

## Artificial Support of the Failing Liver

a report by

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Acute hepatic failure is a devastating disease that, despite recent therapeutic advances, continues to be one of the greatest challenges in clinical medicine. Hepatic failure may develop in the absence of preceding liver disease or as an acute exacerbation of a chronic pathological process (cirrhosis). The majority of patients from the first group, especially those who progress to fulminant hepatic failure (FHF), will die, unless they undergo liver transplantation. The second group of patients will often respond to treatment of the precipitating cause of hepatic decompensation, such as infection, bleeding, dehydration, etc.; if therapy is not effective, they will succumb due to sepsis, hemorrhage, and failure of other organs.

### The Need for Alternative Methods of Liver Replacement Therapy

Currently, no direct treatment of hepatic failure exists and patients must receive a transplant or endure prolonged hospitalization, with significant morbidity and mortality as a consequence. Liver transplantation has become the most effective treatment of FHF and end-stage chronic liver diseases. However, wider application of this therapeutic modality is restricted by the shortage of organ donors, inability to procure livers on short notice, and high cost. Additionally, the majority of patients with 'acute-on-chronic' liver disease are not even placed on the transplant waiting list due to medical or psychosocial contraindications or lack of an adequate healthcare insurance to cover the high cost of transplantation.

While little can be done to increase the number of donor livers, it is reasonable to search for alternative methods of liver replacement therapy that will help maintain liver failure patients alive and neurologically intact until either an organ becomes available for transplantation or their native livers recover from injury. An 'artificial liver' could also support patients during periods of functional recovery after transplantation with marginal livers and after extended liver resections for trauma or cancer. To achieve these effects, an artificial liver should be able to lower blood levels of substances that are toxic to

the brain and liver and provide those whole liver functions that have been impaired or lost. It is generally believed that liver support at this level of complexity requires utilization of a biological component comprising a mammalian liver tissue preparation (e.g. isolated hepatocytes) rather than blood detoxification techniques. It was demonstrated *in vitro*, in animal models of hepatic failure, and, more recently, in human clinical trials that whole liver functions can be provided by hepatocyte-based extracorporeal devices (bio-artificial livers (BALs)).

### Blood-purifying Solutions

Today, only a few extracorporeal treatment options are available, with varying degrees of success. Each type of technological modality is aimed at the same underlying principle of providing the means of toxin removal from the bloodstream. Detoxification helps to stabilize the patient in order to alleviate the exacerbation of their underlying liver disease and/or provide relief of liver failure. However, no blood detoxification measure, including hemoperfusion through adsorbent columns (e.g. charcoal) and, more recently, the molecular adsorbent recycling system known as MARS (Gambro GmbH), has achieved wide clinical use and been shown to improve patient survival.

In the last decade, advances in blood purification technologies, availability of new hollow-fiber membranes, and a better understanding of the pathophysiology of hepatic failure have resulted in the development of new liver assist systems. Several of these therapeutic modalities, including Prometheus (Fresenius, Germany), single-pass albumin dialysis (SPAD), high-flux continuous hemodiafiltration with/without plasma exchange, and selective plasma filtration (Sepet™; Arbios Systems, Inc.) are currently being tested in the clinical setting.

While there are multiple differences between these technologies, they all aim at providing blood purification, i.e. removal of not only classic toxins of hepatic failure (ammonia, phenols, merkaptans, bile acids, aromatic amino acids, etc.) from the blood stream, but also protein-

bound toxins, vasoactive substances, and mediators of inflammation (cytokines, chemokines, lipid A, etc.) that accumulate in the blood during liver failure and cause hepatic dysfunction and neurological abnormalities and aggravate injury to the liver and other organs.

### Sepet Therapy

Interestingly, all putative hepato- and neurotoxins, as well as mediators of inflammation and inhibitors of hepatic regeneration (transforming growth factor (TGF)- $\beta$ 1) have molecular weights lower than 100 kilo Daltons (kDa). Based on this knowledge, Arbios Systems designed the Sepet blood filtration device that facilitates removal of the plasma fraction that contains these substances. At the same time, important blood components that have a molecular weight greater than 100kDa, including immunoglobulins, complement system proteins, 9/13 blood clotting factors, and stimulators of hepatic regenerative response, are retained in the blood circulation. During Sepet therapy, electrolyte solution and a limited amount of fresh frozen plasma and albumin solution are used to

safety and tolerability of Sepet treatment plus standard medical care (SMC) for patients with acute exacerbation of chronic liver disease with stage II–IV hepatic encephalopathy.

### HepatAssist

As of today, only a few cell-based extracorporeal therapies have been tested clinically, including HepatAssist™ liver assist system (Arbios Systems), in which the function of porcine liver cells contained in a hollow-fiber cartridge is supplemented by a detoxification column filled with charcoal particles. HepatAssist was the first BAL tested in FDA-approved clinical trials and the only one studied in a large phase II/III survival trial.

### Clinical Study

A prospective randomized controlled study was conducted in 171 patients who were enrolled in 11 US and nine European medical centers. This trial demonstrated a favorable safety profile of the BAL,

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replace the removed 'toxic' plasma fraction. The exact composition of the fluid replacement therapy is dictated by individual patients' needs (fluid balance, clinical presentation, and results of blood tests).

As a result of blood purification and fluid replacement therapy, the levels of pathological and normal blood components present in the patient's circulation will move toward normal ranges, facilitating recovery from hepatic failure. In addition, removal of cell growth inhibitors with preservation of elevated blood hepatocyte growth factor levels facilitates healing of the injured liver and an increase in functional liver cell mass.

Sepet has been designed and qualified for use with the Prisma hemodialysis system (Gambro, Lakewood, Colorado) and is ultimately for use with any commercially available kidney dialysis system. Arbios is currently performing a feasibility investigational device exemption (IDE) study in order to assess the

but failed to improve 30-day survival in the overall study population. However, when adjusting for the impact of liver transplantation and a two-day advantage in the median time to transplant favoring controls, BAL-treated patients had a statistically significant survival advantage compared with controls receiving SMC. Furthermore, HepatAssist therapy reduced the risk of pre-transplant death by 67% in patients with drug and chemical toxicity ( $p < 0.0140$ ) and by 47% in patients with rapid onset of FHF ( $n = 121$ ;  $p < 0.0428$ ).

Recently, Arbios Systems announced that an improved version of the HepatAssist liver assist system will be tested in phase III clinical trials. The company believes that because of several distinct advantages over the previous generation of devices—e.g. more cells and a more efficient platform—the proof of clinical efficacy of the HepatAssist-2 therapy will be demonstrated and that this important liver assist technology will be introduced into clinical practice. ■