Support for the Acutely Failing Liver: A Comprehensive Review of Historic and Contemporary Strategies

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End-stage liver disease is the tenth most frequent cause of death in the US, causing approximately 25,000 deaths annually. Although only about 2,000 cases of acute liver failure occur each year in the US, the mortality rate remains as high as 28%. The application of orthotopic liver transplantation to acute and fulminant hepatic failure has increased the survival rate dramatically, but this treatment option is costly, and the limited supply of suitable livers precludes this treatment option from being available to all patients who would benefit from it. Approximately 40% of patients with acute or fulminant hepatic failure survive the acute episode with medical therapy alone, and regeneration in the native liver makes orthotopic liver transplantation, an irreversible treatment option, unnecessary. Unfortunately, there is no effective means to distinguish patients who will survive without transplantation from those who will not.

The term acute-on-chronic typically refers to the acute onset or acute worsening of hepatic encephalopathy in patients with chronic liver disease. Some of the events or agents that may precipitate acute-on-chronic liver failure include oral protein intake, gastrointestinal hemorrhage, azotemia, hypoxia, or sedative or hypnotic drugs. Although some degree of neuropsychiatric disturbance is common in patients with chronic liver disease, overt encephalopathy portends a grim prognosis: survival is only 42% at 1 year and 23% at 3 years. Few effective treatment options, as for acute liver failure, exist for acute-on-chronic liver disease except liver transplantation.

Support options exist for patients with failure of other organ systems: hemodialysis and peritoneal dialysis for renal failure, extracorporeal membrane oxygenation for respiratory failure, ventricular assist devices for heart failure, and total parenteral nutrition for gut failure. Such options may serve as temporary treatment options for those patients, obviating the need for transplantation. In contrast to these organ systems, no effective support device exists for patients with acute or fulminant liver failure. Although many attempts have been made over the past 50 years to develop such a device, only recently have clinical studies suggested that these devices may be beneficial to patients with an acutely failing liver (ie, acute or acute-on-chronic liver failure). This review will summarize the pathophysiologic basis for these devices in the setting of both acute liver failure and acute-on-chronic liver disease. Historic treatments of acute liver failure will be reviewed, and the support systems currently in clinical trials will be discussed.

Molecules implicated in the pathogenesis of acute liver failure and its sequelae

The main cause of mortality in patients with acute hepatic failure is brain edema leading to elevated intracranial pressure and subsequent brain herniation. Despite decades of research, the precise etiology of the brain edema seen in acute liver failure remains unclear. Ammonia is perhaps the most thoroughly studied molecule that has been implicated in the pathogenesis of hepatic encephalopathy and brain edema. Ammonia is generated by urease-producing bacteria in the colon, and it accumulates when the failing liver is unable to convert sufficient quantities of ammonia to urea. The conversion of ammonia to glutamine by astrocytes leads to brain edema by increasing intracellular osmolality and causing cell swelling. Cerebral proton magnetic resonance spectroscopy of the brains of cirrhotic patients shows signs of increased intracellular osmolality and increased glutamine concentrations in the presence of hyperammonemia, supporting this process as a mechanism of hepatic encephalopathy and elevated intracranial...
Hyperammonemia also leads to an extracellular accumulation of glutamate. This extracellular glutamate stimulates NMDA (N-methyl-D-aspartate) receptors, triggering nitric oxide synthetase (n-NOS) release and cerebral vasodilation.8,13,14 This might be at least one of the mechanisms for the impairment of cerebral blood flow autoregulation that is a feature of acute liver failure.15-17

Hepatic encephalopathy, another feature of acute liver failure, is thought to be from the accumulation of molecules within the brain. Hyperammonemia increases the cerebral uptake of the albumin-bound neutral amino acids tyrosine, phenylalanine, and tryptophan by modulating a blood-brain barrier L-amino acid transporter18-20 and by modulating the synthesis of the neurotransmitters dopamine, norepinephrine, and serotonin and “false neurotransmitters.”21,22 An accumulation of endogenous benzodiazepines, GABA-like molecules, or both also impairs neurotransmission.23,24 Elevated serum manganese levels lead to deposition of manganese in type II astrocytes and manifest as bilateral, symmetric globus pallidus hyperintensities seen on MRI.25 Other molecules implicated in hepatic encephalopathy include octopamine, mercaptans, γ-aminobutyric acid (GABA)-like molecules, aromatic amino acids, and fatty acids.26,27

Blood and blood component treatments

By 1965, it was generally accepted that acute hepatic failure was a disease of metabolic origin. Treatments for acute hepatic failure at that time included oral antibiotics, corticosteroids, and a protein-free diet.28 Success of exchange transfusions in treating hemolytic disease of the newborn, carbon monoxide poisoning, and acute renal failure led clinicians to apply exchange transfusions to acute liver failure.28-30 This treatment was associated with anaphylaxis, hypotension, and fatal bronchospasm, and also placed a heavy burden on the hospital blood bank by depleting 5 to 50 L of whole blood used.30 Cross-circulation with healthy human volunteers was used as an alternative, but this placed the volunteer at high risk for transmission of viral hepatitis or other hematogenous pathogens.31

Cross-circulation has also been performed with baboons. Anecdotal reports suggest some improvement in liver failure, but anemia developed in the baboons and sudden cardiac death several days after initiation of cross-circulation.32-35 One infrequently used extreme in the use of blood transfusions for acute hepatic failure was “total body washout.” In this procedure, patients with acute liver failure underwent complete exsanguination in conjunction with hypothermic cardiac arrest. Recovery without neurologic sequelae after total body washout has been reported, and proponents recommended such treatment to “avoid the time-consuming attempts at exchange transfusion.”36-38

When physicians at St Vincent’s Hospital in New York were unable to find group B, Rh-negative blood for a patient with fulminant hepatic failure, plasmapheresis was used instead,31 and plasmapheresis subsequently replaced whole-blood exchange transfusions as treatment for acute hepatic failure.39-41 Complications of plasma exchange or plasmapheresis included pulmonary edema, infection, and hypocalcemia from citrate intoxication.41 In addition, intracellular, protein- and tissue-bound toxins were not effectively removed, and there was a theoretic risk of removing unidentified hepatotropic molecules from the circulation.42,43 Although use of plasmapheresis continues today in some centers,44,45 it has largely been abandoned as a treatment of acute hepatic failure.

Acellular filtration systems

Hemodialysis and sorbent hemoperfusion

The success of hemodialysis in treating renal failure in the 1960s encouraged many clinicians to use unmodified hemodialysis for the treatment of acute hepatic failure. Ammonia had been implicated as the molecule responsible for causing hepatic encephalopathy, and although ammonia is removed with dialysis, serum ammonia levels are not substantially lowered with hemodialysis.46 This lack of effectiveness of hemodialysis in the treatment of hepatic encephalopathy led to the development of other filtration devices.

Sorbent hemoperfusion describes the circulation of blood over a sorbent material for the purpose of removing certain molecules from the blood. There are three main classes of sorbents used: charcoal-based sorbents1; synthetic resins3; and anion exchange resins. Charcoal
efficiently removes molecules in the 1,000 to 1,500 kDa range, but removes neither protein-bound molecules nor ammonia very effectively. Resins, on the other hand, are more effective at removing lipid-soluble molecules and protein-bound molecules than smaller, unbound molecules. Potential complications of charcoal hemoperfusion dialysis include platelet aggregation, release of vasoactive substances during platelet activation, and hemodilution that occurs with priming the charcoal column. Charcoal is either coated with albumin or encapsulated in hydrophilic gels such as cellulose to minimize the complement-activation and loss of platelets and neutrophils associated with untreated charcoal. Despite early clinical reports and animal studies showing benefit of charcoal hemoperfusion in the setting of acute liver failure and ischemia-induced liver injury, a controlled study of 137 patients with fulminant hepatic failure showed no survival benefit to charcoal hemoperfusion.

**Hemodiafiltration**

Hemodiafiltration combines charcoal hemoperfusion with a cation exchange resin for improved clearance of positively charged molecules. The procedure was first made available for clinical use as the BioLogic-DT sorption-suspension dialyzer (HemoCleanse Inc), which used a cellulose plate dialyzer, a suspension of powdered charcoal, and a powdered sodium-loaded cation exchanger to selectively remove toxins of up to 5,000 daltons and some protein-bound toxins. The treatment was carried out in a fashion similar to hemodialysis: the patient’s blood was removed through a venous catheter, circulated through the circuit including the dialyzer, the cation exchanger, and the charcoal before returning to the patient’s circulation through the same catheter. The few prospective randomized trials performed with the BioLogic-DT system were unable to show any improvement in survival rate for patients with liver failure and encephalopathy, although some studies did demonstrate some improvement in neurologic function. In 2001, HemoCleanse recalled parts for the BioLogic-DT system. The HemoCleanse Biologic-DT system is no longer available in the US, but will instead be succeeded by the second-generation HemoCleanse-DT device. Unlike the BioLogic-DT system, this second-generation device will be an add-on unit that can be used to modify existing kidney dialysis units for use in liver failure, avoiding the need for a “stand-alone” or dedicated liver dialysis device.

**Albumin dialysis**

The levels of many endogenous molecules found in the intracellular compartment become elevated when acute or acute-on-chronic liver failure impairs albumin synthesis. These molecules include bilirubin, albumin, aromatic amino acids, bile acids, bilirubin, endogenous benzodiazepines, mercaptans, nitric oxide, prostacyclins, and tryptophan. Many potentially toxic therapeutic drugs such as phenytoin are also albumin bound. The capability to bind such molecules formed the basis for the use of albumin as a dialysate in attempts to treat acute and acute-on-chronic liver failure. To date, this has been the liver support device most frequently studied worldwide.

The Molecular Absorbent and Recirculating System (MARS) (Teraklin AG) is currently the most commonly used system for performing albumin dialysis. It is an acellular system that uses extracorporeal albumin dialysis for removal of both water-soluble and protein-bound toxins. The patient’s blood flows through a catheter through an extracorporeal circuit into a hemodialyzer containing a special hollow fiber membrane with albumin-related binding sites that have a 50- to 60-kd limit. This limit prevents the endogenous albumin, hormones, and carrier proteins from passing through the membrane. A counter-current, recirculating albumin solution cleanses the outside of the membrane. This mechanism produces the driving force for protein-bound toxins to pass through the MARS membrane and bind to the albumin in the dialysate. The binding solution is then regenerated using charcoal and is dialyzed itself by a buffered aqueous solution removing toxins such as urea nitrogen and plasma creatinine. After this regeneration, the membrane can be cleansed again by the purified albumin solution. The mean duration of treatment for a 75-kg patient at a flow rate of 200 mL/h is about 6 hours. The coagulopathy present in most patients with liver failure obviates the need for heparin in the extracorporeal circuit in most patients treated with the MARS system.

Early reports on the use of MARS in treatment of acute liver failure demonstrated an attenuation of the hyperdynamic circulation (eg, decrease in systemic vascular resistance and increase in heart rate), even after
a single treatment session. MARS also appears to ameliorate hepatic encephalopathy and decrease the elevations of intracranial pressure (ICP) often seen in acute liver failure. Three patients monitored with intraparenchymal ICP monitors showed a decrease in ICP from 17.3 mmHg (range 12 to 22 mmHg) before treatment to a mean of 11.3 mmHg (range 10 to 13 mmHg) after treatment. Monitoring the jugular bulb oxygen saturation showed a decrease in cerebral oxygen extraction concurrent with a clinical improvement in neurologic status. These improvements in hepatic encephalopathy appear to be independent of plasma ammonia levels or hemodynamic status.

A phase I trial of the MARS system, reporting on the outcomes of nine patients with acute liver failure treated with the MARS system, showed considerable decreases in ammonia and creatinine. Large increases in factor VII levels, albumin levels, and the ratio of branched-chain amino acids to aromatic amino acids were also seen (suggesting recovery of the native livers’ synthetic function). Considerable decreases were seen in ICP and in the severity of hepatic encephalopathy. There were no notable differences in hemodynamic parameters while on the MARS system as compared with baseline values. Of the nine patients, three were bridged to transplantation and one regained full liver function. Shortly after this phase I report, a prospective randomized controlled trial examining the effectiveness of MARS for acute-on-chronic liver failure was published. This trial was stopped early by the study’s ethics committee because of a notable decrease in patient mortality seen with MARS treatment (8.3% 30-day mortality with MARS versus 50% with medical treatment alone; p = 0.0027 in a two-tailed Fisher’s exact test). All patients had a Child-Pugh-Turcotte score of seven or higher. Substantial improvement in hepatic encephalopathy and biochemical parameters, including creatinine, bilirubin and bile acid levels, were also reported after treatment with the MARS system.

The use of MARS for the treatment of hepatorenal syndrome was recently reported. The outcomes of eight patients with type I hepatorenal syndrome treated with MARS and hemodiafiltration were compared with those of five patients who underwent hemodiafiltration alone. All patients had multiorgan failure and a Child-Turcotte-Pugh Score of 12 or higher. The authors reported considerable improvements in serum sodium, serum creatinine, serum bilirubin, and prothrombin time, but no difference was seen in serum albumin, urine output, or mean arterial pressure. MARS treatment did result in a marked increase in mean survival time (25.2 ± 34.6 days in the MARS + hemodiafiltration group versus 4.6 ± 1.8 days in the hemodiafiltration alone group).

Other situations in which MARS has been used include intractable pruritis from hepatitis C or primary biliary cirrhosis, Wilson’s disease, benign recurrent intrahepatic cholestasis, rofecoxib-induced liver injury, liver failure after paracetamol intoxication, primary nonfunction after liver transplantation, cytotoxic mushroom poisoning, acute chromium-copper intoxication, and acute-on-chronic liver failure, all with varying degrees of success.

Recent publications from the International MARS Registry, summarizing the treatment of 176 patients who underwent treatment with MARS have demonstrated that MARS treatment does not lead to severe adverse effects and is beneficial in the treatment of hepatic encephalopathy. A recent metaanalysis, however, reviewed four randomized trials and two nonrandomized trials of MARS therapy for acute-on-chronic liver failure. Only one of the four randomized trials showed a survival benefit associated with MARS treatment, and the metaanalysis of the four randomized trials demonstrated no overall benefit to MARS treatment. In contrast, both of the nonrandomized trials demonstrated survival benefit. Considering the differences in study design, however, it is probable that the different results seen in the randomized and nonrandomized trials might, at least in part, be attributable to patient selection.

The Prometheus system (Fresenius Medical Care AG) represents a variant of albumin dialysis. Incorporating fractionated plasma separation and adsorption with high-flux hemodialysis with a 250 kd semipermeable membrane, the Prometheus system claims better filtration of albumin-bound substances than MARS. A recent publication reported the use of the Prometheus system for 11 patients with acute-on-chronic liver failure and hepatorenal syndrome. Substantial decreases in serum levels of bilirubin, urea, creatinine, and ammonium were seen, but treatment yielded no improvement in degree of encephalopathy, Child-Pugh-Turcotte score, Glasgow Coma score, or Apache score. Complications seen during treatment included hypotension and decreases in albumin and white blood cell counts.
Use of allogeneic livers

Whole and partial liver allografts

Orthotopic liver transplantation has drastically changed the treatment of patients with fulminant hepatic failure, improving long-term survival from 10% to 75% to 40% to 75%. So it remains the gold standard treatment for fulminant hepatic failure.2 The demand for donor livers far outweighs the supply, however: currently more than 17,000 patients are on the liver transplant waiting list in the US, although in the previous calendar year only 5,671 liver transplantations were performed.82 Both the number of people on the waiting list and the average waiting time for a liver transplant have increased, but the number of transplantations performed has increased only gradually over the past 10 years. Orthotopic liver transplantation is irreversible, mandating patients to a lifetime of immunosuppression and its sequelae. In the case of fulminant hepatic failure, this may be unnecessary because the patient’s liver is structurally normal and possibly able to recover after an episode of fulminant hepatic failure.83 But it remains difficult to distinguish patients capable of spontaneously recovering from fulminant hepatic failure from those who would die without a liver transplant.

New techniques have been developed to overcome the shortage of donor organs, including reduced liver, cadaveric split-liver transplantation, and living donor liver transplantation. Split-liver transplantation, initially reported by both Pichlmayr and colleagues84 and Bismuth and associates85 in 1989, consists of dividing a liver graft from an adult donor into two parts. Most commonly, the left lateral segment (Couinaud segments 2 and 3) are transplanted into a pediatric recipient, while the remaining extended right trisegment graft (Couinaud segments 1,4 to 8) are transplanted into an adult recipient.86 It has been predicted that maximal use of split-liver transplantation, that is, splitting all adult livers that are appropriate for the procedure, would increase graft availability by 15% to 25%, enough to supply liver grafts for all patients on the pediatric liver waiting list.87 Recent series have demonstrated equivalent patient survival rates for split-liver transplantation and whole organ transplantation,88-90 although at least one series has shown decreased survival in adults with the highest level of urgency for transplantation compared with survival in patients with less urgent status.90

Living donor liver transplantation has also been used to circumvent the problem of insufficient donor organ supply. This has been used for pediatric patients and adults with fulminant hepatic failure, with patient survival rates ranging from 66% to 90%.91-93 Although living donor liver transplantation has many proponents, at least as many have been critical of the procedure, pointing to some of the potential dangers associated with living donors. First, there is a marked rate of donor morbidity (reported to be as high as 50%) and donor mortality (estimated to be 0.2% to 0.3%).94-97 Many have raised ethical questions doubting the ability of a donor, often a parent of a child for whom few other treatment options exist, to provide consent that is truly informed.98-101

Other strategies have focused on bridging patients with fulminant hepatic failure to recovery by providing only temporary support. Auxiliary liver transplantation has been proposed as one such means of temporary support. In initial auxiliary liver transplantation attempts, the donor liver was placed in a heterotopic position below the native liver.102-106 More recently, the procedure has been modified by performing a partial hepatectomy, then placing a split-liver allograft in orthotopic position, replacing the resected segments of native liver.107 The rationale for this procedure is that by maintaining the native liver in situ, immunosuppression can be weaned after recovery of the native liver. The donor allograft would then either be removed or allowed to atrophy. The most recent series reported 18 auxiliary liver transplantation procedures in 17 patients with acute liver failure (ie, one retransplantation). The 1-year patient survival rate was 65%, and 11 were reportedly alive after a range of 2 to 7 years posttransplantation. Interestingly, regeneration of the native liver occurred in 8 of the 11 survivors (72%), obviating the need for immunosuppressive therapy in 6 of these survivors (54%).107

Total hepatectomy and delayed orthotopic liver transplantation

Total hepatectomy may improve the survival of a subset of patients with acute or acute-on-chronic liver failure and allow patients to be “bridged” until a liver allograft becomes available for transplantation. This two-staged procedure has been reserved for patients with “toxic liver syndrome,” defined by the presence of cardiovascular shock, renal failure, and respiratory failure. In particular, total hepatectomy and delayed orthotopic liver trans-
plantation have been reported for about 50 patients for causes that include fulminant hepatic failure, primary nonfunction, hepatic trauma, acute-on-chronic liver failure, and spontaneous liver rupture secondary to the syndrome of hemolysis, elevated liver function tests, low platelets syndrome, and preeclampsia. In such patients, a portocaval shunt is performed, and the patient is often kept in the operating room until the liver transplantation can be performed. Anhepatic times are typically less than 24 hours, but intervals as long as 48 hours have been reported. It is presumed that hepatectomy improves patient physiology when the failing liver is necrotic, removing a potential source of tumor necrosis factor-α, interleukin-6, and other cardiodepressive factors. Total hepatectomy may ameliorate cerebral edema, metabolic acidosis, and hemodynamic alterations.

Extracorporeal perfusion of whole allogenic livers

Another strategy to provide temporary support to patients with fulminant hepatic failure is the concept of extracorporeal whole-liver perfusion. In this procedure, the arterial and venous blood flow of a patient with fulminant hepatic failure is connected to an isolated, allogeneic whole liver by a circuit. This circuit most often leads from the patient’s radial or posterior tibial artery to the portal vein of the isolated liver, then from the suprahepatic inferior vena cava of the liver to the patient’s radial or posterior tibial vein. A few reports have summarized the experiences of using extracorporeal perfusion of allogenic livers deemed unsuitable for orthotopic transplantation in patients with acute hepatic failure. One published study reported no survivors more than 48 hours after initiation of this procedure. In another series of three patients, improvement in biochemical parameters occurred in all three reported patients, with two of these patients successfully bridged to orthotopic liver transplantation. Despite these advances, drastic increases in waiting list time necessitate the need for more efficacious support methods for these patients until donor livers can be procured.

Hepatocyte transplantation

The concept of transplanting liver tissue or individual hepatocytes was reported as early as the 1890s by Alessandri and Ribbert, the latter performing autotransplantation of small pieces of rabbit and guinea-pig liver into various locations that included the peritoneum, lymph glands, anterior chamber of the eye, and under the skin. Cameron and Oakely described autotransplants of rabbit liver cells into the peritoneum and under the abdominal skin. Although some proliferation of hepatocytes and bile ducts was seen initially, by 10 weeks after the transplantation, all hepatocytes had degenerated and been reabsorbed. Interest in the transplantation of hepatocytes declined, only to resurface within the past 3 decades.

There are many potential advantages that the transplantation of hepatocytes would have over orthotopic liver transplantation. First, a major operation and all its attendant risks, including anesthetic complications, surgical site infections, and complications from the use of venovenous bypass, would be avoided. This would be especially appealing for patients with end-stage liver diseases and structurally normal liver (eg, inborn errors of metabolism). Another advantage is that the native liver is left in place. This would allow for hepatocyte transplantation to act as a temporary measure for such patients, providing support until the native liver recovers and avoiding the need for life-long immunosuppression. Finally, it has been estimated that about 10% to 20% of the normal liver mass is enough to provide adequate hepatic function. Assuming that a high yield of isolated hepatocytes is obtained from a whole liver, this suggests the possibility of transplanting multiple patients with liver failure from a single whole liver. Hepatocyte transplantation would not, however, be able to easily treat patients with end-stage liver disease from cholestatic disease or end-stage liver disease with accompanying portal hypertension, because these livers are abnormal in structure. In addition, complications related to the infusion of hepatocytes into the portal vein may paradoxically worsen portal hypertension in patients with chronic liver disease.

Cells for use in hepatocyte transplantation

Human hepatocytes are the most frequently studied cell source for use in hepatocyte transplantation. Primary human hepatocytes would likely provide the functions needed to ameliorate acute liver failure, but have a limited viability in culture, and quickly lose functional capacity. Hepatocytes may be “immortalized” with SV40 virus-transfected oncogenes to allow unlimited growth and preserved function while in culture. Such cells do have an increased potential for spontaneous, carcinogen-induced, or oncogene-induced neoplastic
Hepatocytes may also be obtained from a patient with liver failure, grown in culture, and genetically modified ex vivo before reimplantation into the patient. A pilot trial using this strategy for familial homozygous hypercholesterolemia reported some transgene expression at least 4 months after reimplantation. Other cell sources that may be available options in the future are any of the cell lineages that are purported to have the capacity to function as a liver “stem cell,” including: oval cells, cholangiocytes, small hepatocyte-like progenitor cells, bone marrow-derived cells, the so-called “side population” cells, and embryonic stem cells.

**Previous clinical hepatocyte transplantation attempts**

At least 50 clinical hepatocyte transplantations have been performed in the US to date. Indications have included liver failure secondary to ornithine transcarbamoylase deficiency, Crigler-Najjar syndrome, \( \alpha \)-antitrypsin deficiency, total parenteral nutrition-and sepsis-induced liver failure, herpes simplex hepatitis, acute or fulminant hepatic failure, and acute-on-chronic liver disease.

The results of hepatocyte transplantation for fulminant hepatic failure or acute-on-chronic liver failure are difficult to interpret, because many of these patients improve with supportive therapy alone. With this in mind, some noteworthy outcomes have been reported. Strom and colleagues published the results of hepatocyte transplantation in five patients with grade III or higher hepatic encephalopathy and multisystem organ failure. These patients were compared with four controls with a similar severity of liver disease. All patients received prostaglandin E₁, cyclosporine, and steroids. After infusion of hepatocytes into the spleen, patients experienced a considerable improvement in their clinical status and improvement in various end points: mean ammonia level of 194 micromol/L before transplantation versus 57.6 after transplantation; aspartate transaminase, 308 versus 58.4 U/L; and IC pressure (ICP) of 20.3 versus 7.3 mmHg. The four control patients, in contrast, experienced no substantial difference in these parameters. Of the five patients in the treatment group, three went on to receive whole organ allografts; these patients were subsequently discharged home and, after 20 months of followup, are alive. One patient had cortical infarcts and a deteriorating neurologic status; the family withdrew life support. Another patient sustained a subdural hematoma related to the intracerebral monitor. At least one patient with hepatocyte transplantation performed for Crigler-Najjar syndrome type I has demonstrated long-term survival of the transplanted hepatocytes. In this case, a 10-year-old girl with this syndrome received two transusions of allogenic hepatocytes as a portal vein infusion. Functional levels of hepatic uridine diphosphoglucuronate gluuronosyltransferase, the enzyme genetically deficient in the syndrome, increased 14-fold after the infusions. The transplanted hepatocytes were reported to have survived at least 9 months. Additional attempts with longterm followup are needed to fully assess the role of hepatocyte transplantation in treating acute and chronic liver disease.

**Use of xenogenic livers**

The scarcity of human liver donors has led to interest in the use of xenogenic livers for the treatment of human liver failure. Although nonhuman primates and pigs have been studied as potential sources of xenogenic liver tissue in the past, the Food and Drug Administration has discouraged the use of nonhuman primate organs in clinical studies, and obtaining FDA approval of any therapies using nonhuman primate organs is difficult. Pigs, as a result, have become the most likely prospective xenogenic organ donors. Humans have a long history of breeding pigs, and breeding pigs is cheaper and less time consuming than breeding nonhuman primates. Pig livers are also a better size match for adult humans than nonhuman primates. Substantial advances have been made in cryopreservation and longterm maintenance of porcine hepatocyte cultures, and researchers have more experience with the genetic manipulation of pigs than other species. Unlike many nonhuman primates, porcine hepatocytes are not susceptible to many human diseases, including hepatitis B. Many species of nonhuman primates are endangered, and ethical objections to the harvesting of organs from pigs are less frequent than objections to harvesting organs from nonhuman primates.

There may, however, be an inherent limit to the ability of xenogenic hepatocytes to treat liver failure and restore normal physiology to a human patient. The porcine liver makes more than 2,000 proteins, many of which have little or no function in humans, and the effectiveness of the porcine liver in detoxifying human blood has also been questioned.
averages only 15 years; such a short lifespan raises questions about the longterm durability of such grafts. The most formidable barriers to successful xenotransplantation to date, however, are xenograft rejection and the potential transmission of zoognoses.

**Xenograft rejection**

Grafts from phylogenetically similar species such as baboon or chimpanzee demonstrate rejection on a delayed time frame similar to that of allogeneic grafts. Such grafts are termed *concordant xenografts*. In contrast, grafts from phylogenetically distant species such as pigs are termed *discordant xenografts*. Unlike concordant xenografts, discordant xenografts elicit hyperacute xenograft rejection, a complement- and preformed antibody-mediated process that results in microvascular thrombosis, interstitial hemorrhage, and the destruction of the xenograft within minutes of perfusion. Because pigs have become the preferred xenogenic liver graft source, researchers have investigated methods of overcoming the hyperacute xenograft rejection process elicited when a pig liver is transplanted into a human. This hyperacute xenograft rejection is mediated mainly by preformed antibodies directed against the pig gal-α1,3-gal (“gal”) cell surface antigens and other antipig antibodies. Humans develop pronounced titers of antigel antibodies through previous exposure to porcine tissue or, more commonly, through exposure to a similar α-gal trisaccharide epitope present on normal human bacterial flora. Complement and preformed antipig antibodies are sufficient for this T-cell independent process, so immunosuppression medications do not seem capable of modifying the host’s hyperacute xenograft rejection response.

Several strategies have been devised to decrease or eliminate the hyperacute xenograft rejection process, including depletion of antipig antibody and complement using plasmapheresis and the development of transgenic pigs that coexpress pig and human cell-surface antigens. To date, these strategies have been unsuccessful. A major advance in overcoming hyperacute xenograft rejection has been the development of a heterozygous galactosyltransferase knock-out pig in 2001, followed by the development of a homozygous galactosyltransferase knock-out in 2002. Organs from these galactosyltransferase double-knockout pigs do not appear to elicit hyperacute xenograft rejection.

Xenografts surviving beyond the phase of hyperacute rejection are, like human allogeneic livers, subject to acute humoral and acute cellular xenograft rejection. Acute humoral xenograft rejection is mediated by T-cells, IgM, and IgG that is directed mainly, but not exclusively, at the gal epitope, causing endothelial cell swelling, interstitial fluid extravasation, and graft destruction within 24 hours of perfusion. Acute cellular xenograft rejection is a T-cell mediated cellular response that also targets xenogenic cells. Finally, a chronic xenograft rejection process leads to graft vasculopathy not unlike that seen in the chronic vascular rejection of vascularized allografts. Because these processes are cell mediated, xenotransplantation proponents hope that these forms of rejection can be ameliorated with pharmacologic immunosuppression.

**Porcine and primate zoonoses**

A second and perhaps more dangerous obstacle to xenotransplantation is the potential for zoonoses, or infectious agents of animal origin that have the potential to infect humans. Zoonoses are problematic because they may be undetectable in their animal hosts yet cause substantial morbidity when transmitted to another species, especially if immunosuppressed. The recombination or reassortment of zoonoses with human proteins or molecules may result in new pathogenic entities that might subsequently be transmitted from human to human. Primates are known to have been the source of several known zoonoses, many of which are retroviruses. Chimpanzees have been found to carry simian immunodeficiency virus and human immunodeficiency virus is thought to have originated in African monkeys. Transmission of baboon cytomegalovirus was detected in a recipient of one of the only two reported cases of baboon-to-human liver xenotransplantation. Primates are not the only animals that have been the source of recent zoonoses, however, as evidenced by the recent endemics of bovine spongiform encephalopathy, Creutzfeldt-Jakob disease and avian flu. The two self-replicating viruses specific to pig are porcine endogenous retrovirus (PERV) and porcine cytomegalovirus (CMV). PERV has been found to infect many types of human tissue cells lines in vitro, including human B- and T-cells, fibroblasts, and kidney epithelial cells, and has been shown to infect immunodeficient mice in an animal model of pancreatic islet xenotransplantation. Despite these animal studies demonstrating that in vivo transmission of PERV does occur, there is no evidence of PERV transmission to patients exposed...
to viable porcine tissue, including patients treated with bioartificial liver devices that include porcine cells or extracorporeal perfusion of porcine kidneys. Some patients, however, have exhibited persistent microchimerism (ie, presence of viable porcine cells in the circulation of the patient) for more than 8 years after treatment with such devices. Although this may represent a longterm repository of potentially infectious retrovirus, the true clinical relevance of this microchimerism is not known. Porcine CMV is a virus similar to human CMV. Cross-species transmission of porcine CMV has been demonstrated in a pig-to-baboon model of kidney xenotransplantation, and active CMV infection was thought to be responsible for the death of at least one baboon in the study.

**Ex vivo xenogenic liver perfusion**

Although the use of the isolated, perfused liver as an experimental model for hepatic metabolism had been in use since 1855, its use for the augmentation of liver function was first reported by Otto and associates in 1958 after their work with Eck fistula (portosystemic shunt) in dogs. During the 1960s, ex vivo perfusion of xenogenic livers was used at many centers as a means of treating liver failure. This was performed by connecting a patient to an isolated, cooled liver through an arteriovenous fistula for a period of approximately 13 to 16 hours. Livers of many different species were used, including calves, baboons, pigs, and lambs, though pig livers were the most commonly used. There have been no randomized trials comparing ex vivo perfusion of isolated livers to standard medical therapy. In a review of 40 patients who experienced 90 episodes of deep hepatic coma, the use of ex vivo perfusion resulted in recovery in 37%, improvement in 45%, and no change in 18% of patients. Among a subset of patients with acute hepatitis and liver cell necrosis who underwent ex vivo perfusion, survival was 35%. The procedure has been largely abandoned because of the advent of success with orthotopic liver transplantation, though there has been intermittent reinterest in its use as a bridge to transplantation.

**Orthotopic liver transplantation with xenogenic livers**

Whole organ xenotransplantation using chimpanzee livers was attempted three times at the University of Pittsburgh between 1966 and 1973. Patient survival ranged from 0 to 14 days, but there was no evidence of hyperacute rejection on postmortem examination. Between June 1992 and January 1993, Starzl and associates reported two cases of whole organ xenotransplantation using baboon liver. The first patient died after 26 days. The second patient, who had pretransplant HIV and hepatitis B infections, survived 70 days after transplantation before succumbing to disseminated aspergillosis. Complement activation, preformed immunoglobulin M, and potentially toxic synthetic products of the baboon liver have also been implicated in the deaths of these two recipients of baboon livers. Baboon cytomegalovirus, as noted above, was detected in the peripheral leukocytes of the second baboon liver xenotransplant recipient after his death.

The most recent attempt at clinical xenogenic liver transplantation occurred in 1995, when Makowa and colleagues transplanted a porcine liver into a woman with fulminant hepatic liver failure and a history of autoimmune hepatitis. The patient was comatose but without evidence of brain herniation. The patient received preoperative plasmapheresis to remove preformed antipig antibodies, and ex vivo perfusion of the pig kidneys was performed for 1 hour before liver transplantation as an additional means to remove antipig antibodies. Despite pre- and intraoperative immunosuppression with four different agents, deposition of complement and antipig antibody caused endothelial swelling as early as 3 hours after revascularization of the xenograft. Hepatopetal portal flow, improved clearance of serum lactate, and decreased prothrombin time was seen up to 24 hours after transplantation, but by the time a suitable allogenic liver donor became available 36 hours post-transplant, massive cerebral edema developed and the patient was pronounced dead. No attempts at xenogenic liver transplantation have since been reported.

**Use of hybrid devices**

The first clinical use of an “artificial liver” was reported in 1959 by Seiji Kimoto from the Tokyo University School of Medicine. The circuit designed by Dr Kimoto included cation and anion exchange reactors, a cellophane dialysis membrane, and one or more donor animals. Dr Yukihino designed a circuit that implemented exchangeable liver slices, representing the first predecessor of the current bioreactor design. Since then, it has been recognized that the functions of the liver are many and complex. Although the ideal liver support device would replace or augment all of these functions, a device...
that could effectively remove toxins involved in the pathogenesis of hepatic encephalopathy alone would represent a notable improvement in the care of patients with liver failure. Because hybrid devices are used as a temporary solution until a suitable donor liver is found, they must also be readily available on demand, easy to use, and cause no harm to the patient.3,179 To date, there is no consensus on terminology to be used to denote biologic systems with hepatocyte function. Virtually every combination of terms (and their corresponding acronyms) expressing “liver” and “support” or “assist” have been proposed or used in recent literature (see Table 1).

**Bioreactor design**

The central feature of a bioartificial liver assist device is a “bioreactor,” a hollow container in which a semipermeable membrane is used to allow hepatocytes contact with whole blood or plasma while preventing efflux of these hepatocytes into the patient’s circulation.180 Estimates of the minimum quantity of hepatocytes needed to improve the clinical condition of a patient with acute liver failure range from as little as 15 billion hepatocytes (150 g, or 10% of normal liver mass) to as much as 36 billion hepatocytes (360 g).181,182 The semipermeable membrane has pores large enough to allow for the influx of plasma, albumin, and toxins implicated in the pathogenesis of acute liver failure and hepatic encephalopathy, yet small enough to prevent exposure of the hepatocytes to immunoglobulins, complement, and immunocompetent cells.183 But designing an effective semipermeable membrane based on pore size has been difficult. Viral particles may range from 30 to 200 nm in size, and hepatoma cells have been found to pass through membranes with a molecular weight cut-off as small as 100 kd.140 Meanwhile, diffusion of toxins is impeded by pore sizes smaller than 200 nm,184 and many of the so-called “middle molecules” (400- to 1,500- kd molecules) purported to play a role in the pathogenesis of hepatic encephalopathy47 would have no contact with hepatocytes if a small pore size is used.

Either plasma or whole blood can be run through extracorporeal devices. The use of whole blood is simpler, but is associated with thrombocytopenia and hemolysis and requires anticoagulation with heparin (prohibitive in patients with invasive IC pressure monitoring devices185). Plasma, on the other had, can be infused through the extracorporeal device by removing the cellular components of blood with a plasma separator. This lessens the thrombocytopenia and hemolysis but requires citrate for anticoagulation.45 Hepatocytes in the bioreactors are dependent on oxygen delivered by the fluid circulating through the circuit. The oxygen content of plasma is greatly decreased compared with that in whole blood, but may be maintained at adequate levels when oxygenation is added to the circuit43 and flow is maintained at a high rate (as much as 5L/min may be needed).186

**Cells for use in hybrid devices**

Although primary human hepatocytes would naturally seem like the optimal cells to replace or augment the function of the failing liver, there are practical limitations that have thus far precluded their use. First, although primary human hepatocytes have remarkable regenerative capacity in vivo, such hepatocytes are difficult to maintain in vitro because they replicate only a finite number of times and require an “anchor” for cell polarity.183,187 Hepatocytes also have a decreased level of function in culture, a problem thought to be related to the loss of gap junctions in culture.188,189 This ultimately leads to loss of phenotype190 and altered metabolism.191 Cryopreservation, which makes storage and transport more convenient, compounds this problem by additionally decreasing function and viability.186 Attaching hepatocytes to a matrix simulates the architecture of the hepatic parenchyma and may stimulate cell-cell interaction, facilitating hepatocyte growth and the maintenance of cell polarity in vitro.192

Alternatives to primary human hepatocytes have been considered. The C3A/HepG2 cell line is derived from a subclone of the HepG2 human hepatoblastoma cell line.190 Interest in the use of these cells stems from the desire for unlimited expansion in vitro. Disadvantages of the C3A/HepG2 cell line include metabolic activity that is inferior to that of primary hepatocytes187.

**Table 1. Terms Currently Applied to Describe Liver Support Devices**

<table>
<thead>
<tr>
<th>Bioartificial liver (BAL)</th>
<th>Bioartificial liver assist device (BLAD)</th>
<th>Extracorporeal hepatic support (ECHS)</th>
<th>Extracorporeal liver assist device (ELAD)</th>
<th>Extracorporeal liver perfusion (ECLP)</th>
<th>Extracorporeal liver support (ELS)</th>
<th>Liver support system (LSS)</th>
<th>Liver assist system (LAS)</th>
</tr>
</thead>
</table>

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and the theoretic risk of tumorigenesis,\textsuperscript{3} which may be decreased by certain countermeasures.\textsuperscript{183} The availability of porcine hepatocytes allows for facile preparation and mass distribution. Immune rejection of xenogenic tissue is not a major problem for extracorporeal devices because the xenogenic hepatocytes are separated from interaction with lymphocytes and antibody by polymer or membrane barriers.\textsuperscript{193} What remains unclear, however, is the degree to which species-specific hepatocyte function may result in metabolic incompatibilities when porcine hepatocytes are used in hybrid liver assist devices.\textsuperscript{194}

**Hybrid liver assist devices currently used in clinical studies**

In addition to the MARS system, many hybrid devices are among the support systems currently being evaluated in clinical trials (Table 2). The Arbios Systems, Inc HepatAssist Liver Support System is an extracorporeal liver support device that incorporates 5 billion cryopreserved porcine hepatocytes on collagen-coated dextran beads, a feature that increases hepatocyte surface area, restores cell polarity, and promotes cell-cell matrix interactions.\textsuperscript{185} Porcine hepatocytes are isolated, cryopreserved, stored in a central location, and then shipped as needed when required for clinical use. Venous blood is withdrawn through a double lumen catheter placed in the superficial femoral vein. The plasma component of the blood is then anticoagulated with citrate, circulated through two charcoal columns, and then passed through a heater, an oxygenator, and finally, a hepatocyte-lined hollow fiber column (Fig. 1). Consisting of a 0.2-micron semipermeable membrane of porous polysulfone fibers.\textsuperscript{195} The effluent is remixed with the cellular blood components, then reinfused back into the patient. The treatment lasts about 6 hours.\textsuperscript{185} A pilot study of 10 patients with acute liver failure demonstrated that HepatAssist treatment substantially decreased serum total and direct bilirubin, alanine trasaminase, and albumin, but also decreased platelet count, fibrinogen level, and factor V levels. Neurologic improvement was seen in six patients, and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Molecular Absorbant and Recirculating System (MARS)</th>
<th>Prometheus</th>
<th>HepatAssist</th>
<th>Extracorporeal Liver Assist Device (ELAD)</th>
<th>Bioartificial Liver Support System (BLSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer (location)</td>
<td>Teraclin AG (Rostock, Germany)</td>
<td>Fresenius Medical Care AG (Bad Homburg, Germany)</td>
<td>Arbios Systems, Inc (Los Angeles, CA)</td>
<td>Vital Therapies, Inc (San Diego, CA)</td>
<td>Excorp Medical, Inc (Oakdale, MN)</td>
</tr>
<tr>
<td>Cell source</td>
<td>None (acellular)</td>
<td>None (acellular)</td>
<td>Primary porcine hepatocytes</td>
<td>Human C3A hepatoma cell line</td>
<td>Primary porcine hepatocytes</td>
</tr>
<tr>
<td>Biorector</td>
<td>Hemodialyzer with hollow-fiber membrane</td>
<td>Hemodialyzer with AlbuFlow filter and fractionated plasma separation and adsorption</td>
<td>Hollow-fiber cartridge with collagen-coated dextran beads and sorbent compartments</td>
<td>Ultrafiltrate generator with fiber semipermeable membrane</td>
<td>Hollow-fiber cartridge</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Coaguloathy, disseminated intravascular coagulation</td>
<td>Hypotension, decreased albumin and white blood cell counts</td>
<td>No substantial increase in hypotension or thrombocytopenia when compared with medical therapy</td>
<td>Thrombocytopenia, hypotension</td>
<td>Hyper- and/or hypotension</td>
</tr>
<tr>
<td>Potential for zoognoses?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>FDA approved?</td>
<td>Phase I/II study completed</td>
<td>No</td>
<td>Phase II/III multicenter prospective randomized trial completed</td>
<td>Phase I/II study completed</td>
<td>Phase I/II study in progress</td>
</tr>
</tbody>
</table>

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![Figure 1. HepatAssist-2 liver support system circuit.](image-url)
hemorrhagic complications were seen in five patients. All 10 patients were successfully bridged to liver transplantation.\textsuperscript{160}

A phase I trial, completed in 1997, demonstrated safety of the device with use in fulminant hepatic failure and primary nonfunction of liver allografts.\textsuperscript{185} The Food and Drug Administration is now requiring, however, that the company complete a full phase III efficacy trial before the HepatAssist can be approved for noninvestigational clinical use. The device has now been evaluated with a phase II/III multicenter prospective, randomized trial. In this study, 171 patients with fulminant hepatic failure or primary nonfunction after orthotopic liver transplantation were randomized in a 1:1 ratio to standard of care or HepatAssist liver support system plus standard of care. The primary end point of the study was patient survival, with or without orthotopic liver transplantation. The 30-day patient survival rates were 62\% for standard of care alone and 71\% for HepatAssist and standard of care, a difference that did not reach statistical significance (p = 0.26). But when a time-dependent proportional hazard model was used to control for the impact of orthotopic liver transplantation on patient survival, the authors demonstrated that mortality of patients with fulminant hepatic failure was almost halved by treatment with the HepatAssist liver support system (p = 0.048). No differences were seen between the two groups in incidence of acute renal failure, brain herniation, increased IC pressure, or hypotension.\textsuperscript{163} Arbios Systems, Inc is now planning to evaluate the second generation HepatAssist-2 device (Fig. 2) in a phase III clinical trial planned for mid-2006 (Jacek Rozga MP. Personal communication, 2005).

The Vital Therapies, Inc Extracorporeal Liver Assist Device (ELAD) is similar to the HepatAssist device but instead uses a patented derivative of a human C3A hepatocyte cell line chosen for its high albumin production and its capacity to grow in a glucose-deficient medium. The device uses continuous venovenous dialysis machines in tandem with ultrafiltrate generators and four ELAD cartridges. Like the HepatAssist-2 liver support system, ELAD cartridges are prepared at a central location and delivered as needed. Three weeks are required for hepatocyte growth, maturation, and attachment to the cartridge. Each cartridge is equivalent to the hepatocyte 200 g of normal liver. The device can function for 48 to 72 hours; use up to 7 days without changing cartridges has been reported.\textsuperscript{196,197} A randomized, open la-

\textbf{Figure 2.} The HepatAssist-2 liver support system and the Performer platform used for the extracorporeal circulation of blood.
The device uses 400 to 600 g of human or porcine hepatocytes. Venovenous bypass is used to circulate a patient’s heparinized blood through a circuit consisting of a warmer, an oxygenator, and a hollow-fiber cartridge containing approximately 70 g of primary porcine hepatocytes. The molecular weight diffusion cutoff of the cellulose acetate fibers in the bioreactor is 100 kd. The initial treatment is a 1,212-hour perfusion period; after a 12-hour interval, a second 12-hour perfusion session may follow. A report of the phase I clinical trial results of four patients has shown that treatment with the Bioartificial Liver Support System is tolerated well; patients on this system presented with transient hypertension and hypotension responsive to IV dextrose and fluid administration, respectively. The completion of this phase I/II study is currently underway.

Modular Extracorporeal Liver Support System (MELS) is a liver assist device designed by Sauer and colleagues, of the Charite Virchow Clinic in Berlin, to support longterm viability and function of hepatocytes in culture. This has been accomplished with several improvements to the hollow fiber-design bioreactor. Hepatocyte adherence to the cell attachment surfaces of the reactor is stimulated by coating the surfaces with basement membrane products (including collagen type IV, laminin, heparan sulfate, and proteoglycans). Viability and cell-cell contact was promoted through hepatocyte aggregate culture and coculture with endothelial liver cells, typically separated from hepatocytes during the isolation process and discarded. The capillary system used also serves as a three-dimensional support. Hepatocytes in the MELS liver assist device demonstrate a three-dimensional tissue-like structure with cell junctions and bile canaliculi-like structures, resembling liver sinusoids. The device uses 400 to 600 g of human or porcine primary hepatocytes to seed the bioreactor. Hepatocyte viability and function can be maintained for at least 3 weeks in the MELS device.

Primary human hepatocytes have been used in the MELS device to successfully bridge three patients with acute liver failure to transplantation. Primary porcine hepatocytes were used in the MELS device for another eight patients with acute liver failure. These patients were given continuous support from 8 to 24 hours. Treatment was well tolerated, with no short- or longterm sequelae reported. All eight patients were successfully bridged to transplantation and have remained alive at 3 years or more after transplantation.

**Future developments in hybrid assist devices**

Also in development are devices using polyurethane foam modules with pores in which hepatocytes form multicellular spheroids capable of maintaining hepatocyte function for at least 10 days in culture. The circuit runs plasma through the bioreactor using a plasma separator. Preclinical studies using rat, dog, and pig liver failure models were successful.

A group of researchers representing Monsanto Co reported on a bioreactor in which hepatocytes were not cultured on flat plates but rather allowed to circulate and collide and form aggregates more similar to the structure of the liver parenchyma. These aggregates were formed using a packed bed of glass beads. Hepatocytes were reportedly viable for up to 15 days in this culture. This design was marketed by Exten Industries (Xenogenics Corporation) as the Sybiol synthetic bio-liver device, and phase I trials were planned for 2002. But Exten Industries opted to do more testing, in an effort to financially restructure the company, before moving forward into clinical trials.

Other researchers have investigated the possibility of a totally implantable, nonmechanical hybrid device. Using a rat partial hepatectomy model, one group implanted 25 × 10^6 allogenic rat or xenogenic guinea pig hepatocytes into a device with semipermeable hydrogel membranes constructed with hollow fibers. This device was placed into the peritoneum of posthepatectomy rats. Survival of groups of rats who had received the implantable bioartifical liver was considerably better than that of groups that had not (61% to 69% versus 7% to 27% 7-day survival; p < 0.05). Histologic examination of the bioartificial livers after 7 days showed viable hepatocytes and an absence of host inflammatory cells.

In conclusion, much progress has been made since
clinicians first applied cross-circulation to patients with acute liver failure. Current strategies for supporting the acutely failing liver include albumin-based dialysis, modified techniques of orthotopic liver transplantation, hepatocyte transplantation, xenogenic liver transplantation, and hybrid bioartificial devices. Acute and fulminating hepatic failure may represent the ideal opportunity for the application of such strategies because in most cases, support is needed only for the finite period during which the liver regenerates. Other potential uses or these strategies might be bridging patients to orthotopic liver transplantation. None of the strategies described in this review has had clearly demonstrated benefits to long-term survival.

The use of these experimental strategies has been described in the literature predominately in the form of case reports or case series. Few of these experimental options have been evaluated in the context of a prospective, randomized clinical trial. Although costly, time-consuming, and challenging to design and implement, prospective randomized clinical trials using objective and clinically relevant end points represent the best study design for evaluating the efficacy of these strategies in treating patients with acute and chronic liver disease. The role of these treatment strategies will be more clearly defined, as more such trials are performed.

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