

CHAPTER 130

Extracorporeal Liver Support Devices

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OBJECTIVES

This chapter will:

1. Discuss the theoretical basis for the use of extracorporeal liver support devices (ECLSDs) in acute and chronic liver failure.
2. Describe the structure and function of current artificial and bioartificial ECLSDs.
3. Review the current literature regarding the effectiveness of ECLSDs in the management of acute and chronic liver failure.

The last 50 years have seen the increasingly successful use of extracorporeal devices to support failing organ systems. There are proven extracorporeal therapies for use in renal failure and more recently, cardiac and respiratory failure. However, the development of a proven extracorporeal support device for liver failure remains elusive. Mortality and morbidity from acute and chronic liver failure remain high, and transplantation remains the most effective treatment.^{1,2} The liver is a complex organ intimately involved in maintaining body-wide homeostasis. Specifically, the liver has key detoxification, synthetic, and immunologic roles. The development of liver failure results in loss of all three functions. Although the synthetic and immunologic roles, to a degree, can be supported medically, replication of the detoxification role is more difficult to achieve.

The literature suggests that there up to 500 different toxins produced in liver failure, the most important being ammonia, urea, bile acids, branch-chained aromatic amino

acids, reactive nitrate, and nitrite species and proinflammatory mediators such as the tumor necrosis factor (TNF) and interleukin families.^{3–7} The combination of these toxins contributes to the characteristic findings in liver disease of a systemic inflammatory response and encephalopathy.^{1–3} The difficulty developing an effective extracorporeal liver support device (ECLSD) has been most likely the result of the complexity in the magnitude, variation in molecular weights, degree of protein binding, and volumes of distribution exhibited by this toxic milieu.⁶

Despite these difficulties there has been continued impetus for research into an ECLSD, largely because of a shortage of appropriate transplantable organs and recently, increasing recognition of the liver's unique ability to regenerate in the setting of an acute insult. Subsequently, the rationale for an ECLSD is now clearer; to act as a bridge to transplantation, a bridge to recovery, or potentially providing symptom relief. There are currently two main approaches being pursued: an artificial liver support system, using or adapting preexisting renal replacement technology with adsorbent or detoxifying capacity or a bioartificial support system with the integration of living hepatocytes into an extracorporeal circuit, with provision of metabolism and synthetic function (see [Box 130.1](#) and [Table 130.1](#)).

BOX 130.1

Indications for Extracorporeal Support

Bridge to transplantation
 Bridge to recovery
 Potential symptom relief

TABLE 130.1

Selected Extracorporeal Devices

LIVER SUPPORT DEVICE	TECHNIQUE	CLINICAL STUDIES
Artificial Devices		
Single-pass dialysis	Albumin dialysis via 2%–5% albumin	Equivalent biochemical parameters compared with MARS, possible concerns with citrate anticoagulation
Molecular adsorbent recirculating system	Albumin dialysis via 20% albumin	Improved toxin clearance, improved hemodynamics, no evidence of improved survival in acute or chronic liver failure
Prometheus	Plasma separation, adsorption, resin, and anion adsorbent	Limited survival data in acute or chronic liver failure
Therapeutic plasma exchange	Removal of patients' plasma and replacement with fresh frozen plasma	Improved hemodynamics, clinical and biochemical parameters, increased transplant-free survival
Select plasma exchange therapy	Plasma filtration, higher filter membrane cutoff	No current studies
Bioartificial Devices		
HepatAssist	Plasma separation, adsorption, porcine hepatocytes	Improved clinical and biochemical parameters in acute liver failure and primary graft nonfunction, no survival benefit
Modular extracorporeal liver system	Albumin dialysis human hepatocytes	Successfully used as bridge to transplantation
Academic Medical Centre bioartificial liver	Porcine hepatocytes, new human cell line	Improved biochemical and clinical parameters as a bridging therapy
Extracorporeal liver assist device	Hemodialysis, human hepatocytes	Trials currently in progress
Spheroid reserve bioartificial liver	Porcine hepatocytes, spheroid reservoir	Safe in acute and chronic liver failure
		Animal studies only—improved survival, decreased ammonia, decreased intracranial pressure

MARS, Molecular adsorbent recirculating system.

ARTIFICIAL SYSTEMS

Artificial liver support systems are based upon the concept that pathophysiology of liver failure is secondary to impaired hepatic detoxification and the subsequent accumulation of normally cleared toxins.^{1,8,9} Artificial support systems have been developed from the success of renal replacement technology in correcting the metabolic and electrolyte disturbances of renal failure. Correspondingly, they use various combinations of dialysis, filtration, and adsorption. The main approaches are discussed later in this chapter (see Fig. 130.1 and Table 130.1).

Hemofiltration and Hemodiafiltration

Hemofiltration and hemodiafiltration involve the use of traditional continuous renal replacement therapy (CRRT) apparatus in patients with liver failure and currently has only limited application. The process involves the exposure of blood to a dialysate moving in a countercurrent direction via a hollow fiber membrane, allowing toxins and electrolytes to move either via convection or diffusion down their concentration gradient.^{10,11} The membrane used in CRRT has a pore size of approximately 60 kilodaltons (kDa), allowing the removal of small and mid-sized water-soluble molecules.^{11,12} The membrane pore size does not allow the transfer albumin, therefore prohibiting the removal of albumin-bound toxins.

However, there is increased interest in the use of CRRT in liver failure patients for two reasons. First, because there are potential similarities between the SIRS response in both populations, high-volume filtration has been proposed to modulate the impact of inflammatory cytokines.^{13,14} Evidence from pediatric liver failure suggests that it can improve hemodynamics and neurologic state and possibly is considered standard of care.^{14,15} However, in the general

adult critical care population, high-volume filtration has not been shown to affect patient outcomes.¹⁰ Second, ammonia, a key mediator of neurotoxicity associated with liver failure, is water soluble and has a molecular weight similar to urea; therefore it is removed easily by traditional CRRT. Indeed, a study from the United Kingdom demonstrated that CRRT at 35 mL/kg/hr and 90 mL/kg/hr was very effective at removing this important toxin; however, survival data in this setting are currently lacking.¹³

Plasma Exchange

Plasmapheresis, or plasma exchange, involves the use of CRRT apparatus along with a plasma filter membrane or centrifuge to separate blood into its plasma and cellular components and replace the discarded plasma 1:1 with fresh frozen plasma. Consistent with the use of plasma exchange in other critical care populations, plasma replacement is empirically weight based at approximately 15% to 20% body weight and is repeated daily for up to 3 days.^{16,17} This approach has had increased interest in the management of acute liver failure. The rationale behind plasma exchange is that by the removal of circulating cytokines and toxins, multi-organ failure may be limited or prevented. In addition, this process may be assisted by the replacement of depleted substances via the provision of fresh frozen plasma. Indeed, plasma exchange has been shown to improve hemodynamics and grade of encephalopathy and decrease vasopressor requirements.^{18–20} In the largest randomized control trial to date, 182 patients were randomized to standard care or high-volume exchange, with plasma exchange cohort showing a significant improvement in transplant-free survival, which was most marked in patients who did not receive a transplant.¹⁶ In addition, plasma exchange was shown to decrease significantly the markers of the innate immune response.¹⁶ One theoretical concern with plasma exchange is that the removal of cytokines and growth

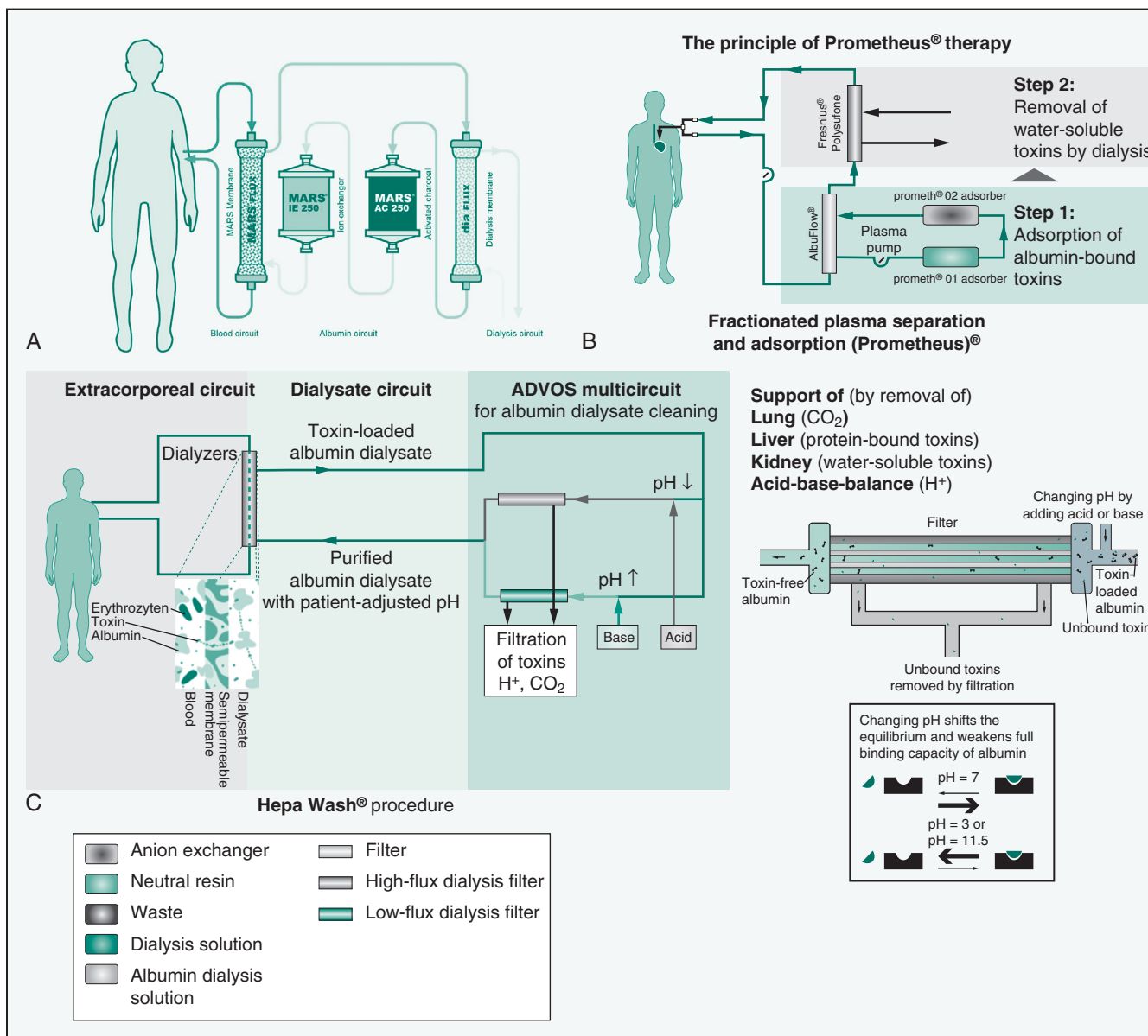


FIGURE 130.1 1A, Molecular Adsorbent Recirculating System. (MARS®, Gambro, Stockholm, Sweden). 1B, Fractionated plasma separation and adsorption. Copyright Fresenius Medical Care Deutschland GmbH. 1C, Hepa Wash® procedure. (Hepa Wash GmbH, Munich, Germany).

factors may include those that have an important role in hepatic regeneration.²¹ Recently, the Li-ALS system has been introduced, which uses the combination of low-volume plasma exchange—exchanges approximating 2.5% body weight—coupled with high-flux hemodiafiltration and, although only in a pig model of acute liver failure, there is evidence of improved survival.²²

Albumin Dialysis-Based Approaches

The importance of albumin in many aspects of liver failure is recognized more frequently.²³ Albumin has a molecular weight of approximately 68 kDa and is the predominant carrier protein in the body. Many of the toxic substances produced in liver failure are highly protein bound and therefore bind with varying affinity to albumin.²³ Albumin’s

molecular weight renders it impermeable to conventional CRRT membranes; however, it can undergo adsorption and therefore the removal of protein-bound toxins. Therefore much research has been invested in the development of ECLSDs to create a system that efficiently adsorbs toxins from albumin, or “albumin dialysis.” There are numerous systems that have been developed, and these are explored below.

Single-Pass Dialysis

Single-pass dialysis (SPAD) is the most basic form of albumin dialysis. SPAD consists of a normal CRRT high-flux membrane that is impermeable to albumin. Plasma is run countercurrent to an albumin-based (approximately 5%) dialysate solution. Low-molecular-weight toxins bound to

albumin diffuse down their concentration gradients and bind to the dialysate albumin before being discarded. Despite the attractive simplicity of the approach, the results of SPAD are inconsistent, with studies showing at least equivalent clearance compared with more sophisticated albumin dialysis techniques^{24–26} but no improvement in survival.²⁷ A recent randomized crossover trial found no difference in clinical or biochemical parameters between molecular adsorbent recirculating system (MARS) and SPAD, although the SPAD cohort had higher levels of acid-base disturbance in the setting of citrate anticoagulation.²⁸ The advantage of SPAD is that it is inexpensive and easy to use with existing CRRT technology and may be beneficial when the more sophisticated ECLSs are unavailable.

Molecular Adsorbent Recirculating System

The MARS has been the most widely researched and used ECLSD to date. MARS uses a hollow-fiber polysulfone dialysis membrane with low (less than 60 kDa) cutoff, rendering it impermeable to albumin. Similar to SPAD, albumin-bound toxins are removed via the counter current albumin enriched dialysate. The albumin dialysate then undergoes regeneration, first by charcoal and then anionic adsorption, before undergoing conventional hemodiafiltration to remove remaining water-soluble toxins.²⁹ Research in the acute liver failure and chronic liver failure populations has shown that MARS is able to decrease bile acid, bilirubin, and ammonia levels; improve encephalopathy grade; and significantly improve systemic and portal hemodynamics.^{25,26,30–34} In addition, early research showed potential in the treatment of hepatorenal syndrome and alcoholic hepatitis.^{32,35} However, improvement in patient-centered outcomes has not been borne out by larger, randomized control trials. The largest study followed 102 acute liver failure patients and found no 6- or 12-month mortality benefit with MARS therapy compared with standard therapy.³⁶ However, conclusions regarding MARS's efficacy in this population are limited by the short time to liver transplantation (less than 24 hours) and the treatment arm receiving a median of only a single session.³⁶ It is possible that MARS may be more beneficial in a sicker cohort of patients as a bridge to transplantation. This is supported by observational data from Norway that demonstrated MARS may be beneficial in the most critically unwell acute liver failure as a bridge to transplantation or recovery.³⁷

Studies also have examined outcomes in patients with acute-on-chronic liver failure. The largest trial of patient outcomes in acute-on-chronic liver failure, with 189 patients, showed no mortality benefit at 28-day and 90-day transplant-free survival.³⁸ Consistent with other studies, they did show improvements in encephalopathy grade and circulating toxin levels.³⁸ Despite concerns regarding worsening coagulopathy, infection, and electrolyte disturbance with MARS, trials in both populations have demonstrated an acceptable safety profile with no significant increase in complication rate.^{36,38} Finally, studies thus far all have displayed varied dosing and timing of MARS therapy. What remains unclear is whether a benefit exists in patients with severe multi-organ dysfunction and how many treatments should occur before a relevant clinical outcome is possible. An extension of this is whether the efficacy of MARS in its current configuration is insufficient and whether higher dose is required. Researchers are beginning to address this question by adding two extra adsorption columns to the existing MARS circuit. Preliminary results indicate that this can achieve higher clearance of bilirubin and bile acids.³⁹ Whether this can be translated to improved clinical outcomes

is still uncertain. Finally, MARS has an evolving indication as a bridge to symptom relief in its use to treat intractable cholestatic-induced pruritus.⁴⁰

Fractionated Plasma Separation and Adsorption

Fractionated plasma separation and adsorption, or Prometheus (Fresenius Medical Care AG, Homburg, Germany), is a further extension of albumin detoxification, whereby albumin is detoxified separately to blood. This technique involves the use of specific high-molecular-weight cutoff membrane (approximately 250 kDa) to separate albumin and other plasma proteins from the cellular blood components.^{41,42} The separated plasma filtrate then passes through a renin adsorption column and an anionic exchanger. The now-detoxified plasma is returned to the patient's circulation via a conventional high-flux dialysis membrane.^{41,42} Similar to other albumin-based dialysis techniques, fractionated plasma separation and adsorption is effective in acute liver and acute-on-chronic liver failure in facilitating the clearance of bilirubin, bile acids, ammonia, urea, and creatinine.^{43–45}

The role of fractionated plasma separation and adsorption in acute liver failure has not been studied extensively. The largest series of 18 patients treated was observational and reported a survival of 50% in nontransplanted patients.⁴⁶ Unfortunately, it is not possible to draw any further conclusions regarding impact upon patient survival in acute liver failure. In contrast, a larger randomized control trial (RCT) in acute-on-chronic liver failure, $n = 145$, found no overall impact upon 28-day or 90-day survival between treatment and standard management groups.⁴⁷ However, the subgroup analysis suggested improved survival in patients with higher-model end-stage liver disease scores and those with hepatorenal syndrome.⁴⁷ Research into utility of Prometheus in hepatorenal syndrome is currently underway (LUTHOR study universal trial number U1111-1115-4645).

Other variants of albumin detoxification are in development but currently have limited clinical data. Select plasma exchange therapy (SPECT) is a simpler but more selective variant of Prometheus model of plasma filtration. In SPECT a membrane filter with a cutoff of approximately 100 kDa is used to separate plasma and albumin; the resultant plasma filtrate then is discarded directly and replaced with albumin. The use of SPECT has theoretical benefits in preventing the loss of important larger molecular weight molecules such as coagulation factors, immunoglobulins, and potentially cytokines required for hepatic regeneration.⁴⁸ HepaWash uses the principle of albumin dialysis but uses alterations in pH and temperature to detoxify and regenerate the toxin-bound albumin.⁴⁹ Recent publications indicate that preclinical animal studies and clinical trial results are promising.⁵⁰

Comparison of Extracorporeal Liver Support Devices

Overall evidence for improvement in patient survival is lacking for ECLSs. There have been three meta-analyses and one Cochrane review comparing ECLSs that have revealed conflicting results. The majority of research published has involved the two main devices: MARS and Prometheus. Compared with MARS, Prometheus has a significantly better removal of protein-bound toxins and water-soluble toxins, similar effects on patient hemodynamics, encephalopathy, and a comparable low incidence of adverse events.^{51,52} A 2003 meta-analysis of artificial and bioartificial support systems suggested that artificial support systems have a mortality benefit in acute-on-chronic liver failure but not

acute liver failure, nor benefit as a bridge to transplantation.^{53,54} A follow-up Cochrane review published in 2009 supported these findings.⁵³ A meta-analysis from 2004 looking solely at MARS found no mortality benefit.⁵⁵ In 2011 a meta-analysis looking solely at 12 recent (1995 to 2010) publications only assessing artificial support systems found a mortality benefit in acute liver failure but not acute-on-chronic liver failure.⁵⁶ The latest meta-analysis published in 2013 incorporated 19 RCTs up until 2013 paradoxically suggested artificial support devices improve mortality in acute-on-chronic liver failure but not in acute liver failure.⁵⁷ Clearly, these varied findings highlight the difficulties in assessing patient outcomes in ECLSDs and possibly the evolution of ECLSDs over time. Currently, it is difficult to recommend the use of any particular ECLSD outside specialized centers and research settings.

Extracorporeal Devices and Anticoagulation

Regardless of the bioartificial system used, anticoagulation frequently is required to maintain circuit patency and life. However, there currently are limited data to guide decisions in this area. The use of no anticoagulation has been shown to be a common method used in a small retrospective study of liver failure patients with and without transplantation; however, the study gives no data on filter life, bleeding, or thrombotic complications.⁵⁸ Similarly, the same small retrospective study revealed that heparin was used in less than 20% of all patients.⁵⁸ Although heparin commonly is used in other critically ill populations, there are concerns regarding the effectiveness of heparinization resulting from the antithrombin deficiency in liver disease and associated heparin resistance.⁵⁹ Other modalities include the use of prostacyclin, which, although it has the theoretical risk of worsening raised intracranial pressure, is used commonly in some major liver centers. Citrate anticoagulation is increasingly popular because of its ability to provide regional anticoagulation, ease of use, and low risk of complications. Theoretical concerns regarding the inability of the failing liver to metabolize citrate appear to be not borne out by recent clinical experience. A recent randomized controlled crossover trial revealed that compared with no anticoagulation in patients with MARS, citrate anticoagulation was safe and provided prolonged circuit patency and correspondingly increased efficacy.⁶⁰ Similarly, a large multicenter observation study exploring citrate anticoagulation for conventional renal replacement therapy in patients with various grades of liver failure demonstrated it to be safe and efficacious.⁶¹ Underpinning any decision regarding the type of anticoagulation is the increasingly complex understanding of hemostasis in all types of liver failure. Acute and chronic liver failure possess a delicately balanced hemostatic system, which may be unbalanced in either a prothrombotic or prohemorrhagic direction, and traditional measures of coagulation may not provide adequate guidance in this area. Consequently, the choice of circuit anticoagulant should be considered in light of an individual patient's coagulation status, potentially by the use of advanced hemostatic assessment such as thromboelastography, to more accurately assess the risk of either thrombosis or hemorrhage.

Bioartificial Support Devices

Bioartificial support devices are designed to replace all the detoxification, synthetic, and metabolic functions of the liver by the incorporation of a bioreactor into an existing extracorporeal circuit. In this setting, the bioreactor consists

of hepatocytes that are cultured in a three-dimensional extracellular matrix and surrounded by a hollow-fiber capillary system to allow plasma perfusion.⁶² In addition, hemodialysis or albumin dialysis can be coupled to the circuit. Optimal hepatocyte function requires a steady supply of oxygen independent to plasma perfusion, and, unlike earlier systems, the new bioartificial circuits have a separate but integrated oxygenator for oxygen supply and carbon dioxide removal⁶² and an additional glucose supply for the hepatocytes. A number of different bioartificial systems have been developed, although none are yet in widespread clinical practice (see Fig. 130.2).

The extracorporeal liver assist device (ELAD) uses a bioreactor composed of HepG2/C3A human hepatoblastoma cells and an integrated hemodialysis circuit.⁶³ It has been shown to be safe for use in patients with acute and acute-on-chronic liver failure and potentially may have a survival benefit in viral hepatitis induced acute-on-chronic liver failure.^{63–66} There are currently trials further assessing the potential of the ELAD in alcoholic hepatitis and acute-on-chronic liver failure (NCT01829347, NCT01471028).

The Academic Medical Centre Bio-artificial Liver (AMC-BAL) was one of the original bioartificial support devices developed and correspondingly has been researched extensively. It is composed of a three-dimensional matrix of hepatocytes that is exposed directly to patient plasma rather than separated by a membrane.⁶⁷ Initial studies looked at 12 patients with acute liver failure and demonstrated that the AMC-BAL was effective in improving biochemical and clinical parameters and in all patients provided a bridge to transplantation or recovery.^{67,68} The initial model used porcine hepatocytes for the bioreactor; however, because of concerns regarding poor urea cycle function, a new cell line of HepaRG hepatoblastoma cells has been developed. In animal studies, the new cell line has demonstrated greater functionality with respect to urea cycle function and ammonia clearance and, in acute liver failure models, improved survival.⁶⁹

The modular extracorporeal liver system (MELS) is a hybrid bioartificial device consisting of a combination of either harvested human or porcine hepatocytes, engrafted into a hollow fiber matrix with an integrated an albumin dialysis circuit.⁷⁰ The MELS has been used successfully as a bridge to transplantation in nine patients, with a primary nongraft function, idiopathic, and drug- and viral-related acute liver failure.^{26,71}

The HepatAssist is another hybrid device combining a hollow-fiber porcine bioreactor with a charcoal adsorbent system. Plasma is separated and undergoes adsorption before exposure to the hepatocyte then returned to the cellular components and returned to the patient. A theoretical benefit is the removal of toxins from the circulating plasma that may be toxic to the device's hepatocytes. The HepatAssist has undergone a large randomized control trial of 171 patients that demonstrated clinical efficacy in improving biochemical and clinical parameters in acute liver failure and primary nongraft function but did not have any effect on 30-day mortality.⁷²

A novel bioartificial device is the spheroid reserve bioartificial liver. This device is based upon the serendipitous finding that porcine hepatocytes naturally aggregate into spheroids when gently oscillated.⁷³ The potential major benefits of spheroid formation are greater cell stability and viability, improved oxygen delivery, micronutrient perfusion, metabolic function, and the ability to support a greater hepatocyte cell mass.⁷⁴ A preclinical trial of this device in a porcine model of acute liver failure showed improved survival, ammonia clearance, and intracerebral pressure.⁷⁵

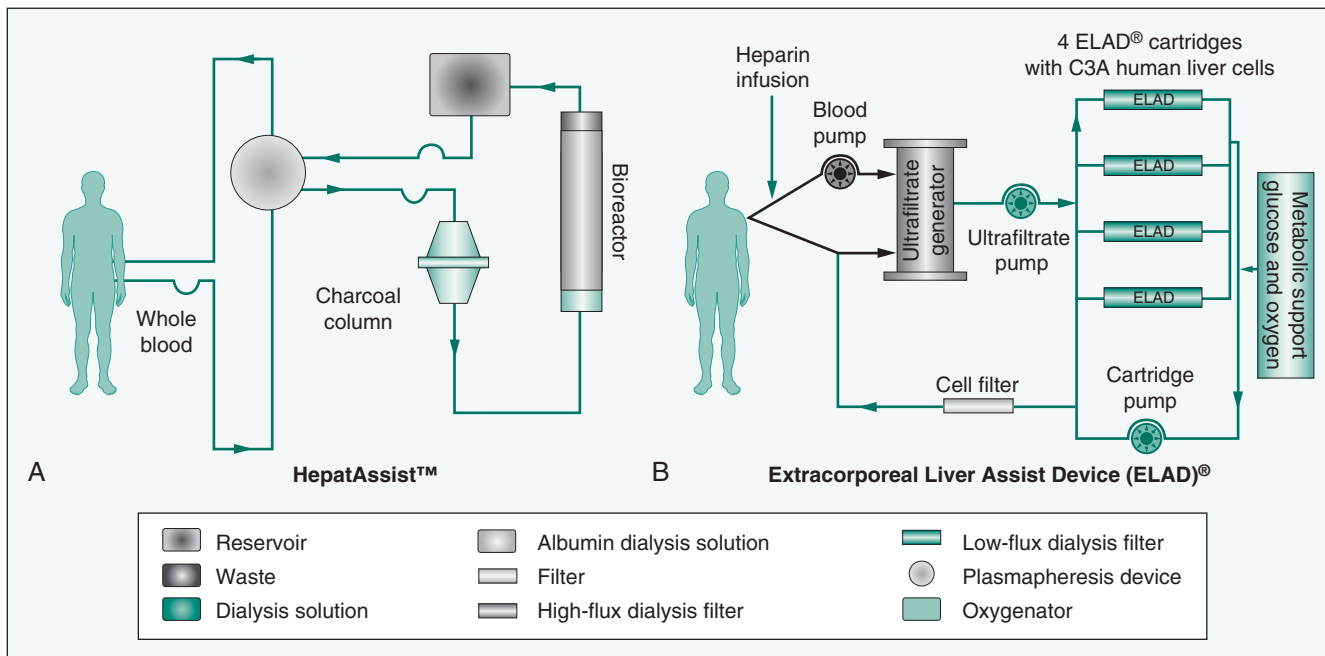


FIGURE 130.2 Bioartificial liver support devices aim to combine detoxification with the synthetic and regulatory functions of hepatocytes. **2A**, HepatAssist™ system. (Alliqua Inc., Langhorne, PA, USA). **2B**, Extracorporeal Liver Assist Device. (ELAD®, Vital Therapies Inc. San Diego, CA, USA).

Despite the impressive improvements in technology and conceptual attractiveness of bioartificial devices, significant challenges and questions remain. One key question is the type of hepatocyte that should be incorporated into the bioreactor. Research has focused on human or porcine hepatocyte cell lines. Primary human hepatocytes are the ideal choice because they have higher biocompatibility and possibly replicate the functions required by the liver.⁷⁶ However, their use is limited by difficulties in culturing, logistical difficulties in obtaining an adequate supply, and the rapid loss of metabolic capacity compared with other hepatocyte populations,⁶² although co-culture with mesenchymal stem cells is showing promise. The human hepatocyte option has been pursued further by the use of immortalized tumor cell lines such as the hepatoblastoma cell line.⁷⁶ These have been used successfully in a number of bioartificial devices, but concerns remain regarding the risk of malignant spread in the setting of membrane rupture and their capacity to meet hepatic metabolic requirements.⁷⁶ Porcine hepatocytes also have concerns regarding the risk of zoonosis, in particular porcine retroviruses.⁷⁷ Studies have shown postbioartificial device treatment porcine DNA has been detected in patient serum; however, it was cleared quickly.⁷⁶ The impact of this on patients who may require long-term immunosuppression is currently unclear. The role of stem cells in the development of hepatocytes is an area of increasing research; currently research is hampered by a number of issues including the inability for stem cells to maintain differentiation and ethical concerns regarding use.⁷⁶ Another unresolved question is the mass of hepatocytes required for efficient function. Studies and results from the animal models and the surgical literature have demonstrated that one requires 200 to 400 g of liver tissue for adequate function.^{76,78} This results in considerable logistic challenges in maintaining such a readily available store of hepatocytes and manufacturing challenges to ensure continued hepatocyte viability within the bioreactor.

CONCLUSION

Liver failure is a condition that, despite advances in transplantation medicine, continues to have a high morbidity and mortality. There is an ongoing need to find technologies and approaches to support a failing liver to either transplant or recovery. The failure for conclusive evidence to support one particular artificial or bioartificial approach most likely stems from our slowly but increasing recognition of the complexity of the role the liver plays in maintaining body-wide homeostasis. Research into artificial support devices suggests that simply detoxifying the blood may not be sufficient to treat patients with liver failure. The potentially critical role of albumin has been explored, but systems based upon albumin dialysis have not shown any additional benefit. The incorporation of hepatocytes into an extracorporeal system shows promise. However, simply replacing hepatocytes and supplementing the metabolic role of the failing liver may not be sufficient because it does not address the immunologic and other hormonal roles of the liver. Extracorporeal techniques are, and will remain, key technologic devices for the delivery of support to patients with liver failure. Future research must address the current limitations of our understanding of the multitude of the roles of the liver and technology required to support a patient with liver failure.

Key Points

1. The liver is a highly complex organ with many metabolic, detoxification, immunologic, and hormonal roles.
2. Multiple artificial extracorporeal liver support devices have been developed around the basis of

conventional renal replacement therapy, with and without albumin-based technology.

3. Artificial devices are effective at removing toxins associated with acute and chronic liver failure.
4. No artificial device has shown a positive impact upon patient survival.
5. Bioartificial devices are promising extracorporeal support devices but remain experimental at this stage.

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