

Extracorporeal liver support devices in the ICU

Abstract

Liver failure is common and carries high morbidity and mortality. Liver transplantation (LT) is the only definitive treatment available performed as an emergency in acute liver failure and electively for chronic liver disease. The increasing gap between organ availability and rising number of patients on waiting list and the complications and lifelong immunosuppression associated with LT highlights the importance of the need to develop a liver support device to bridge patients with acute or acute on chronic liver failure to liver regeneration and spontaneous recovery or LT, and provide periodic relief from debilitating symptoms such as intractable pruritus and fatigue associated with some form of chronic liver disease.

In the last 50 years, a number of extracorporeal liver support devices and modifications have emerged , some of them purely mechanical in nature aimed at detoxification (MARS, Prometheus, SPAD, and plasmapheresis), while others are cell based systems possessing bio-transformational (synthesis and metabolism) capability. Mechanical devices are mainly based on albumin dialysis, albumin a key transporter protein which is severely deficient and irreversibly destroyed in liver diseases. Despite a sound scientific rationale and good safety profile, none of the currently available devices have shown enough promise to be incorporated in routine clinical practice, their use limited to specific clinical situations such as MARS therapy for the treatment of pruritus. The quest therefore for an ideal device goes on. In this chapter we describe currently available devices, their operational characteristics, current evidence of their utility and limitation, and the future developments in the field of extracorporeal liver support.

Key messages

1. There is an unmet need for a liver support system because of the increasing organ shortage for transplantation and the complications associated with the procedure.
2. In theory, acute liver failure and acute decompensation of chronic liver disease secondary to a precipitating event are potentially reversible, and in this context an extracorporeal liver support can temporarily substitute liver functionality to allow natural recovery through regeneration of hepatocytes and elimination of the precipitating event.
3. Goals of liver support system are to provide all functions of the liver including synthetic and metabolic functions, and to remove as well as reduce the production of pro-inflammatory mediators to attenuate the inflammatory process.
4. Currently existing devices are either purely mechanical or cell based or a combination of the two solutions. Detoxification is provided by both systems but biological activities are limited only to the cell based systems. Albumin dialysis is the major component of mechanical devices because albumin is irreversibly destroyed in liver failure
5. Cell based or bio-artificial systems are essentially 'mini livers' but their success is limited by the lack of a continuous and abundant supply of high-quality hepatocytes.

Keywords: Liver failure, extracorporeal liver therapy, liver detoxification, albumin dialysis, bio-artificial liver support.

Introduction

The burden of liver disease continues to rise, with 10% of the current world population estimated to suffer from chronic liver disease. Annually, over a million people die from liver-related illnesses; severe acute liver failure associated with 50-60% mortality, and deaths from cirrhosis-related complications are projected to be the ninth most common in the developed world by 2015¹.

Liver transplantation (LT) remains the only optimal treatment for the majority of patients, but the expanding gap between organ availability and increasing waiting lists results in a significant mortality for patients awaiting transplantation. In the UK, the average waiting time for chronic liver disease patients is between 3-18 months; >500 patients are on the waiting list at any one time with 15-20% dying without LT becoming available².

An extracorporeal liver assist device with the capacity to support liver function and provide a temporary holding measure as a bridge to transplantation, or ideally, facilitate natural recovery of native liver function is an urgent need. The quest for such devices dates back to the 1960s, but the realization of developing an ideal liver device has only been partially achieved.

Liver failure syndromes

Liver failure can be broadly viewed as a spectrum of disease ranging from acute to acute-on-chronic and end-stage liver failure. This classification captures different clinical phenotypes of liver illness and allows formulation of appropriate treatment plans.

Acute liver failure (ALF) is characterized by a rapid decline in liver function (within days to weeks) secondary to massive necrosis of hepatocytes following an acute insult (infective, metabolic, vascular or drug-induced). This occurs in patients with previously normal liver function and results in varying degrees of coagulopathy and hepatic encephalopathy (HE); eventually progressing to extra-hepatic organ involvement and failure. Cerebral complications, and superimposed sepsis and multiple organ dysfunction syndrome, account for most deaths in these patients. ALF stratification, based upon the length of time elapsed between the appearance of first symptoms and the development of HE, into the hyper acute

(1-7 days), acute (8-28 days), and sub-acute (28 days-24 weeks) sub-varieties, in conjunction with markers of acute physiological derangement (blood pH and lactate levels), patient age and the etiology of ALF, informs prognosis and identifies patients unlikely to survive without emergency or super-urgent LT³. LT is a life-saving procedure but is a major intervention with attendant morbidity and mortality, requires life long immunosuppression, is expensive and is limited by organ availability.

Acute on Chronic Liver Failure (ACLF)

ACLF is an increasingly recognized clinical entity referring to the coincidence of either an identified or unidentified acute precipitating event (either superimposed liver injury or extra hepatic factors such as infection) in patients with existing compensated or decompensated cirrhosis, culminating in further deterioration of liver function, and development of end-organ damage leading to high short term mortality⁴. The final common pathway of a precipitating event - infection, variceal bleed or additional liver injury - seems to be the development of an unquenched dysregulated systemic and hepatic inflammation resulting in worsening encephalopathy, aggravation of portal hypertension, development of renal dysfunction and hemodynamic embarrassment, and retardation of liver regeneration.

End-stage liver disease (ESLD)

End-stage liver disease is an irreversible condition representing the terminal phase of liver failure, with little capacity for regeneration by the native liver. The only treatment known to improve survival in this situation is LT.

Liver support systems – types, technical issues, operational and functional characteristics, and current clinical evidence (summarized in Table 2)

The liver is a complex organ, central to the body's metabolic processes. It has an unparalleled ability to handle multiple tasks required to maintain metabolic homeostasis and to act as the major regulatory player in the organ cross-talk framework. Hepatocytes perform a range of functions including: a) detoxification (of drugs, toxins and chemicals such as ammonia and lactate), b) metabolic and biotransformation activities (e.g. drug metabolism, maintenance of glucose homeostasis and thermogenesis), c) synthesis (of coagulation proteins, albumin, globulins, acute phase and transporter proteins, and d) immune modulation functions.

Hepatocellular failure results in toxin (ammonia, bilirubin, lactate, mercaptans and bile acids) accumulation, an imbalance of metabolic substrates, and increased levels of inflammatory mediators.

The premise and concept behind an ideal extracorporeal liver support device therefore hinges on its ability to detoxify blood, perform synthetic, metabolic and immune functions, and remove and/or inhibit production of inflammatory signalling molecules (e.g. cytokines). This breaks the vicious circle of liver injury characterized by production of inflammatory mediators and propagation of further liver injury, the ultimate aim being stimulation and promotion of liver regeneration. Because of the temporary nature of the support offered by the currently available devices, their clinical application is targeted largely to situations where liver injury is acute, as in ALF and ACLF. In addition, these devices can be used to improve and alleviate symptoms arising from cholestasis such as pruritus (Table 1).

There are two types of liver support systems, namely, (i) artificial (non-biological) systems which are purely mechanical dialysis devices based on blood detoxification and (ii) bio-artificial devices, which are cell-based devices incorporating hepatocyte-derived cells that can potentially substitute liver metabolic function. Blood purification devices are also added to some of these systems.

Artificial devices

Conventional blood purification methods such as continuous hemofiltration or hemodiafiltration, though highly effective in removing small, water-soluble toxins, are no longer used as the sole means of detoxification in liver failure patients. This is due to their inability to remove protein-bound substances and their ineffectiveness in liver failure. They are still used in conjunction with liver support devices to augment elimination of water-soluble toxins. The first generation of liver devices utilized activated charcoal hemoperfusion as the basis for toxin adsorption but failed to demonstrate significant benefit and is now largely superseded by albumin-based systems. Albumin is the most abundant circulating plasma protein and maintains plasma oncotic pressure. In addition, current literature consistently points towards a number of other biologic functions such as fatty acid transport, drug binding, metal chelation and antioxidant activity performed by albumin, rendering it an

important detoxification molecule and a candidate protein to be targeted in liver dialysis systems⁵. In addition to quantitative hypoalbuminemia in liver failure, there is a severe functional impairment of the available albumin rendering it an inefficient transporter protein⁶.

The two most commonly used artificial systems are the Molecular Adsorbent Recirculating System (MARS) and the Fractional Separation of Plasma and Albumin Dialysis (Prometheus). Both forms of treatment are relatively new; MARS was used clinically for the first time in 1993 and Prometheus in 2003.

MARS (Gambro, Sweden) combines albumin dialysis with conventional hemodialysis to remove both water-soluble and protein-bound toxins. The patient's blood is detoxified of protein-bound substances via an albumin-impregnated polysulfone dialysis membrane (50 kDa) against a concentration gradient exchange mechanism by the albumin solution stored in the adjacent chamber (600 ml 20% human albumin). The selective pore size stops the patient's own toxin-laden albumin from crossing the membrane. The albumin dialysate is passed through an activated charcoal and anion exchange resin to regenerate the protein to allow its continued use as a detoxification medium (Fig. 1A). The hemodialysis circuit in the system removes water-soluble substances.

Prometheus (Fresenius, Germany) combines plasma separation and adsorption in a double circuit design. A high cut-off membrane of 250 kDa filters the patient's albumin into a secondary plasma circuit. The albumin-rich plasma then passes through two columns of adsorbent resins (1. neutral and 2. anion exchange, Fig. 1B), to remove bound toxins before recombining with the cell fraction prior to return to the patient. A high-flux dialysis system is applied to the blood circuit to enhance elimination of water-soluble toxins.

Single-Pass Albumin Dialysis (SPAD) is a non-commercial simplified system of albumin dialysis designed to remove protein-bound toxins using an albumin solution (typically 5%) as the dialysate separated from the patient's blood by a high-flux albumin-impermeable membrane. Unlike MARS where the albumin dialysate is recirculated, it is discarded after a single pass (Fig. 1C). Continuous veno-venous hemodiafiltration can be added to augment removal of

water-soluble substances. The SPAD system is simple, safe and has similar efficiency to MARS in removing bilirubin, ammonia, bile acids and creatinine.

Plasmapheresis (plasma exchange) separates the patient's plasma from cellular blood components to be then replaced by donor fresh-frozen plasma and/or albumin. It is effective in removing circulating antibodies, inflammatory cytokines and other toxic substances, as well as toxins bound to tissue sites, and is used for a number of autoimmune conditions. In liver failure, enhanced or high volume plasmapheresis (>10 L of plasma removed and replaced per day) has demonstrated clinical improvement in hepatic encephalopathy, hepatic and cerebral blood flow, and even a survival benefit in patients with ALF (when used for up to 10 days of therapy)⁷.

SEPET (Selective Plasma Filtration Technology) incorporates a 100 kDa hollow-fiber membrane where the ultrafiltrate is replaced by a mixture of electrolyte, albumin and fresh-frozen plasma solutions.

Safety profile and clinical efficacy of artificial devices

MARS is the most studied device with over 5000 patients having been treated for more than 20,000 therapy sessions, followed by Prometheus which has also been used extensively. These are largely safe procedures, with no serious side effects reported for either treatment. Reported complications have included modest thrombocytopenia, bleeding episodes, transient hemodynamic instability, a need for more anticoagulation treatment, and reversible leukocytosis unrelated to sepsis.

Both MARS and Prometheus effectively remove water-soluble and albumin-bound toxins as well as cytokines but without significant reduction in plasma cytokine levels, reflecting an imbalance between the modest cytokine elimination ability of these systems, and their continuous production during liver failure⁸. Both systems lose detoxification capability significantly after 6 hours' use.

Most of the published evidence relates to the two main artificial devices. The MARS system has received US FDA approval as a therapy for use in hepatic encephalopathy, in addition to

previous approval for the management of drug toxicity. Both MARS and Prometheus systems are effective in supporting patients with severe liver dysfunction either following surgery, or as a bridge to transplantation. Crucially, neither system could show an independent survival benefit (in the absence of transplantation) in phase III multi-center trials^{9,10} Albumin dialysis/detoxification has been shown to be very effective for Intractable pruritus, and provides symptom relief for prolonged periods (3-4 months)¹¹. As these patients often will not qualify for LT based on their liver function, this treatment option can play a vital role in improving their quality of life. (Table 2A)

Biological or bio-artificial liver system (BAL system)

A BAL employs biochemically active cells contained in a bioreactor. In theory it is capable of carrying out a proportion of the metabolic, synthetic and immune function provided by the liver. A blood purification device is often added to improve efficacy. The essential prerequisites for a functioning BAL system are: a) high quality, well-differentiated cells retaining a high degree of hepatocyte function, which are stable *in vitro*; b) a sufficient quantity of these cells equating to up to one-third of normal liver mass as extrapolated from data on large liver resections; and c) ready and unlimited availability of these cells at any time. Cell sources most commonly studied have been derived from primary human and porcine sources, immortalized human cells, and cells derived from hepatic tumors such as hepatoblastoma. The cells are used as either tissue slices, homogenates or as single cell layer columns supported on matrices similar in appearance to dialysis filters.

The disadvantages of human cells are limited availability, while porcine hepatocytes tend to be less stable and carry a theoretical risk of zoonosis which, although not yet reported, will prevent their use in Europe and the US. On the other hand, cell lines such as C3A derived from human hepatoblastomas lose functionality following transformation, e.g. their ureagenesis capacity is limited only to the arginine aspect of the urea cycle and thus cannot completely detoxify ammonia.

Currently available BAL systems

The ELAD C3A-based BAL system is currently under development and undergoing clinical trials (Vital Therapies, San Diego, USA). Small-scale studies have shown survival benefit, or use as a

bridge to transplantation, though a large-scale pivotal survival study has not yet been undertaken. Other systems are in varying stages of development, seeking to optimize the bioreactor design or the cell type contained within them. It is not yet clear as to how successful these technologies will be. A major limiting factor in whether BAL systems will be adopted widely would be the considerable cost of therapy associated with generating, shipping and maintaining bioreactors. Clinical studies therefore need to demonstrate clear, unequivocal survival benefit of ELAD over other treatment options before they are accepted into the majority of healthcare systems. (Table 2B)

Conclusion

Specific therapies aimed at targeting factors identified in relation to the progression of liver injury are being developed for the next generation of liver dialysis systems. Proof-of-principle systems have shown clinical benefit by combining endotoxin removal filters with albumin dialysis¹². These endotoxin filters, developed as therapies for sepsis, are used to reduce the on-going inflammatory stimulus associated with end-stage liver disease. Another approach is to improve the quality and functional capacity of the patient's albumin during therapy. The disease process damages albumin binding and transport capability, so methods to replace the damaged protein to restore function rather than just to dialyse the bound toxins is the next logical step in system design. Improved BAL systems may be able to demonstrate a large functioning cell mass that can effectively replace liver function for a prolonged period, though this would still appear to be some way from the clinic. Current artificial liver dialysis systems offer effective support for a number of applications. Though they are not able to replace the failing liver, they do offer detoxification functions and can act as a bridge to transplantation.

Acknowledgement: Authors wish to extend sincere thanks to Dr Nathan Davies for his contribution in providing schematic diagrams of various devices depicted in Figure 1 and proof-reading the manuscript.

Table 1. Potential indications for liver supportive therapy

1. ALF patients

- a. Failure to reach criteria for emergency LT, but remain at high risk of dying (10-15% of non-survivors do not fulfil King's College Criteria for emergency transplantation).
- b. Patients either precluded from LT due to medical, surgical or psychological reasons, or those who continue to deteriorate rapidly while on the emergency transplant list.

2. ACLF patients

- a. These patients are currently not considered for emergency LT in the UK, so a device can provide support until spontaneous recovery to pre-injury levels of liver function
- b. As a bridge to LT, especially for those patients who are high up on the waiting list and would receive LT within the next few weeks.

3. End Stage Liver Disease

Patients with ESLD lack reversibility. Since currently available liver assist devices are unable to sustain liver support for longer than a few weeks, the only role of liver devices pertains to symptom reduction and quality of life improvement as in:

- i. intractable pruritus,
- ii. hepatic encephalopathy
- iii. severe chronic fatigue.

4. Other Indications

- a. Primary graft non-function after transplantation, and waiting for super-urgent re-transplant
- b. Small-for-size syndrome
 - i. Development of liver failure following extensive resection for malignancy
 - ii. Following donor hepatectomy in living donation liver transplantation.

Table 2A. Artificial Devices

Device	Principles of therapy	Clinical Studies
<u>SPAD</u> (Single-Pass Albumin Dialysis)	Albumin dialysis against 2-5% albumin	Improvement in biochemical parameters, comparable with MARS. Only single case studies available, ¹³ no RCTs
<u>MARS</u> (Molecular Adsorbent Recirculating System)	Albumin dialysis against 20% albumin.	Improved hepatic encephalopathy ¹⁴ , improved quality of life, no significant survival benefit. ⁹
<u>Prometheus</u> (Fractionated Plasma Separation and Adsorption - Prometheus)	Plasma separation, adsorption using neutral resin and anion adsorbers	Improvement in biochemical parameters. No significant benefit at 28 days. ¹⁰
<u>SEPET</u> (Selective Plasma Filtration Technology)	100 kDa hollow fiber membrane, albumin and fresh-frozen plasma mixture as replacement fluid	No human RCTs. Animal models show improved survival. ¹⁵
<u>HVPE</u> (High Volume Plasma Exchange)	Patient's plasma removed and replaced with fresh frozen plasma	Improved transplant-free survival in ALF. ⁷

Table 2B. Bio artificial Devices

Device	Principle & Cell Type	Main concern	Clinical Studies
<u>Hepat Assist</u>	Plasma separation, charcoal adsorption, porcine hepatocytes	Zoonoses	176 patients, no survival advantage in fulminant and sub-fulminant ¹⁶
<u>MELS</u> (Modular Extracorporeal Liver System)	Plasma separation then plasma passed through human hepatocytes	Supplies low, function difficult to maintain	8 patients, successfully bridged to transplant ¹⁷
<u>ELAD</u> (Extracorporeal Liver Assist Device)	Human hepatoblastoma cell (C3A cells)	Tumorigenicity	6 human studies, 150 patients treated. Survival benefit in ACLF study in 49 pts. ¹⁸
<u>BLSS</u> (Bio artificial Liver Support System)	Porcine hepatocytes	Zoonoses	Phase I study in 4 patients, no serious adverse events. ¹⁹
<u>AMC-BAL</u>	Porcine hepatocytes	Zoonoses	12 patients treated, 11 bridged to transplant. ²⁰

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Figure legend:

Figure 1 Schematic representations of (i) Molecular Adsorbent Recirculating System (MARS), (ii) Fractional Separation of Plasma and Albumin Dialysis (Prometheus), and (iii) Single Pass Albumin Dialysis (SPAD) artificial systems.

Abbreviations:

ALF	Acute Liver Failure
ACLF	Acute on Chronic Liver Failure
ESLD	End Stage Liver Disease
BAL	Bioartificial liver support
MARS	Molecular Adsorbent Recirculating System
SPAD	Single Pass Albumin Dialysis
ELAD	Extracorporeal Liver Assist Device