, organ access to critical patients was expanded to a widespread geographic area and since then, the waiting time for recipients with MELD >35 have reduced in half (18 days in 2012 to 9 days in 2014) [16]. Despite exhaustive policies and standardization over the past few decades, disparity between available donor grafts and the candidates awaiting LT continues to grow.

The liver organ shortage in North America creates impetus for Extended Criteria Donors (ECD) since deceased donor grafts are the primary source of grafts. ECD includes the split and living related/donor LT (LDLT), steatotic livers, and Donation after Cardiac Arrest-

Circulatory Death (DCD) donors [23]. In recent years, LDLT has evolved as an important strategy to address the shortage of donor pool with comparable outcomes to cadaveric liver transplant. The number of LDLT in 2011 was 247 and that number has increased to 359 in 2015. This number is still low when compared to 6,768 deceased donors LT carried out in 2015 [24]. LDLT is limited by perioperative complications including biliary complications, bleeding and infection [25]. However, recent data reveals no significant difference for survival, complications between LDLT and deceased donor liver transplantation [26,27].

Strategies have evolved to improve organ preservation and viability of the graft. Current procurement technique includes removal of liver from a brain dead donor or DCD by cross clamping the aorta. The abdominal cavity is filled with ice cold water in order to immerse liver in a hypothermic milieu. Livers are then transported via ice filled solutions in coolers. This “static cool storage” diminishes cellular metabolism and preserves cellular function by minimizing ATP loss due to ischemia [28]. However, despite cooling techniques, organ anaerobic metabolism continues to deplete ATP. On the other hand ex vivo normothermic techniques, also termed as Normothermic Machine Perfusion (NMP), provide preservation of organs under body physiologic temperatures. This technique requires the delivery of continuous nutrients and oxygen to the organ. Evidence has shown that NMP maintains viability of marginal graft, e.g. steatotic liver and DCD donor, which may not be possible with static cold storage [29-31]. Hopes to utilize discarded livers and expand the donor pool has led to widespread industrial efforts to create machines to preserve liver grafts. The Organ Ox Metra has recently shown promise in preserving grafts *via* NMP. Trials are underway and are actively recruiting liver transplant recipients to compare LT outcomes in liver procured by NMP using the Organ Ox Metra *vs.* static cold storage technique (ISRCTN39731134).

Extracorporeal Liver Devices (ECLD) provides a temporary support until patients become a recipient for LT or hepatocyte self-regeneration (Table 1). In theory, the devices are aimed to capture the liver's ability to detoxify nitrogenous waste products, hence, reducing the occurrence of brain edema and multi-organ system failure. Since the first success of exchange transfusion by Lee and Tink in 1958, ECLD technology has grown tremendously [32]. Earlier studies in the past few decades aimed to restore liver function via hemodialysis, exchange transfusion, and plasmapheresis. These efforts eventually paved the way to more sophisticated albumin-based dialysis machines which are now being utilized [33-36]. Currently, there are two types of ECLD: 1) The Artificial liver support device (ALS) and 2) The Bio-Artificial Liver Support Device (BALS). Primarily, the ALS devices eliminates toxins by non-cell based techniques such as adsorption and filtration, albumin based dialysis and fractional plasma separation, and adsorption. Devices that utilize albumin based dialysis technique are: 1) Single Pass Albumin Dialysis (SPAD<sup>®</sup>), 2) Molecular Adsorbent Recycling System (MARS<sup>®</sup>), and 3) Prometheus<sup>®</sup> [35,37-39]. The efficacy of MARS<sup>®</sup> was tested in patients with ACLF in the RELIEF trial. Patient population (n=189) was randomized to standard therapy (n=94) or MARS<sup>®</sup> intervention (n=95). There was no difference in 28-day survival in either group. However, improvement in hepatic encephalopathy, renal function, and bilirubin levels were noted [37]. A recent randomized control

trial compared conventional MARS<sup>®</sup> with SPAD<sup>®</sup> therapy in patients with acute liver failure (n=32). The authors did not find any significant difference in bilirubin reductions between the two groups [39]. The BALS utilizes hepatocytes to naturally detoxify biochemicals and, in addition, maintains the synthetic function of the hepatocytes. The current Bioartificial device (BAL) utilizes plasma perfusion through porcine hepatocytes. In a randomized multicenter trial, the authors compared BAL with a control group in 171 patients with acute liver failure. The authors found that 28-day survival benefit in BAL group (relative risk = 0.56 p=0.048) when compared to the control group [40]. Despite the developmental advances of ECLD, the mortality benefit remains unproven. In a systematic review of twelve randomized control trials, mortality benefit was not evident for combined artificial and bioartificial liver support systems. In a stratified analysis, 33% mortality benefit was apparent in patients with acute on chronic liver failure when compared to standard therapy [41].

The concept of plasma exchange to treat acute liver failure is not a new ideology. Total plasma exchange is thought to reverse coagulopathy and eliminate toxins. In 1995, Larsen et al. showed improved cardiac output and systemic vascular resistance in 10 patients with acute liver failure [42-45]. This report was followed by studies showing improvement of liver function, hepatic encephalopathy, and coagulopathy reversal with high flow plasma exchange. These changes were thought to occur due to the effect of exchange transfusion in dampening the immune response, resulting in increased systemic vascular resistance, and cerebral and hepatic circulation [34,44]. The success of these studies paved the way to commence a prospective randomized multicenter trial in 1998 by Larsen et al. The high flow plasma exchange (n=92) group was compared to standard therapy (n=91). The authors showed an improved survival rate in patients treated with high flow plasma exchange (58.7%) *vs.* standard therapy (47.8%). These changes were attributed to attenuated inflammatory response and reductions in levels of TNF- $\alpha$ , IL-6 and IL-8 after high flow plasma exchange [46]. To date, this report provides the most up-to-date evidence suggesting survival benefit in acute liver failure.

In recent years, Hepatocyte Transplantation (HT) has gained popularity after successful use in patients with Crigler-Najjar Syndrome [47]. Human hepatocytes are procured from adults or neonates *via* collagenase perfusion techniques. Hepatocytes are then infused into the portal or splenic vein [48]. HT has been found to offer several advantages. The minimally invasive nature of the procedure reduces perioperative complications. However, several considerations including scarcity of highly viable hepatocytes, limited half-life of hepatocytes, and storage issues, have precluded its widespread alternative to LT [48]. Stem cell transplantation is currently being investigated as an alternative option. Randomized control trials are underway to explore the role of autologous macrophage transplant (ISRCTN10368050) and bone marrow stem cell transplant (ISRCTN16139487) to replace damaged hepatocytes. Transplant centers continue to struggle with the shortage of liver donors. Recent efforts in the field of stem cell transplant, hepatocyte transplant, and high flow plasma exchange hope to address the scarcity of liver donor pools in the near future.

## Conclusion

Liver transplantation remains the mainstay of management for acute liver failure and acute on chronic liver failure. Common complications of liver failure include hepatic encephalopathy, gastrointestinal bleeding, and infection. First line management of hepatic encephalopathy includes the use of lactulose and rifaximin. Successful management of these conditions includes a multidisciplinary approach and monitoring patients in the ICU. Liver donor pool shortages have led to the use of ECD grafts. The ECD includes the use of split and Living related/Donor LT (LDLT), steatotic livers, and Donation after Cardiac Arrest-Circulatory Death (DCD) donors. LDLT has previously shown to have increased biliary complications. Current data reveals equal outcomes in LDLT when compared to cadaveric liver transplantation. The Extracorporeal liver assist devices, which includes artificial and bioartificial liver support systems, may provide a temporary bridge to liver transplantation or self-recovery. High flow plasma exchange has recently shown improved survival in acute liver failure. New techniques such as hepatocyte and stem cell transplantation may revolutionize contemporary management of liver diseases.

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