Editorial

Fulminant Hepatic Failure and the Need for Artificial Liver Support

Fulminant hepatic failure (FHF) is the acute failure of liver function occurring in a patient with no antecedent liver disease and in whom hepatic encephalopathy supervenes within 8 weeks after the onset of clinical symptoms. The syndrome of FHF remains among the most challenging and difficult problems encountered by clinicians. Although some controversy exists about the management of this syndrome, the development of new and sophisticated intensive care unit monitoring equipment and treatment modalities has likely resulted in improved survival among patients with FHF. The rate of survival from FHF in patients with stage 4 hepatic encephalopathy (hepatic coma) treated with supportive care in a liver unit in 1987 was probably approximately 20 to 35%. In a personal series of 21 patients managed during the past 2 years, before the performance of orthotopic liver transplantation for FHF, 7 patients survived with good supportive care alone. Although this result may indeed be an improvement in comparison with earlier survival figures of 10 to 20% reported more than a decade ago,1 the poor prognosis still underscores the need for a better understanding of the pathophysiologic aspects of the complications associated with FHF and their treatment. In particular, the observation that many patients with FHF now die of complications of increased intracranial pressure (ICP), which accounted for 9 of the 14 deaths recently observed at our institution, makes it imperative that patients with FHF be carefully monitored for signs of increased ICP and that appropriate therapy be instituted.2 Naturally, some investigators have expressed opposition to the routine placement of ICP monitors in patients with FHF because of their coagulopathy and risk for infection. In the few centers that have instituted this policy, however, experience has shown that the procedure can be done safely.

Unfortunately, whether measurements of ICP obtained by placement of an epidural catheter are actually useful in the management of patients with FHF remains unclear. Part of this controversy resides in the fact that the most appropriate treatment for increased ICP in patients with FHF has not been definitely determined. Furthermore, no published data have indicated that the control of increased ICP is associated with a better outcome, although intuitively this relationship seems reasonable.3 Mannitol, but not dexamethasone, has been shown to be useful in this setting in most patients; however, some patients with preexisting profoundly elevated ICP will paradoxically have a further increase in ICP with mannitol therapy, presumably as a result of disruption of the blood-brain barrier and a vasogenic cerebral edema.4 Our understanding of the pathogenesis of the increased ICP and cerebral edema that accompany FHF is poor, and further basic and clinical investigation is needed.

In the meantime, attention has also turned to techniques that involve extracorporeal circulation for “artificial liver support” on the assumption that most of these techniques (for example, ultrafiltration) will achieve at least a dual effect: (1) removal of the toxins responsible for causing cerebral edema and (2) removal of fluid and correction of electrolyte or osmolality problems that might aggravate a vasogenic or cytotoxic cerebral edema. In this light, the pilot study reported by Rakela and colleagues in this issue of the Proceedings (pages 113 to 118) must be interpreted. Although several techniques of artificial liver support have been used in recent years, no single technique has been widely applied or generally accepted. This circumscribed use is related to the fact that most techniques have been attempted only in pilot series with small numbers of patients and the technique for which the most experience has been accumulated (charcoal hemoperfusion) has been performed at a single institution (King’s College Hospital in London) by Gimson and colleagues5 and never subjected to a randomized controlled trial. In fact, no putative therapy for FHF has ever been subjected

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to an adequate randomized and controlled trial. Nonetheless, the value of pilot studies such as the one described by Rakela and co-workers is not disputed. First, their pilot study has demonstrated that the technique of postdilution hemofiltration (PDHF) is possible in most instances, even in critically ill unstable patients with FHF, and furthermore that the technique may ameliorate hepatic encephalopathy. Unfortunately, no data are available on the effect of PDHF on increased ICP, a deleterious condition presumably present in most of the patients. Some early initial personal experience with a combined charcoal hemoperfusion and ultrafiltration technique and direct measurements of ICP has suggested that ultrafiltration is associated with a decrease in raised ICP in most patients. Some techniques of artificial liver support may result in improved survival by virtue of their ability to lower increased ICP; accordingly, these techniques are as much cerebral support techniques as liver support techniques.

Second, the Mayo group encountered the important and serious problem of thrombocytopenia in their patients, a common observation with extracorporeal circulation techniques despite the improving availability of biocompatible columns and filters. They mention the possible inclusion of prostaglandin preparations in the treatment protocol to achieve platelet cytoprotection and to improve biocompatibility. Caution will be necessary in the interpretation of results of any treatment protocols that include prostaglandin preparations because experimental data and, more recently, exciting clinical data suggest improved survival among patients with FHF with the use of various prostaglandin preparations alone.

Finally, Rakela and his associates point out the adjunctive relationship between artificial liver support systems and orthotopic liver transplantation in the management of FHF. Although I predicted in 1986 that “it is unlikely that orthotopic liver transplantation will ever play a major role in the treatment of FHF,” the courage of the transplant surgeons and the improving results of liver transplantation in nonurgent cases have resulted in the use of this operation in patients who have FHF with good results and survival rates of 60 to 70%. Major issues remain, such as the precise indications for and timing of transplantation in patients with FHF and the long-term (that is, 1- to 2-year) follow-up results, most series having been conducted recently and thus reporting limited follow-up. Most important, however, is the issue of organ availability inasmuch as patients with FHF require donor organs on an emergency basis. In combined data obtained from seven centers performing liver transplantation for FHF, 32 of 116 patients (28%) died before an organ became available. In this group of patients, techniques of artificial liver support are badly needed, not only to improve the chances of avoiding liver transplantation but also, if necessary, to sustain the patients awaiting an organ and perhaps decrease perioperative complications and improve postoperative survival. This situation is analogous to peritransplantation dialysis in the setting of renal transplantation. Techniques such as PDHF, on-line plasmapheresis, and hemoperfusion, singly or in combination, may prove useful in this regard. Recent data from Japan have rekindled interest in plasma exchange procedures that use new techniques of on-line plasma separation and replacement, this approach necessitates further review.

Along with the excitement and promising results of liver transplantation in FHF, pilot studies of techniques of artificial liver support must continue and advance to the state of randomized controlled trials when promising techniques are identified. Studies must be performed carefully with meticulous collection of data and attention to potential complications. Direct measurement of ICP with use of epidural catheters would provide useful information in such studies and facilitate patient management. Such information could also aid in the identification of the need for and timing of orthotopic liver transplantation. Liver transplant centers are the obvious sites for the performance of these controlled trials because they are likely to encounter the large numbers of patients with FHF necessary for such studies and are able to provide transplant therapy when other therapy fails. The endpoint of studies of techniques of artificial liver support must now incorporate both the need for liver transplantation (with well-defined indications) and death statistics. Problems will exist with such studies, however, because the apparent initial success with liver transplantation in FHF threatens to lead to a situation in which patients may be considered for transplantation earlier and earlier without attempts at less heroic treat-
ment. This approach could result in liver transplantation in patients who could survive with supportive care alone or with application of some effective technique of artificial liver support. A more concerted effort to identify factors predictive of fatality in patients with FHF is sorely needed in this regard as well as to assist in deciding which patients should receive some mode of artificial liver support—all of which are potentially dangerous, as reported by Rakela and co-workers. The collective experience with techniques of artificial liver support to date has indicated that the provision of detoxification alone is not enough, and just as it is naive to believe that one event is the most important in the pathogenesis of FHF, it is probably naive to think that one single technique of artificial liver support will prove to be the “magic potion.” Most likely, multicomponent artificial liver support systems that incorporate pharmacologic input and central control units will be necessary.12

The study of FHF and its management is an exciting area that will continue to undergo major changes and see innovations during the next decade. Such investigations should be associated with a better understanding of the pathogenesis of the disorder and, most importantly, with improved patient survival. Although prediction in clinical medicine may be hazardous for both patients and academic consultants (as I have already demonstrated), it would be most unfortunate if this prediction proves incorrect and patients with FHF and the potential for complete recovery continue to die.

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REFERENCES
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