Acute hepatic failure, defined as the development of altered mental status (hepatic encephalopathy) and coagulopathy within 8 weeks of the onset of an acute hepatic disease, is a rare but lethal disease [1]. The incidence of acute hepatic failure is approximately 2000 cases per year in the United States, and the mortality rate approaches 80% in patients who do not receive liver transplants [2]. The causes of acute hepatic failure include viral hepatitis, toxins such as aflatoxins from the poisonous mushroom family *Amanita phalloides*, Reye’s syndrome, acute fatty liver of pregnancy, acute Budd-Chiari syndrome, and drug toxicities. Drug toxicities include both idiosyncratic reactions as well as drugs with predictable toxicity when taken in excess. Isoniazid, halothane, valproate, disulfiram, and phenytoin, among many others, have been reported to cause acute hepatic failure. The analgesic acetaminophen causes dose-dependent hepatic failure and is now the single most common cause of acute hepatic failure in the United States [3]. Acetaminophen toxicity may be the result of either intentional overdose during an attempted suicide or accidental overdose. The toxicity of acetaminophen is exacerbated by starvation and alcohol [4]. Acute hepatic failure causes death by producing cerebral edema, which leads to uncal herniation and brain death [5]. Cerebral edema in this setting is the end stage of hepatic encephalopathy.

**Acute hepatic failure: diagnosis and treatment**

The onset of encephalopathy is characterized by agitation, confusion, and delusions and may precede the appearance of jaundice. In most cases, coma develops rapidly, although in some instances the patient may teeter on the edge of consciousness for days or even weeks. The precise pathophysiology of hepatic encephalopathy and cerebral edema has not yet been elucidated, but evidence
suggests that it is related to an accumulation in brain of neurotoxic substances including ammonia, aromatic amino acids, mercaptans, manganese, and benzodiazepine-like substances [6,7]. Treatment with the benzodiazepine antagonist flumazenil has been shown to be effective in improving hepatic encephalopathy score, but its effects are modest at best and there are no data to suggest that flumazenil is able to prevent or even delay cerebral edema [8].

Treatment of hepatic encephalopathy using lactulose and bacterial decontamination of the gut with topical antibiotics such as neomycin is the standard therapy for patients with chronic liver disease. These treatments are usually minimally effective in patients with acute liver failure [9]. Patients with acute liver failure who progress to the confusion stage of hepatic encephalopathy should usually be transferred to an intensive care setting to monitor for the development of cerebral edema. It is sometimes difficult to recognize this stage of acute hepatic failure because patients can manifest agitation and belligerence before the development of a clouded sensorium and progressive somnolence. As cerebral edema evolves, treatment should focus on preservation of cerebral perfusion to prevent cerebral ischemia. A cornerstone in the management of cerebral edema is direct measurement of intracranial pressure [10]. Measurement of intracranial pressure is important to guide therapy, particularly intraoperatively if a liver becomes available. It can also be helpful when patients reach deep hepatic coma, a situation that can be fully reversible if herniation has not occurred. An intracranial pressure that equals mean arterial pressure is incompatible with posttransplant survival.

Cerebral perfusion pressure (systemic blood pressure minus intracranial pressure) should be maintained above 40 mm Hg. Typically, intracranial pressure fluctuates widely on a minute-to-minute basis, but persistent intracranial pressure above 20 mm Hg should be treated with mannitol (0.3 to 0.4 g/kg body weight) to an end point of 310 mOsm. Tilting the head up to 45° should be avoided because it actually decreases cerebral perfusion pressure [11]. Dexamethasone and hyperventilation, which are commonly used to prevent cerebral edema following closed-head injury, are not effective therapies for cerebral edema because of hepatic encephalopathy [12]. Pentobarbital lowers intracranial pressure and therefore may be potentially useful; however, it makes accurate clinical assessment of the patient impossible and therefore is seldom used.

The definitive treatment of patients with acute liver failure is liver transplantation. Patients in the United States with acute liver failure are currently assigned status 1 priority for transplantation by the Organ Procurement and Transplantation Network policy. Status 1 patients receive priority over other candidates for liver transplantation in their region, which amounts to an average donor pool population of approximately 25 million. Despite priority access to livers, the median waiting time for a suitable liver for all patients listed as status 1 in 2002 was 11 days [13]. Patients who are small or have an unusual blood type would be expected to wait even longer. Because cerebral edema and death may occur before a liver is available, numerous methods of bridging patients to transplantation by artificial means have been proposed. Although the ideal bridging
technology would provide synthetic as well as metabolic functions, the most important element appears to be the ability of the system to either remove or metabolize and detoxify the toxins that eventually produce cerebral edema. Support for the synthetic role of the liver can be accomplished to a significant degree by using infusions of fresh frozen plasma.

**Hepatic assist techniques**

Hepatic assist techniques can be divided into two major categories: biologic and nonbiologic. Biologic liver assist techniques include extracorporeal whole-liver perfusion and hybrid systems that involve perfusion of hepatocytes from various sources. Nonbiologic liver assist methods include plasma exchange, charcoal perfusion, hemodiabsorption, and albumin dialysis. Evaluating the effectiveness of these therapies based on the medical literature is difficult for two reasons: many studies do not use randomization, thus they are subject to selection bias, and the availability of liver transplantation confounds the analysis of efficacy because significant numbers of patients receive life-saving transplants and thus become censored from analysis.

Early attempts at liver assist methods were primarily nonbiologic. Pure hemodialysis and hemofiltration have been tried, but to date there are no data suggesting that these therapies offer a beneficial effect on cerebral edema in the setting of acute liver failure, although plasma ammonia level may be reduced. This probably relates to the fact that cerebral edema is primarily related to an accumulation of high molecular weight substances that are not removed by conventional dialysis membranes. These techniques are therefore usually reserved for patients who have acute hepatic failure with superimposed acute renal failure. Charcoal hemoperfusion has been evaluated extensively and appears to have the ability to improve physiologic parameters such as bilirubin levels; however, this method was not found to have clinically meaningful efficacy in the only randomized controlled study [14]. Currently, the hepatic assist systems that appear most promising are hemodiabsorption, albumin dialysis, and hybrid bioartificial systems.

**Hemodiabsorption**

The Biologic-DT sorbent-based hemodialysis, or hemodiabsorption can remove hepatic toxins of less than 5000 Da that are not tightly bound to protein such as aromatic amino acids, glutamine, mercaptans, benzodiazepine-like substances, false neural transmitters, ammonia, and manganese [15]. This system has been further refined by the addition of a plasma-permeable hollow-fiber plasma filter downstream from the dialyzer to improve the ability of the system to remove protein-bound toxins and large molecular weight toxins, including cytokines and bilirubin [16]. Although the system does not provide metabolic
or synthetic support, an additional potential benefit of this device may be its ability to remove deleterious inflammatory mediators [17]. Clinical trials using this type of system have shown slight improvement in the neurologic status of patients as well as improvement in some physiologic parameters in treated patients compared with controls [18,19]. An improved outcome for treated patients is suggested by the data, but to date there is insufficient evidence to conclude that this method of hepatic support achieves the goal of prevention of cerebral herniation in states of acute hepatic failure. A larger, multicenter trial will be needed to answer this important question.

**Albumin dialysis**

A novel system to efficiently remove albumin-bound toxins has been developed by Stange et al [20]. The molecular adsorbent recycling system (MARS) removes protein-bound substances by the use of a high-flux dialyzer and an albumin solution circulating on the dialysate side. This method resulted in effective removal of unconjugated bilirubin and highly protein-bound substances, and can alter the ratio of branched chain to aromatic amino acids [21]. In preclinical studies MARS appears able to improve some physiologic parameters [22–24]. In a prospective, randomized trial, MARS was shown to improve renal function in cirrhotic patients with type 1 hepatorenal syndrome [25]. As with the Biologic-DT system, however, it is not yet clear whether this system is able to alter the natural history of patients with acute liver failure. This question will be answered only by randomized multicenter trials with large numbers of patients.

**Bioartificial liver support systems**

Logically, the best method of providing complete hepatic support for a patient dying of acute liver failure would be perfusion of a whole liver through an extracorporeal system. This technique has been shown to be reasonably effective when using either human or porcine livers [26]; however, there are major practical limitations to these techniques. Concerns over porcine endogenous retrovirus transmission to the recipient have limited the applicability of porcine organs for this purpose, despite a paucity of data to date showing that porcine endogenous retrovirus transmission occurs [27,28]. Additionally, porcine livers do not appear to be as effective at complex metabolism as human livers. The availability of human livers that are suitable for perfusion but not useable for transplantation also limits the applicability of this technique. Therefore, numerous bioartificial devices have been designed to overcome these limitations. These hybrid systems use a variety of cellular components and a variety of bioreactor designs. There are currently three main types of hybrid systems. The bioartificial liver (BAL) system developed by Demetriou and co-workers [29] is composed of a bioreactor containing porcine hepatocytes perfused by plasma that has been
prefiltered through a charcoal column. The extracorporeal liver assist device (ELAD) developed by Sussman and co-workers [30] is composed of human C3a/HepG2 hepatoblastoma cells grown in a cartridge through which whole blood is perfused. The third system, developed by Gerlach [31] includes multiple membranes to produce a three-dimensional bioreactor that includes both hepatocytes as well as sinusoidal endothelial cells. A recent meta-analysis of the animal studies on these types of devices concludes that treated animals have improved survival in comparison with controls [32]. Unfortunately animal models of acute liver failure fall short of accurately reproducing the human acute liver failure disease process.

Human experience with hybrid bioartificial liver support systems is still limited. A phase 1 pilot study of the BAL system showed reductions in intracranial pressure, bilirubin, and ammonia levels in both patients with acute liver failure and acute exacerbations of chronic liver disease [33]. Encouragingly, in this initial report all patients with fulminant liver failure were successfully bridged to transplantation in this uncontrolled series, although the average time on artificial liver support was only 39 hours before a liver became available. The efficacy of the ELAD system has been examined in a small randomized, controlled trial that included patients with potentially recoverable disease processes [34]. Greater improvements in encephalopathy score were seen in the patients treated with the ELAD, but this trial was confounded by the fact that survival in the control group was much higher than expected. The Gerlach device has been tested on eight patients and found to be safe, although data showing it to be efficacious are not yet available [35]. In summary, like the nonbiologic devices, randomized controlled data are needed to determine whether bioartificial liver systems provide meaningful improvement in clinical outcome. Because of the uncommon nature of acute hepatic failure, it will almost certainly be necessary for these trials to be conducted at multiple centers. Agreement on study design, indications for enrollment, and study end points will be crucial to resolving the current uncertainties.

References


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