

ARTIFICIAL LIVER SUPPORT

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The treatment of acute liver failure has many unknowns and the mortality is still high in organ transplantation.¹ Starting 1950, the liver artificial support was proposed as a temporary modality of maintaining the liver function², with later development of long-term artificial liver devices.

Initial devices (hemodialysis, hemofiltration, etc.) had a limited effectiveness on portal encephalopathy and even less on patient's outcome. Extracorporeal liver perfusion (ECLP) is a better method, but does not represent a long-term solution. Research in the field was abandoned for a while, due to the success of liver transplantation. However, the reduced number of available organs and the role of artificial liver support in the improvement of transplant outcome, have led to a new stage of reevaluation and development of artificial liver support devices.

Artificial liver support methods may be classified, after the presence of hepatocyte cell substrate, in biological and nonbiological systems.³

1. Complete artificial liver support (nonbiological):

a. Conventional methods: hemodialysis, hemofiltration, exchange transfusion, plasmapheresis.

b. Combined treatments: hemodiabsorbtion (liver dialysis unit Biologic-DT, Biologic-DTPF, MARS – Molecular Adsorbents Recirculating System, Prometheus) and hemodiafiltration.

2. Biological systems (hepatocyte-containing devices): cross-hemodialysis and cross-circulation, hepatocyte transplantation, extracorporeal liver perfusion (ECLP).

3. Hybrid systems (bioartificial liver): ELAD (Extracorporeal Liver Assist Device), HepatAssist, BAL (Bioartificial Liver), Monsanto/St. Louis, Regenerex/Minnesota

Adham² suggests a classification of liver artificial support systems in 2 large categories:

1. Chemical systems (without cell components-“hepatocyte-free devices”): hemodialysis, hemofiltration, exchange transfusion, plasmapheresis. Later on, standard methods of removal of circulating toxins were adapted, in order to create the artificial liver with improved purification functions.

2. Systems of global replacement of liver function (biological systems): cross-circulation, cross-hemodialysis, extracorporeal liver perfusion (ECLP).

The role of artificial liver support is to effectively eliminate the circulating toxins. The source of these toxins may be the bowel (ammonia) or the necrosis liver itself. These substances differ by molecular weight, the type of protein binding, and possibility of elimination. Toxins may affect the mental status, may participate in the multiple organs failure syndrome, or may interfere with liver regeneration capacity.

Hepatic encephalopathy is a major complication of hepatic insufficiency, with brain edema and fulminant hepatic failure as the main causes of death. The improvement of the mental status was the criterion used to estimate the efficiency of artificial liver support systems. Ammonia is the classical example of hydrosoluble molecule with low molecular weight, which may be dialyzed. Glutamine formation in astrocytes is the first important step in brain edema development. Ammonia elimination in the normal liver and in the extracorporeal system depends on the blood flow, because the involved ion is removed at the first pass by clearance mechanisms. Many of the extracorporeal systems use a blood flow of 100-300 ml/min, which is less than the liver blood flow, i.e. 1500 ml/min.

Multiple organs failure syndrome, noticed in patients

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with fulminant hepatic failure, may have as a trigger the injured liver itself: hepatocyte necrosis, apoptosis or inflammatory cells infiltration.

The artificial support systems can eliminate from circulation both inhibitory factors of liver regeneration (TGF- β , γ -interferon, etc.) and promoting factors (HGF); this may be a boundary for these devices.

1. NONBIOLOGICAL SYSTEMS

Standard hemodialysis

Conventional hemodialysis was proposed as hepatic failure therapy, for the first time by Kiley and collaborators in 1956.⁴ Further studies have proved that reducing ammonia using semipermeable membrane, and brain edema could improve fulminant hepatic failure encephalopathy, with no modifications in patient's outcome.² In the seventies, polyacrylonitrile membranes were introduced, with better results in the evolution of the neurological syndrome, probably because they made it possible to remove molecules with medium molecular weight, but the final outcome was not different. Hemodialysis was useful in some patients, in the successful bridge-to-the-liver transplant.

The patients with hepatic failure often develop renal failure, rendering necessary an artificial renal support. In this case, continuous dialysis is recommended as standard dialysis procedures make an maldistribution in body's liquids, which worsen brain edema.⁵

The significant inconvenience of the dialysis is the fact that protein-bound toxic substances cannot be removed. Albumin dialysis or polysulphone membranes allow detoxification of substances with affinity for proteins such as bile acids and fatty acids.³ Even if hemodialysis doesn't prevent death in acute hepatic failure, studies on animals prove its efficiency if indicated early after liver injury.

Hemofiltration

The substances with molecular weight less than 10,000 d, medium molecules such as immunoglobulin and cytokines, can be removed using the convection of high volumes of liquids and electrolytes, a process used in hemofiltration. Continuous venovenous hemofiltration seems to be the method of choice for the patients with both liver and renal failure. Combined with dialysis (hemodiafiltration) it may also remove molecules that pass through a high performance membrane in diffusion process.⁶

Exchange transfusion and plasmapheresis

Exchange transfusion was abandoned because it had no beneficial effects on the outcome, and even had worse results than in control groups. In our country, this method was used with satisfactory results by

Voiculescu and Sandu for viral acute hepatic failure.⁷ Plasmapheresis was used for nonselective removal of the protein-bound toxins and for coagulation factors supply. The method did not improve the survival, but improved the neurological state. The explanation may consist in the fact that plasma, in high quantity, inhibits hepatocyte regeneration. This method for fulminant hepatic failure is currently undergoing reevaluation, in Scandinavian countries.⁵

Hemoperfusion

Removal of toxins is obtained if blood is circulated through absorbent systems, using changing ions resin or activated charcoal, a method called hemoperfusion. This method, removes water soluble and lipophilic substances, associated with hepatic encephalopathy, as: ammonia, neurotransmitter metabolites, polypeptide, aromatic amino acids, bilirubin; but no protein-bound substances. It is partially useful in hepatic coma, but encompasses a high risk of leucopenia, thrombocytopenia, hypotension, pulmonary embolism. In order to decrease the risk of these complications the procedure was modified, using active charcoal microencapsulated with membranes based on albumin or cellulose nitrate. Plasma separation and its passing through absorbent system ("plasma perfusion") is another modality of decreasing the hemoperfusion risks.

Hemodiabsorption

Hemodiabsorption is a method that combines hemodialysis with absorption and consists in blood actively passing through a flat dialyser with cellulose membrane (efficient for MW molecules up to 5,000 d), but the dialysate, continuously renewed, contains activated charcoal suspension and cation changing resin. Large exchange surface and no direct contact between blood and absorbent substances are the two advantages of this method.

This system, *Biologic-DT*, known as *Liver Dialysis Unit*², has entered in clinical studies with promising results. A further technical modification was made, in order to improve the results: plasma filtration with an absorbent wrapping of membranes ("push-pull pheresis system"), *Biologic-DTPF* device. These are the artificial support systems, approved by Food and Drug Administration from USA.⁷ A multicentric prospective study on 56 patients with acute hepatic failure (31 were treated with Liver Dialysis Unit) proved a physiological and neurological status improvement.² If for acute-on-chronic hepatic failure, there were 71.5% cases with hepatic functional recovery, compared to 35.7% in the control group, in fulminant hepatic failure there were no differences between treated vs. control group. The

device proved its utility in acetaminophen intoxication cases.

The Molecular Adsorbents Recirculating System (MARS)

This device functions based on the hypothesis of albumin linkage with toxic products. It consists in a compartment with a membrane for separating the blood from albumin dialysate, followed by compartments with ion changing resin, activated charcoal, hemodialysis. It allows the removal of protein-bound toxins as well as the soluble toxins: ammonia, bilirubin, bile acids, aromatic amino acids, medium and short chain fatty acids, tryptophan, copper, creatinine, urea, diazepam. For starting the treatment 600 ml albumin 20% is necessary and approximately 6 liters of priming and dialysate solution. A study on 176 patients treated with MARS (56% with cirrhosis, 22% with fulminant hepatic failure, and 4% hepatic resections) confirmed efficiency and safeness of this method.² The experience of the Internal Medicine Centre from Fundeni Clinic Institute Bucharest includes 12 patients presenting severe hepatic failure, with good results recorded using MARS.⁸



Figure 1. The Molecular Adsorbents Recirculating System (MARS) allows the removal from circulation of protein-bound and water soluble substances. . This system has the advantage of allowing the control of electrolytes and acid-base balance of patient, as well as that of glycemia and lactate level.

“All-in-one” Prometheus device combines “fractionated plasma separation and adsorption”-FPSA with high flow hemodialysis, for a complete body detoxification.

The metabolites associated with hepatic failure have different molecular weights, physical and chemical features. A great part of toxins are linked with albumin: unconjugated bilirubin, bile acids, amino acids and fatty acids. Prometheus may clearance the blood from these albumin-bound substances, using plasmapheresis and adsorption procedures, with no need of priming with exogenous albumin. Another large proportion of toxins are water soluble and with small or medium molecular weight, and accumulate due to hepatic failure (ammonia) and associated renal failure (urea, creatinine).

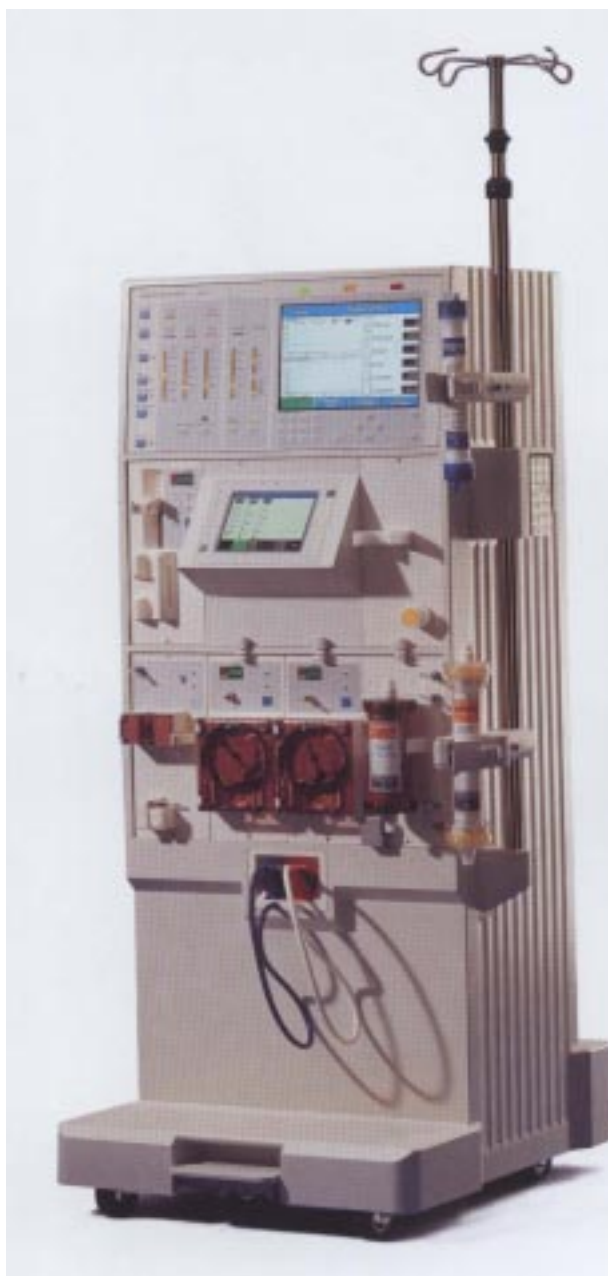


Figure 2. All-in-one Prometheus device achieves the hepatic and renal detoxification by plasmapheresis, adsorption and high flow hemodialysis.

Using high flow hemodialysis method, which may be performed subsequently or separately from the first two methods, Prometheus offers the possibility to remove these substances.

2. BIOLOGICAL SYSTEMS

Hepatocyte transplantation

The use of hepatocyte in hepatic failure has recently entered first phase clinical studies, after promising results on animals. The encephalopathy in animals with porto-caval shunts was improved and the animals with total hepatectomy (Schumacher et al.⁹) had tripled the rate of survival after 3% hepatocyte implantation in rat's spleen. The injection of hepatocytes isolated from human liver in the spleen (through spleen artery) or liver (through portal vein), was followed by coma improvement and survival prolongation (Bilir et al.¹⁰). Postmortem examinations proved the new hepatocytes injected grafting.

In the field of hepatocyte transplantation, there are still enough technical difficulties. In order to have available hepatocytes, when needed, special freezing conditions are requested. Hepatocyte immortalization may be a solution. The critical mass to be injected is still unknown.

Extracorporeal Liver Perfusion (ECLP)

Otto and collaborators described, in 1958, the first experimental ECLP, convinced that the best hepatic support is the liver itself. There were used organs from many species (dog, cow, baboon, pig); in some cases there were experimented different species on one patient. In baboon case, the perfusion on 14 patients lasted between 5 and 27 hours, with 1-4 perfusions/patient, and the survival rate was 50%.¹¹ Biocompatibility is an important issue in using the liver from other species. Using transgenic pig liver, capable of producing human proteins for the control of the complement, seems to be a future trend. Levy and collaborators² reported the first two cases of patients with ECLP, using transgenic pig's liver (Hcd55/Hcd59), successfully bridged to transplant.

3. HYBRID SYSTEMS

Recent progresses in viable cell cultures preservation allow advances in bioartificial liver device, described for the first time by Wolf, in 1970. This is a device for hepatic toxins clearance containing animal or human hepatocytes. These devices (BAL or ELAD) aim to correct secondary metabolic disorders of the hepatic failure, in order to facilitate the hepatic recovery. These active biological systems are crossed by patient's blood or plasma and are containing a cartridge similar to the one used in hemodialysis. This cartridge has

semipermeable capillary fibres, with two compartments: a room, in which the blood or plasma is pumped, and second one in which the hepatocytes are protected by a semipermeable membrane, avoiding direct contact between patient lymphocytes and xenogenic hepatocytes. This isolating membrane is impermeable for some particular proteins, antibodies in particular, the permeability limit being of 10,000 d.

The Workshop on Fulminant Hepatic Failure from 1994,¹² recommend as ideal solution the human hepatocytes, with normal phenotype, capable of growing in cell culture, stabled for long time in a well differentiation condition, and capable of covering the whole hepatic function spectrum. The human cell usage is limited by their low availability and low proliferation in culture of adult liver cells.

Residual hepatic mass, that allows the survival rate after hepatic resection, is 20% or 300g.³ Recent studies in transplantation from living donor indicate that estimated ratio between the grafting weight and recipient body weight, has to be over 0.7%, or the ratio between grafting and recipient's liver, over 30%, in order to provide a satisfactory hepatic function. The hepatocytes from artificial liver are only 2% for BAL, in comparison with bioreactor capacity of 20% for ELAD. These figures may not reflect the effect of hepatocytes from artificial device on hepatic function; the hepatocytes requirement is related to their capacity of division, of detoxification and of allowing liver recovery.

Long lasting hepatocytary stability is still unsolved for liver cells of pig origin, which in culture are losing their function of differentiation after few passages. For example, in BAL daily replacement of hepatocytes is needed. New modalities for prolonging stability are explored. It must be mentioned that ELAD and BAL devices have already entered in advanced second and third phase clinical studies.

The first results of hepatic artificial support usage have revealed a neurological status and some biological parameters improvement, without an increase in percentage of patients with fulminant hepatic failure survival. The usage of devices for dialysing the substances with molecular weight under 15,000 d, improves hepatic encephalopathy, but does not change the survival rate. Some of these devices are in use for the management of severe metabolic acidosis, hyperpotasemia, or volume overload: hemodialysis, artery or veno-venous continuous hemofiltration. The plasmapheresis may also be used for patients with hepatic failure treatment, who are waiting for a liver transplant; and it is limited by hypotension, coagulation disorders or brain edema presence.

These artificial support methods, combined with

hepatic transplant, are improving the survival, the election method accepted as the radical treatment of acute hepatic failure remaining only the orthotopic liver transplant.

Artificial liver devices have the advantage of being available and carry no tumor or xenogenic cell element, so the patient is exempted from unnecessary risks. The absence of the synthesis function of hepatocytes is the main disadvantage of this method.

Nowadays, hepatic artificial support methods are orientated to bioartificial liver extracorporeal system usage. For an optimal hepatic support the minimal hepatocitary mass should be defined in correlation with the body weight, or, better, with hepatic failure level. Taking into account these facts, it must be said that no artificial or bioartificial system can totally replace the biosynthesis function. From all systems, it seems that only ECLP may offer a global hepatic support, with its purification and synthesis possibilities.

Hepatic support must be indicated based on outcome criteria, which are taking into consideration not only the unfavorable evolution, in the absence of the artificial support, but also the chance that the patient has to improve by recovering his own hepatocitary function. The identification of recoverable patients is difficult because there are no predictive criteria for the recovery of the hepatic function. The criteria for setting on or off the hepatic support are also difficult to be established. Most of the studies are focused on artificial support setting up criteria, but no study establishes when this support should be stopped.¹³⁻¹⁵

These are the main indications for hepatic artificial support:

1. The patient with fulminant hepatic failure and primary graft failure waiting for hepatic transplantation.

2. The patient clinical status' improvement during hepatic transplant. The postoperative outcome can be improved in this way (less graft disorders, fast patient discharge, better survival rate, especially when borderline liver grafts are used).

3. Time necessary for hepatic recovery, which allows fulminant hepatic failure patients' survival; thus hepatic transplant can be avoided.¹⁶

4. Patient with acute-on-chronic hepatic failure, for hepatic transplant further procedure; in this case the functional recovery based on hepatocitary recovery process is excluded, the transplant acceleration is the only solution left.

5. Patient with liver cirrhosis undergoing hepatic or nonhepatic surgery intervention support, or for extensive hepatectomy in patients without cirrhosis; in these cases the hepatic artificial support must be established as soon as possible, before cholestasis and

infectious complications and multiple organs disorder occur.

6. For the future: long-lasting intermittent hepatic support for the patients with end-stage liver disease.

Intracranial pressure increase is the critical event in the evolution of fulminant hepatic failure encephalopathy. When brain edema and intracranial pressure develop, the therapeutic window decreases. Small adjustments of blood volume may affect intracranial pressure, with no connection with any beneficial effect of artificial hepatic support; another reason for early institution of this therapy.

Actual artificial hepatic supports cannot be a complete solution for the complex disorders leading to hepatic failure. They can achieve the clearance of toxins but cannot substitute the hepatic synthesis and recovery functions.

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