

Current Strategies and Future Developments in Artificial Liver Support

a report by

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While liver transplantation has proven to be a life-saving procedure for patients with liver failure, the shortage of organs and unpredictability of organ availability for liver transplantation makes this option unattainable for many individuals. One potential solution to this problem is the use of an extracorporeal liver support system.

Artificial liver support has been attempted for over 40 years. Temporary systems have been developed to endeavor to expedite recovery from acute decompensation, facilitate regeneration, or serve as a bridge to liver transplantation. Various non-biological approaches have met with limited success, presumably because of the role of the liver in synthetic and metabolic functions that are inadequately replaced in these systems. Hemodialysis, hemoperfusion over charcoal or with resins or immobilized enzymes, plasmapheresis, and plasma exchange have all been utilized. Purely biological approaches have shown encouraging results, but have been difficult to implement in the clinical setting. These have included whole organ perfusion and perfusion of liver slices.

Bio-artificial devices typically incorporate isolated cells in a bioreactor to simultaneously promote cell survival and function and provide for a level of transport seen *in vivo*. Several different systems differing in their geometry, cells, and perfusate have been evaluated in clinical trials.

Goals of Artificial Liver Support

Artificial liver support for both acute (i.e. a previously healthy patient) and chronic (i.e. a patient with a history of established liver disease) forms of liver failure aims to serve as a bridge to liver transplantation, provide time for spontaneous recovery of the injured liver, prevent dysfunction of extrahepatic organs (i.e. renal dysfunction), reverse manifestations of hepatic encephalopathy (i.e. coma, cerebral edema, and brain death), modulate humeral and molecular mechanisms of liver regeneration, and quench the systemic inflammatory syndrome caused by release of cytokines from the necrotic liver tissue.

In both acute and chronic liver failure, a common goal of liver assist therapy is to stabilize patients prior to liver transplantation. In doing so, stable patients are more likely to tolerate the transplant procedure and experience improved long-term survival.

If the liver assist treatment is successful, time becomes available to allow the possibility of spontaneous recovery of the patient's acutely injured liver. Auxiliary liver support by liver assist therapy may prevent the dysfunction of extrahepatic organs, such as the kidneys, that are often associated with hepatic failure.

Reversal of hepatic encephalopathy is another important goal of liver assist therapy in both the acute and chronic settings of liver failure. In the acute setting, liver assist reverses the build-up of toxins that are associated with cerebral edema and intracranial hypertension, a potentially life-ending neurological manifestation of acute liver failure. Liver assist devices may also be used to assess the extent of neurological injury and evaluate the possibility of neurological recovery by patients with advanced acute liver failure prior to liver transplantation.

Other benefits of liver assist therapy include providing hepatic function such as gluconeogenesis, synthesis of proteins (i.e. albumin and clotting factors), and detoxification activities (i.e. bilirubin metabolism and ureagenesis).

Potential candidates for liver assist therapy can be categorized according to the chronicity of disease (acute versus chronic liver disease) and severity (hospitalized versus non-hospitalized). The number of patients with chronic liver disease and subsequent liver failure is significantly greater than the number of patients with acute liver disease. Therefore, a therapy that is effective for patients with chronic liver disease would have the greatest impact on overall patient care.

However, most studies of liver assist therapy have enrolled hospitalized patients with acute failure due to

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Table 1: Current Liver Assist Systems

Liver Assist System	Type	Current Manufacturer	Previous Manufacturer
HemoCleanse-DT	Liver dialysis	HemoCleanse, Inc.	HemoTherapies
Molecular Absorbents Recirculating System (MARS)	Albumin dialysis	Gambro	Teraklin
Prometheus	Dialysis with adsorber treatment	Fresenius	
Extracorporeal Liver-assist Device (ELAD)	C3A hepatoblastoma cells	Vital Therapies, Inc.	Vitagen, Hepatix
HepatAssist (BAL)	Porcine hepatocytes	Arbios Systems, Inc.	Circe Biomedical

the urgency of their condition.¹⁻⁵ Patients with acute liver failure are considered most appropriate for an experimental therapy, such as use of a liver assist device, due to their low likelihood of spontaneous recovery (approximately 25%) and a high likelihood of death (34%) while awaiting liver transplantation.⁶ Studies of liver assist therapy have also included patients with chronic liver failure with some suggestion of benefit.⁷⁻¹⁰

A review by Kjaergard et al.⁹ suggests that liver assist systems may be more effective in the setting of chronic liver failure than in the setting of acute liver failure. However, the authors also concluded that randomized trials in both settings continue to be justified.

Current Liver Support Devices

Several different systems continue to be evaluated as

potential liver assist devices (see Table 1). Most of these devices have undergone several stages of evolution. Almost all systems have moved from the original company they were developed with, and have been acquired by other companies.

The HemoCleanse-DT, while US Food and Drug Administration (FDA)-approved, has not received wide acceptance or use. It is indicated for:

- acute hepatic encephalopathy due to decompensated cirrhosis or fulminant hepatic failure; and
- serious drug overdose, such as acetaminophen, tricyclics, or all drugs dialyzable and bound to charcoal.

This system is a blood-cleaning device for liver dialysis and other detoxifying therapies that transfers blood filtrate or plasma obtained from a dialyzer or plasma filter to a sorbent reactor that selectively removes unwanted substances. The reactor creates a sorbent flow pattern that optimizes clearance of unbound and bound toxins. Blood filtrate or plasma with high toxin concentrations enters in the center of the swirling sorbent suspension and is easily cleansed as it moves radially outward toward a separation membrane. Cleansed filtrate is returned to the dialyzer or plasma is returned directly to the patient.

The Molecular Absorbents Recirculating System (MARS) has been utilized in approximately 4,500 patients in 130 hospitals, predominantly in Europe. In this therapy, the patient is connected to a conventional hemodialysis machine that pushes blood through an extracorporeal circuit into a MARS Flux dialyzer. Although this filter is similar to a renal dialyzer, it dialyzes the patient's blood against a recirculating saline and

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human albumin solution rather than bicarbonate-based dialysate. Once the toxins are transported across the MARS Flux membrane and attached to the albumin in the dialysate, the albumin dialysate is passed through two different columns. These columns are designed to extract the toxins bound to albumin, thus 'regenerating' the albumin so that it can be recycled back to the MARS Flux for additional toxin removal. The final step is dialysis of the solution against standard bicarbonate dialysate in a conventional low-flux dialyzer to remove water-soluble substances from the albumin dialysate. There has never been a published prospective randomized multicenter controlled trial of MARS use in spite of large numbers of patients treated. Most reports have been on patients with acute or chronic liver disease and in small numbers of patients.

The Prometheus system combines a typical dialysis procedure with an adsorber treatment. The Prometheus machine pumps blood through a filter that retains blood cells and large protein molecules. The blood plasma, along with albumin and smaller protein molecules, is then fed through two adsorbers that separate and bind toxins from the albumin. Following adsorption, the blood plasma and the detoxified albumin are joined with the cells retained by the filter and undergo dialysis to remove the remaining water-soluble toxins. The filtered blood is then reintroduced into the patient. This system has, thus far, only been utilized in 20 patients in an assessment of safety and in a pilot trial of efficacy in seven patients. Larger trials are planned in Austria and Germany.

The Extracorporeal Liver-assist Device (ELAD[®]) system comprises four hollow-fiber cartridges containing 440g of cells and 32,000 fibers mounted on a standard blood-pumping unit. Immortalized human liver cells are grown on the outside, and the patient's plasma flows through the inside of pore-size hollow fibers that allow appropriate transfer of toxins and nutrients. The system uses a C3A human hepatocyte cell line (hepatoblastoma), which can be grown in unlimited quantities and stored and shipped worldwide. Four clinical trials of the ELAD system have been conducted based on data at the Vital Therapies website. Two initial trials were completed under an investigational device exemption (IDE) from the FDA, one at Baylor College of Medicine and the other at King's College in London, UK. Phase I and II trials have been conducted under an investigational new drug (IND) from the FDA at 12 different clinical sites in the US and UK. A total of 52 patients have been treated with the ELAD system in the four studies. While the total number of critically ill patients treated with the product is relatively small, the product demonstrated safety.

The HepatAssist system is an extracorporeal liver failure therapy device, in which the function of porcine liver cells

is supplemented by a detoxification column filled with charcoal particles. During therapy, the patient's blood is first separated into plasma and cellular components using membrane plasmapheresis. The plasma first goes through the charcoal filter, which removes small-molecular-weight toxins. After this initial detoxification, the plasma runs through the hollow-fiber column lined with cryopreserved matrix-anchored porcine liver cells. The plasma that has been cleaned and processed by the liver cells is then reunited with the blood cellular components and returned to the patient. During therapy, a heater and an oxygenator are used to warm the plasma and provide oxygen to liver cells.

Demetriou et al.⁵ published the only prospective randomized multicenter controlled trial of liver assist therapy utilizing the HepatAssist system. The system contained approximately 7 billion (70g) cryo-preserved porcine hepatocytes. One hundred and seventy-one patients (86 control and 85 bioartificial liver (BAL)) were enrolled; 147 patients had fulminant or sub-fulminant hepatic failure and 24 patients had acute liver failure due to primary graft non-function after liver transplantation. Survival for the entire patient population at 30 days was 71% for the BAL group versus 62% for the control group ($p=0.26$). After exclusion of primary graft non-function patients ($n=24$), survival was 73% for BAL patients versus 59% for control patients ($p=0.12$; $n=147$). The study demonstrated safety and improved survival in the subset of patients with fulminant/sub-fulminant liver failure compared with controls. Exclusion of patients with primary non-function was rationalized due to the fact that these patients were much less likely to develop neurological sequelae of liver failure such as cerebral edema, herniation, and brain death. Despite this favorable report, FDA approval of this BAL device was not obtained. Although research in this field remains active, no BAL devices have yet been approved for clinical use outside of an experimental protocol. Use of these systems in children has been limited to case reports in the literature.

In summary, liver assist devices have the potential to serve multiple roles, both in the treatment of cirrhotic patients with chronic liver failure and previously healthy patients with acute liver failure. Current data, including the trial by Demetriou et al.⁵, indicates a role for liver assist devices as a treatment for acute hepatic encephalopathy. Enhancements to the liver assist devices, such as design provisions for continuous therapy and increasing the number of metabolically active hepatocytes, will likely be associated with greater efficacy in future clinical trials. It remains uncertain whether liver assist devices can ever achieve a status in the treatment of liver failure that is comparable with the status of hemodialysis in the treatment of renal failure. ■