Molecular Adsorbent Recirculating System and Bioartificial Devices for Liver Failure

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KEYWORDS

• Albumin dialysis • Acute liver failure • Acute-on-chronic liver failure
• Extracorporeal liver assist device • Hepatic encephalopathy

KEY POINTS

- Substitution of the detoxification, synthetic, and regulatory functions of the failing liver is the rationale for the use of extracorporeal liver support systems in patients with liver failure.
- In contrast to artificial liver support systems, bioartificial systems incorporate a module containing living cells/hepatocytes to provide synthetic functions.
- Artificial and bioartificial liver support devices have shown certain detoxification capabilities and improvement of intermediate endpoints in patients with liver failure, but their effects on survival remain inconclusive.
- Identification of target populations and adequate endpoints, optimization of therapy delivery, and improvement of current prototypes seem essential steps for extracorporeal liver support devices to achieve their long-desired goals.

INTRODUCTION: WHY ARE LIVER SUPPORT DEVICES NECESSARY?

Liver failure may occur in a person without preexisting liver disease (acute liver failure [ALF]) or in a patient with chronic liver disease that suffers an acute decompensation (acute-on-chronic liver failure [ACLF]). In both cases, the sudden impairment of liver

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function leads to characteristic clinical manifestations such as hepatic encephalopathy, jaundice, coagulation disturbances, increased susceptibility to infections, hemodynamic instability, hepatorenal syndrome, and eventually multiorgan failure. Despite recent improvements in its clinical management, the morbidity and mortality of liver failure remains unacceptably high.[1,2] Liver transplantation remains the only therapy with a well-proven beneficial effect on survival,[3] but this procedure is not applicable to all patients because of the shortage of donor organs and the frequent presence of contraindications. In this scenario, the development of extracorporeal liver support devices would be important for maintaining the patient's condition until the spontaneous recovery of liver function occurs or until a donor organ becomes available.

The aim of this review is to summarize the current state of liver support devices in the clinical management of liver failure.

TECHNICAL CHARACTERISTICS OF EXTRACORPOREAL LIVER SUPPORT SYSTEMS

A full description of the types and characteristics of liver support systems is out of the scope of this review, but an understanding of some technical aspects is important.

The extracorporeal liver support systems that have been tested clinically belong to one of the following 2 categories:

1. Artificial Liver Support (ALS) systems, also known as nonbiological or cell-free techniques. The ALS systems are based on the principles of adsorption and filtration and are aimed at removing circulating toxins by using a variety of membranes and adsorbents.
2. Bioartificial Liver Support systems are hybrid devices that incorporate liver cells/hepatocytes to improve the detoxification capacity and to support the failing synthetic liver function.[4]

Overall, most liver support systems combine diverse therapeutic units, ranging from conventional hemodialysis or hemofiltration modules, to specific adsorption systems. In the case of bioartificial systems, the extracorporeal circuit includes bioreactors loaded with liver cells.[5] A summary of devices is provided in **Table 1** and a comparison of pros and cons is provided in **Fig. 1**.

RATIONALE FOR THE USE OF LIVER SUPPORT SYSTEMS IN LIVER FAILURE

From a theoretic perspective, an effective extracorporeal liver support system should replace 3 major functions of the liver: detoxification, biosynthesis, and regulation. In liver failure, the main goals would be to remove putative toxins preventing further aggravation of liver failure, to stimulate liver regeneration, and to improve the pathophysiologic features of liver failure.[6,7] None of the devices currently available, however, fulfill these requirements completely.

Elimination of Toxins

The deterioration of liver function leads to the accumulation of toxic substances such as bilirubin, bile acids, ammonia, protein breakdown products (aromatic amino acids, phenol, mercaptans), lactate, glutamine, mediators of oxidative stress, free fatty acids, endogenous benzodiazepines, inflammatory cytokines, and others. Many of these toxins play key roles in the pathogenesis of liver failure and result in a toxic state that alters the functional capacities of serum albumin,[8] increases the susceptibility to infections, and induces circulatory disturbances and end-organ dysfunction.[9] Secondary liver damage occurs as a consequence of the vicious circle that results from the release of inflammatory mediators, oxidative stress, and sinusoidal endothelial cell damage.