Orthotopic Liver Transplantation for Fulminant and Subacute Hepatic Failure

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Fulminant and subacute hepatitis are conditions characterized by rapid liver failure, which can lead to death in 80 to more than 95% of the cases with medical supportive care only. The etiology can be viral, drug-, or other chemical-induced, metabolic, etc. Orthotopic liver transplantation emerged during the 1980s as a powerful means for dealing with these diseases. The existence of this therapeutic modality has brought about major changes in the diagnosis, patient selection, treatment, and outlook for fulminant/subacute liver failure. The authors present the results of orthotopic liver transplantation for the treatment of 47 cases of acute/subacute hepatic insufficiency at the University of Pittsburgh between March 1980 and July 1987. The results of this series demonstrate that liver transplantation is the most effective means for treating this condition. ***ASAIO Transactions*** **1988; 34: 959-964.**

Fulminant and subacute hepatic failure (FHF/SAF) are conditions characterized by diffuse necrosis of hepatic parenchyma, due to any number of liver insults (in order of frequency: viral infections, chemicals and toxins, metabolic disorders, and others). Hepatic failure is defined as *fulminant* when it occurs within 8 weeks of the onset of the symptoms and *subacute* when the hepatic insufficiency manifests itself sometime between the 8th and 20th week after onset of the symptoms of liver disease.

True FHF presents with progressive and rapid deterioration of hepatic function, leading to deepening jaundice, acute onset and progression of hepatic encephalopathy, "foetor hepaticus," ascites, edema, severe derangement of clotting and, in the later stages, hepatorenal syndrome, sepsis, hypoglycemia, acidosis, multiorgan failure, and eventual death. True FHF is a syndrome with an exceedingly advanced degree of morbidity and mortality. The mortality is age- and etiology-dependent and is approximately 80% when stage IV coma has been reached, despite intensive and sophisticated medical care.[1-4] In adult patients, reaching stage IV coma raises the mortality rate to 95% or more.

On the other hand, SAF has a slower evolution, although with a similar outcome in most cases.

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In this context, transplantation of the liver (ortho- or heterotopic) was a tempting alternative to non-operative (medical) therapy since the very beginning of trials with hepatic replacement in humans. Unfortunately, the poor results obtained with liver transplantation throughout the 1960s and 1970s blunted the efforts of organ replacement for patients with acute liver failure. In fact, it is only recently that whole organ liver replacement has achieved a success rate justifying its use for FHF/SAF.[3-5]

We describe our experience with the pre-, intra-, and postoperative evaluation, management, and decision-making process with regard to liver transplantation in patients with FHF and SAF. A presentation of the results achieved by our group with orthotopic liver transplantation for FHF/SAF will then follow.

Etiology

A large number of causes for FHF have been identified. In order of their frequency, they are: viruses (hepatitis A, B, and non-A, non-B), toxic substances (e.g., acetominophen), volatile solvents and anesthetic agents (e.g., halothane) and a few metabolic disorders (especially fulminant Wilson's disease). Despite intensive medical treatment, most patients with chemically-induced hepatitis, halothane hepatitis, and most cases of fulminant viral hepatitis die (>95%) without liver replacement.[6,7] In the case of fulminant Wilson's disease, the mortality with non-operative treatment is 100%. Consequently, it is of the utmost importance and urgency to establish the etiology of the liver failure to be in a position to decide whether or not and when to advise and proceed with liver transplantation. Similar considerations apply for SAF, although the sense of urgency is somewhat reduced.

Preoperative Evaluation and Management

Fulminant hepatic necrosis is generally the consequence of viral infection (type A, B, or non-A, non-B) or chemical insult, either from drugs (involving overdosage or hypersensitivity) or from toxic agents. Establishing an etiology is important not only from an academic point of view but also to guide therapy, avoid further parenchymal damage, and make a prognosis. An attentive history and a high degree of suspicion will, as a rule, reveal any recent exposure to drugs or other chemicals, or any risk factors for contracting viral hepatitis. A family history of liver failure and/or severe neurologic disorders may provide a clue as to the possibility

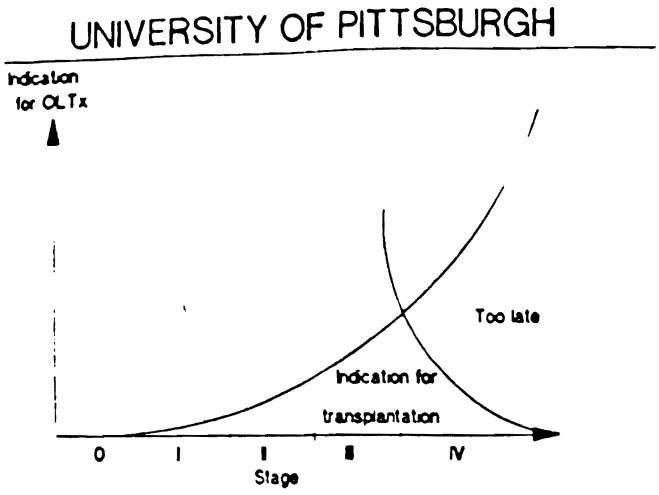

Figure 1. As liver insufficiency progresses, the indications for transplantation increase, up to a point where the degree of irreversibility of the coma causes these indications to decrease as a result of unacceptable morbidity/mortality.

of fulminant Wilson's disease as the etiology for hepatic failure.

As soon as the patient is admitted, a complete serologic profile for viral liver disease (A, B, non-A/non-B, Epstein-Barr virus, Herpes simplex virus, and cytomegalovirus) is done; a toxin screen and the measurement of urinary copper and serum ceruloplasmin levels are done as well. Massive hemolysis and renal failure of recent onset are strongly suggestive of fulminant Wilson's disease[6,7] or of hepatitis associated with glucose-6-phosphatase deficiency. On the other hand, granulocytopenia with or without lymphocytosis suggests fulminant non-A, non-B hepatitis or one of the other more infrequent causes of viral hepatitis.

Next, the tentative determination of the prognosis is fundamental in the decision of whether or not transplantation is indicated and, if it is, on what the right timing should be. Rapidly progressing encephalopathy, development of cerebral edema and/or a rapidly shrinking liver, severe hemolysis, onset and progression of hepatorenal syndrome, and/or deepening jaundice are all ominous signs and should alert physicians that irreversible liver damage is likely and liver transplantation is necessary and imminent (Figure 1). Transplantation in the presence of grade IV coma, bacteremia, severe hepatorenal syndrome, spontaneous bacterial peritonitis or other sepsis, and massive gastrointestinal hemorrhage has a very poor prognosis. This is why the decision to transplant a patient with FHF is one of the most difficult and agonizing that a physician will ever face. The favorable "window" for transplantation may be extremely brief and temporizing may compromise the patient's chance for survival (Figure 1). Specifically, rapid deepening of hepatic coma, a steady prolongation of the prothrombin time (which becomes unresponsive to infusion of fresh frozen plasma), the development of the hepatorenal syndrome, hypoglycemia, and uncorrectable metabolic acidosis are all signs of impending death, which can only be avoided by emergency liver transplantation. Frequent evaluation of the patient's condition, as often as hourly, is needed in such a situation to allow the physician to make the correct decision. The decision to recommend and to proceed with hepatic transplantation for FHF or SAF (also called "late-onset hepatic failure") is less difficult nowadays, thanks to the vastly improved results obtained with organ replacement.

Another essential point is that patients with FHF must be placed on the urgent transplant list as soon as they are admitted to the hospital. Age, blood type, height, weight, and chest circumference must be obtained to permit a good donor/recipient match, if possible. Matching for blood type is desirable, although not essential; on the other hand, a good size match is necessary for technical reasons. The clinical situation of the patient must be assessed every time a potential donor organ becomes available, and a liver transplant should be done if the patient's condition is thought to be irreversible without organ replacement and if the donor is suitable. In particularly desperate situations, a liver that is of a different blood type and/or size can be used, even if such grafts result in less than ideal transplant outcomes; a liver that is too large can be "trimmed" before implantation by means of a partial hepatectomy on the back-bench. In addition to the above mentioned blood tests, the work-up should include sonography to assess the patency of the portal and suprahepatic veins, an abdominal computed tomographic scan for measurement of liver volume, viral hepatitis and toxic screens, urine copper excretion, and serum ceruloplasmin level. All potential infection must be avoided, and any existing infection must be treated early and aggressively. The coagulation status should be corrected as much as possible with fresh frozen plasma (FFP) infusions and the administration of exogenous vitamin K, while renal function must be guaranteed, and nutritional status must be maintained via enteral or parenteral routes, using hepatoprotective formulas. If the patient is obtunded, nasogastric suction is recommended to prevent aspiration pneumonia, and the stomach pH should be kept alkaline by administration of antacids and/or histamine-2 blockers. Should any doubt exist as to the possibility of aspiration, the patient's airway must be protected with prophylactic intubation. Any increase in the intracranial pressure must be prevented and controlled, at the earliest signs of onset, by hyperventilation and mannitol infusion, provided that renal function is adequate; if kidney function is impaired, ultrafiltration can be used to rid the patient of extra fluid. Plasmapheresis or charcoal hemofiltration may be used as temporizing measures, particularly in the case of drug toxicity or fulminant Wilson's disease.

Another extremely important point is that any patient with FHF/SAF must be transferred to a center that performs liver transplantation procedures early in the course of their disease, so that they can be monitored adequately, worked up, and (if necessary) transplanted under optimal conditions. It is unfortunate that, all too often, the transfer takes place very late, after everything else has failed at the original hospital and when the patient's condition is too advanced to allow successful transplantation.

Intraoperative Management

The intraoperative management of patients with FHF/SAF undergoing transplantation is a titanic effort that requires the full and exclusive involvement of the surgical and anesthesiologic teams. Technically, transplantation under these conditions is not extremely challenging, since these patients do not usually have any adhesions from previous surgery or portal hypertension. On the other hand, given the precarious, if not plainly terminal condition of the patient, the operation must be done in a virtually perfect fashion to avoid large blood losses and/or hypotension, which could cause irreversible damage to the brain already at risk from encephalopathy or coma. But, while the operation is not a major technical challenge, in some cases cross-clamping of the portal vein and inferior vena cava, with the obligatory reduction of the venous return to the heart to less than half the normal levels can be disastrous, particularly in a patient with cerebral edema and advanced hepatic encephalopathy. This was one of the most important factors in explaining the dismal results of liver transplantation for FHF/SAF during the "pioneer" years. The introduction of veno-venous bypass, therefore, has had a major impact on improved survival during the last few years.

The main challenge of liver transplantation for FHF/SAF really rests with the anesthesia team who must deal with and correct all the imbalances related to a state similar to that found in septic shock (increased cardiac output and decreased peripheral vascular resistance), compounded by severe coagulopathy, acid-base imbalances, renal dysfunction with a decreased or absent urine output, and many electrolyte abnormalities. The electrolyte and coagulation imbalances are particularly severe at the end of the anhepatic phase of the operation. The anesthesia team is therefore faced with a highly complex situation requiring unfaltering attention throughout the procedure. The correction of fluid and electrolyte abnormalities is done continuously; coagulation is also monitored by means of thromboelastograms (TEG) and corrected as needed with fresh frozen plasma, platelets, cryoprecipitates and/or epsilon-aminocaproic acid. Intraoperative electroencephalogram (EEG) monitoring is recommended, since the presence of seizure activity cannot be otherwise ascertained under general anesthesia, although this requires either an EEG technician or an anesthesiologist versed in EEG interpretation. Vasopressors to control hypotension during the operative procedure must be administered extremely cautiously since they can damage the allograft by decreasing splancnic blood flow.

Postoperative Management

The postoperative management of patients transplanted for FHF/SAF is different from that of other liver transplant patients. Specifically, they may still have residual renal failure, requiring adjustment of their cyclosporine (CsA) doses. As a result, they may require the addition of other immunosuppressive agents to compensate for the lower CsA level

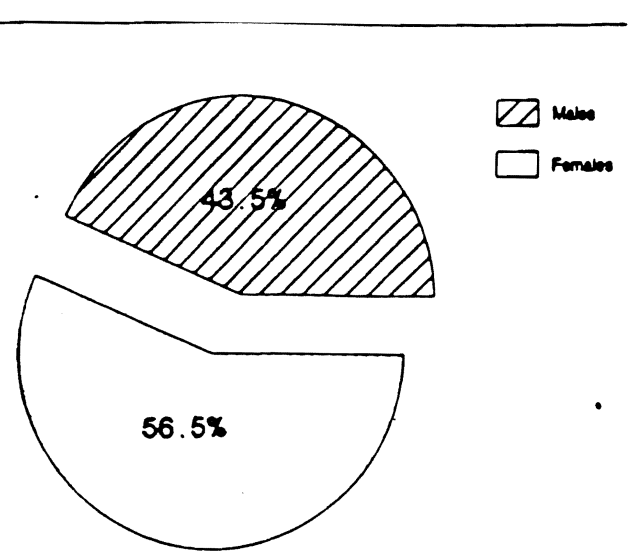

Figure 2. The male/female ratio in this series.

(azathioprine, antithymocyte globulin (ATG), or a monoclonal antibody preparation (OKT3)). Hemodialysis is necessary at times until renal function recovers. In such cases, liver function must be monitored more carefully than is usual since primary nonfunction of the allograft tends to be more lethal in patients whose brain is already impaired as a result of preexisting encephalopathy. If the allograft function during the early postoperative period is not excellent, retransplantation should be done as an emergency to limit further patient deterioration. A characteristic, although fairly rare complication of fulminant non-A, non-B hepatitis is aplastic anemia, which can be observed before or after transplantation. While generally reversible, this condition can be intrinsically fatal. On the other hand, the reduction in immunosuppression necessary during the period of maximal leucocyte count depression may lead to severe rejection once the leukocyte count returns to normal levels.

Results of Liver Transplantation for FHF/SAF

Our experience includes a subset of 47 of 1000 patients who underwent liver transplantation for FHF/SAF utilizing cyclosporine/prednisone therapy between March 1980 and July 1987. Of these 47 patients, 21 (43.5%) were male and 26 (56.5%) were female (Figure 2). Their ages ranged from 4 to 62 years (overall mean, 22.02), with a range of 4 to 62 years (mean, 20.30) for males and a range of 6 to 60 years (mean, 23.35) for females (Figure 3). Nine patients (19.1%) had hepatitis type B (three males and six females); 20 (42.5%) had hepatitis type non-A, non-B (nine males, 11 females); six (12.9%) had fulminant chemical toxicity (four males, two females); ten (21.3%) had fulminant Wilson's

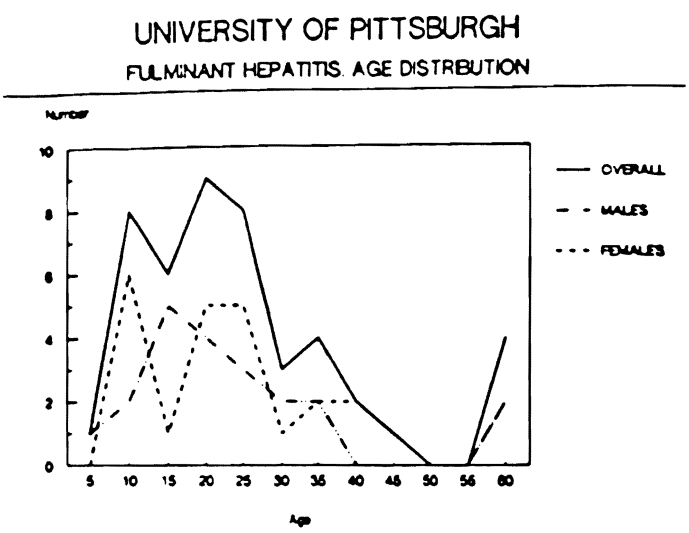

Figure 3. Age distribution of the patients; generally speaking, two peaks are noted, one in the second to third decades and another one in the sixth decade.

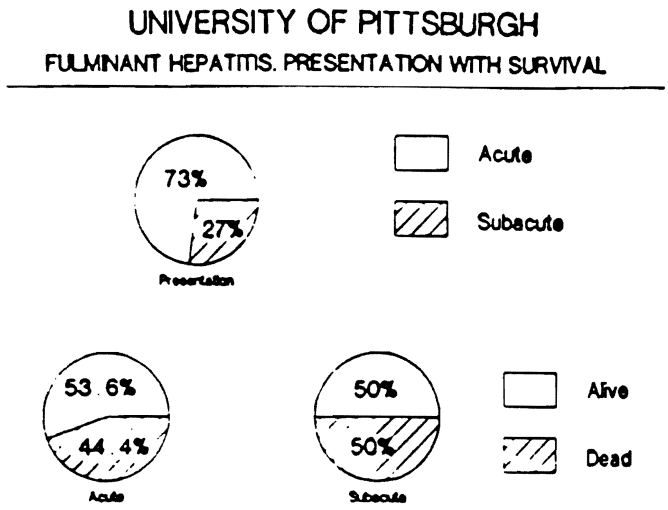

Figure 5. Ratio of acute *versus* subacute presentation in this series and respective raw mortality.

disease (four males, six females); one female (2.1%) had FHF of unknown etiology (possibly Reye's syndrome); and one male (2.1%) had acute hepatic insufficiency secondary to ligation of the hepatic artery during surgery for pheochromocytoma (Figure 4). Thirty-five (73%) had FHF (17 males and 18 females), and 12 (27%) had SAF (four males and eight females) (Figure 5). Seven (14.9%) had very mild or no encephalopathy, nine (19.1%) had grade I hepatic coma, seven (14.9%) had grade II hepatic coma, nine (19.1%) had grade III hepatic coma, and 14 (32%) had grade III/IV or IV coma (Figure 6). The interval from the onset of clinical disease to the time of transplantation ranged from 0 to 25 weeks (mean, 5.11 ± 5.19), the total pretransplant hospital time ranged from less than 1 to 45 days (mean, 10.91 ± 11.52), the pretransplant intensive care (ICU) time ranged from 0 to 11 days (mean, 2.11 ± 2.29), while the time spent on a respirator before transplantation ranged from 0 to 5 days (mean, 0.86 ± 1.11). Twenty-six patients (55.4%) survived (12 males and 14 females), while 17 (44.6%) died (nine males and eight females) (Figure 7). There was no significant statistical difference in the total pretransplant, hospital, and ICU time between the survivor and nonsurvivor groups. A trend toward a longer time spent on the respirator before transplantation was evident in nonsurvivors (0.71 ± 0.86 days for survivors *versus* 1.05 ± 1.36 days for nonsurvivors) although the number of patients in this group was too small to achieve statistical significance. No mean age difference was noted between survivors and nonsurvivors (22.35 *versus* 21.60 years).

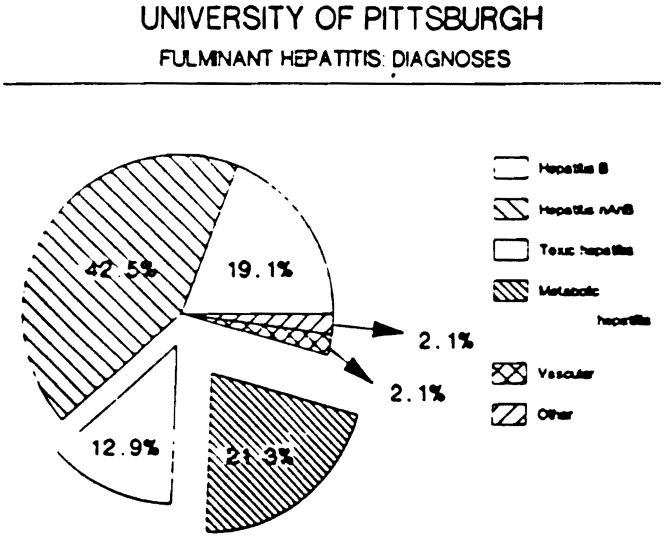

Figure 4. The etiology of the FHF/SAF in this series.

Of the 47 patients in our series, 28 (59.5%) had a good neurologic outcome, meaning a complete recovery of their neurological and intellectual performance, without any evidence of neurologic sequellae; three patients (6.3%) had a fair neurologic outcome, with persistence of some sequellae, and, finally, 16 patients (34.2%) had a poor outcome (Figure 8). This latter group included all the nonsurvivors, who never awoke after the transplant operation and two patients who survived for at least 6 months or longer but never regained sufficient capacity to function independently. There was no statistical difference in the total pretransplant, hospital, and ICU time between the patients with a good and a poor neurologic outcome; there was a trend toward a difference between the two groups when the time spent in the ICU and on a respirator preoperatively was considered (1.96 ± 2.65 days for a good outcome *versus* 2.20 ± 1.70 in the ICU for a poor outcome and 0.58 ± 0.67 days *versus* 1.40 ± 1.40 days on a respirator, respectively). The number of patients in each group, however, was too

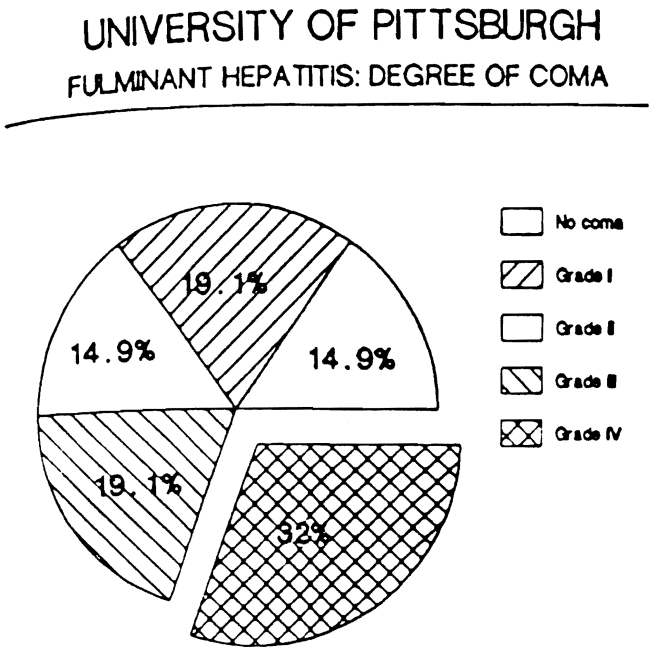

Figure 6. The proportion of patients presenting with the various degrees of encephalopathy/coma.

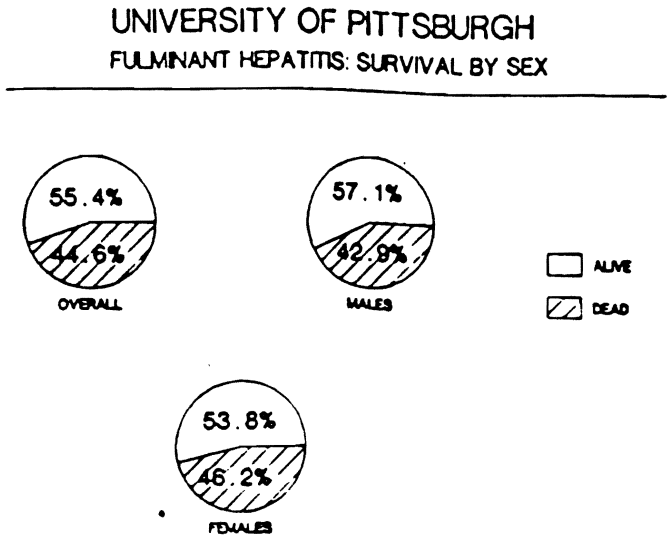

Figure 7. Raw survival, in general and by sex distribution.

low to achieve statistical significance. A notable difference between good and poor neurologic outcomes was observed when the degree of coma was analyzed: eight of 16 patients with a poor outcome (50%) had grade III/IV or IV coma, while only six of 28 (21.4%) patients with a good outcome had advanced coma.

Discussion

Given the otherwise dismal prognosis, liver transplantation is a particularly attractive alternative for FHF/SAF. Until just a few years ago this was not feasible in practice since the results of liver transplantation in general were rather poor, and the additional handicaps associated with FHF only compounded the problem. Since the introduction of CsA to the transplantation armamentarium, results of liver transplantation have improved enormously (**Figure 9**). As most patients with FHF, regardless of etiology, have a survival of only 20% or less with even the most intensive medical treatment, while transplantation offers immediate survival of at least 55%, this form of therapy evidently offers a distinct advantage. In addition, the greater availability of donors has made liver replacement for FHF a reasonable proposition. All other available methods of temporary hepatic support have only provided additional time during which a donor organ can be sought actively, although none represents a valid definitive alternative to liver transplantation. These methods should be used routinely, however, whenever possible during the pretransplant period to slow the progression of the hepatic failure, thus allowing the patient to be transplanted while still in the best possible condition. Especially valuable in this respect are the use of activated charcoal hemofiltration, plasmapheresis, and prostacycline infusion for prevention of platelet aggregation.[1,2]

It is interesting that all cases of FHF due to hepatitis B virus infection but one have had recurrence of the disease, although not usually in a fulminant form. The first perioperative survivor of a transplant for hepatitis B and FHF (surgery done in 1974) appeared to be hepatitis B negative by radioimmunoassay after the procedure. Subsequent records for this patient are, unfortunately, incomplete, and he died 3 months later of complications of the transplant unrelated to his original disease. One patient died on the operating table.

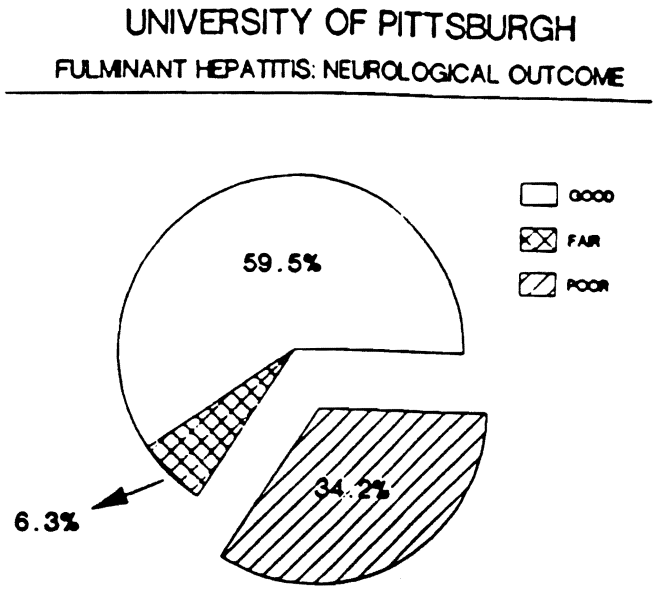

Figure 8. Neurologic outcome for FHF/SAF.

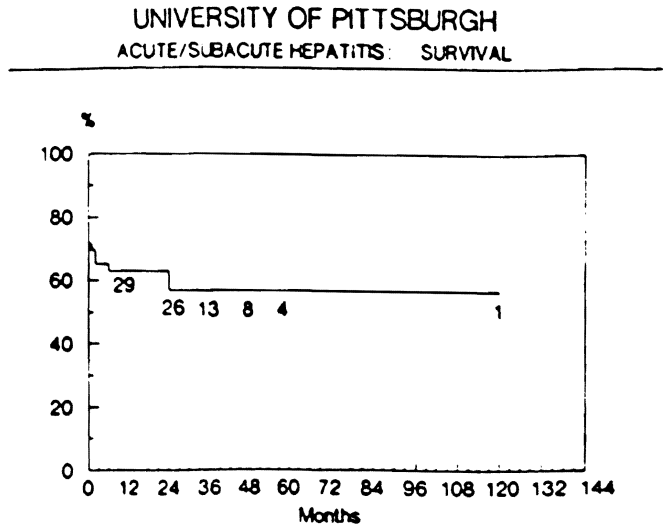

Figure 9. Actuarial survival for patients with FHF/SAF.

All the others (62.5%) have continued to be serologically positive after the transplant, many with biopsy-proven recurrence of the disease. All but one are stable and well now, although with active low-grade disease, 8 months to 3 years after their transplant. One patient has had retransplantation for chronic active hepatitis B.

As in previous studies,[8] a remarkable negative impact of retransplantation on survival was observed, particularly when the retransplantation was necessary because of primary graft non-function (**Figure 10**). Interestingly enough, in this series the only patient who received four consecutive liver transplants survived. In this context, it appears that the need for very early retransplantation adversely affects survival. This can be explained by the devastating effect of a poor quality graft on an already impaired brain.

Of all types of FHF, toxic hepatitis seems to have the poorest prognosis: only one of six patients (16.6%) has survived. In fact, one young woman, transplanted after sudden onset of rapidly deteriorating liver failure after exposure to volatile substances, now has what appears to be a low-degree chronic hepatitis, with negative viral hepatitis screen, suggesting that she may have had non-A, non-B hepatitis from the outset. Without this case, there would be no survivors from fulminant chemical hepatitis in our series. The main reason for this phenomenon is that these forms of hepatic failure can be extremely rapid in their progression to irreversible coma; if the patient is not transferred immediately to a center capable of liver transplantation, the fulminant course will deny them the benefit of this life-saving form of therapy.

A slight, although not statistically significant increase of mortality among female patients (46.2% *versus* 42.9%) was noted. This probably represents an artefact (**Figure 7**). The same observation can be made about the small difference in mortality for patients with acute or subacute hepatitis (44.4% *versus* 50%, respectively) (**Figure 5**).

In light of our data, as well as that of others, there is little doubt that liver transplantation for FHF/SAF is not only justified but indicated. The continuous progress made in early diagnosis, patient selection, technique, postoperative care, and immunosuppression means that transplantation should be offered as an alternative earlier than ever before, and in some cases, even before spontaneous recovery can be ruled out completely.

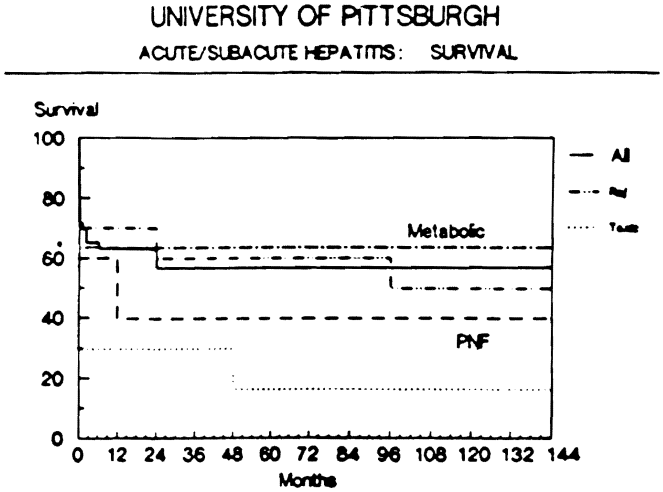

Figure 10. Differences in actuarial survival for the various etiologies for FHF/SAF. Rej. = rejection. Although rejection and primary nonfunction (PNF) are not the original causes of fulminant hepatic failure in this series, the mortality secondary to these conditions after the transplant is shown to demonstrate their impact.

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