

# Liver Transplantation for Fulminant Hepatic Failure in the Pediatric Patient

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**Objective:** To review the clinical characteristics, outcomes, and risk factors for survival among 57 pediatric patients undergoing orthotopic liver transplantation for fulminant hepatic failure at the University of California, Los Angeles, Center for the Health Sciences.

**Design:** The medical records of 57 consecutive pediatric patients undergoing orthotopic liver transplantation for fulminant hepatic failure from July 1, 1984, to June 25, 1997, were reviewed and survival data were analyzed via univariate and multivariate statistical methods. The type and incidence of posttransplant complications were determined as was the quality of long-term graft function. Median follow-up period was 3.38 years (range, 0-10.02 years).

**Results:** The 1-, 3-, and 5-year actuarial patient survival rates were 77%, 77%, and 77%, respectively, while graft survivals were 73%, 65%, and 65%. Stepwise Cox regression analysis revealed that recipient age and ventilator dependency at the time of transplantation were independently and significantly correlated with patient survival, whereas no association was found between survival and grade of encephalopathy, prior abdominal surgery, recipient weight, pretransplantation values for total bilirubin or prothrombin time, ABO match, allograft type, peak posttransplantation aspartate aminotransferase lev-

els, or the presence of posttransplantation hepatic artery thrombosis. Non-ventilator-dependent patients demonstrated a 96% 1-, 3-, and 5-year survival as compared with only 56% at these same time points for those children requiring ventilator support at the time of transplantation ( $P < .001$ ). At the time of most recent follow-up, median values for total bilirubin and aspartate aminotransferase concentrations were 10.3  $\mu\text{mol/L}$  (0.6 mg/dL) and 56 U/L, respectively, in the 40 surviving patients.

**Conclusions:** In children undergoing liver transplantation for fulminant hepatic failure: (1) overall results are comparable to those achieved for less emergent non-neoplastic indications in this same age group; (2) ventilator dependency prior to transplantation is the strongest predictor of ultimate survival, followed by recipient age; (3) 5-year survival exceeds 90% in recipients who are ventilator independent immediately prior to liver transplantation but is significantly compromised once the need for mechanical ventilation supervenes, particularly in those younger than 4 years; and (4) prompt referral and timely liver replacement are the cornerstones of optimal outcome.

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**A**CUTE OR fulminant hepatic failure (FHF), defined as massive liver necrosis with encephalopathy developing within 8 weeks from the first sign of illness in a patient without underlying chronic liver disease, is one of the most dramatic and challenging syndromes in clinical medicine. While FHF is a relatively rare condition in the pediatric patient population, it is frequently fatal in the absence of liver replacement. Causes of FHF in the pediatric patient include infectious agents, drugs and toxins, inherited metabolic disorders, infiltrative disease, autoimmune hepatitis, and ischemic or irradiation dam-

age. A proportion of the cases are cryptogenic. The etiology with most metabolic disorders differs depending on the age of the child, while some specific infectious agents predominate in the neonatal period or in infancy (age  $< 2$  years). In children older than 2 years, the causes are similar to those found in adults.<sup>1</sup>

In the absence of transplantation, FHF carries a grim prognosis with an 80% to 85% mortality rate.<sup>2</sup> Death is usually due to decerebration as a result of cerebral edema.<sup>3</sup> Critical to the decisions regarding patient management is the assessment of the likelihood of spontaneous recovery. Supportive medical therapy has proven to be largely

## SUBJECTS, MATERIALS, AND METHODS

### PATIENT POPULATION

Between July 1, 1984, and June 30, 1997, 57 patients younger than 18 years underwent orthotopic liver transplantation for FHF at the UCLA Center for the Health Sciences. All patients had acute hepatic injury with jaundice and encephalopathy without an antecedent history of liver disease. Patients with FHF superimposed on chronic liver disease were excluded. Fulminant hepatic failure was defined as acute hepatocellular necrosis complicated by the development of hepatic encephalopathy within 8 weeks of the onset of jaundice. Encephalopathy was graded as follows: grade 1, depression of responsiveness, decreased appetite; grade 2, drowsiness, hyperreflexia, and asterixis; grade 3, marked confusion, disorientation, irritability, agitation, or reaction only to vocal stimuli; and grade 4, deep coma without reaction to vocal stimuli, response only to noxious physical stimuli. All patients with grade 3 and 4 hepatic encephalopathy underwent computed tomographic evaluation of the head. Invasive intracranial pressure monitoring was performed selectively in patients with either clinical or radiographic evidence of increased intracranial pressure. Data for this study were obtained by reviewing the inpatient and outpatient hospital medical records of the respective patients. The median follow-up period was 3.38 years (range, 1 month to 10.02 years).

Median pretransplantation age and weight were 4.52 years (range, 44 days to 17.1 years) and 18.0 kg (range, 4.4-87.0 kg), respectively. Seven patients (12%) were younger than 1 year at the time of transplantation, while 25 patients (44%) were younger than 4 years. Six (10%) of 57 patients weighed less than 10 kg at the time of liver replacement. The degree of hepatic encephalopathy at transplantation consisted of 1 patient with grade 1, 19 patients with grade 2, 16 patients with grade 3, and 21 patients with grade 4 encephalopathy. Twenty-eight patients (49%) were ventilator dependent at the time of liver replacement, while 29 patients (51%) were not. Fifteen patients (26%) had undergone intra-abdominal surgery prior to liver replacement. The mean values for pretransplantation prothrombin time, total bilirubin level, and serum creatinine level were 30.1 seconds, 428  $\mu\text{mol/L}$  (25.0  $\text{mg/dL}$ ), and 70.7

$\mu\text{mol/L}$  (0.8  $\text{mg/dL}$ ), respectively. All patients were intensive care unit bound (United Network for Organ Sharing status 1) immediately prior to transplantation.

Liver allograft types comprised 40 whole organs, 11 reduced-size, 8 living-related donor, and 2 in-situ split livers. Fifty-three patients (93%) received a single allograft, whereas 4 patients (7%) required retransplantation. Hepatic artery thrombosis was the indication for retransplantation in 2 patients, while primary nonfunction and portal vein thrombosis were the indications in 1 each of the other 2 patients.

### IMMUNOSUPPRESSION

Prior to July 1994, immunosuppression consisted of cyclosporine administered intravenously or orally to maintain a trough level between 250 and 300  $\text{ng/mL}$ , as measured by whole-blood radioimmunoassay. Methylprednisolone therapy was begun at 20 to 30  $\text{mg/kg}$  per day and rapidly tapered for 5 days to 0.3 to 0.5  $\text{mg/kg}$  per day. Maintenance oral prednisone was later substituted at the same dose. Intravenous azathioprine administration (2  $\text{mg/kg}$  per day) was started on the first postoperative day and subsequently was converted to oral administration (1  $\text{mg/kg}$  per day). Leukocyte counts less than 400/ $\text{mL}$ , systemic sepsis, or pancreatitis were contraindications to initiating azathioprine or continuing its use.

From July 1994 onward, dual-drug immunosuppression was employed. Tacrolimus (FK506, Prograf, Fujisawa USA, Deerfield, Ill) was given orally (0.1-0.2  $\text{mg/kg}$  per day) every 12 hours to maintain a whole-blood trough level of 10 to 15  $\text{ng/mL}$ . Methylprednisolone was tapered from 20 to 30  $\text{mg/kg}$  per day to 0.3  $\text{mg/kg}$  per day for 5 days and was followed by oral prednisone at 0.3  $\text{mg/kg}$  per day.

### STATISTICAL EVALUATION

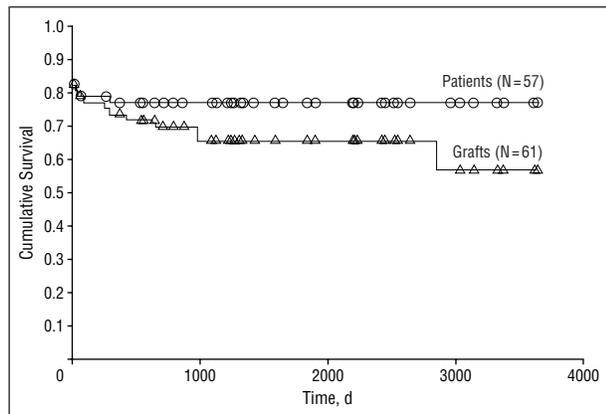
The Mantel-Haenszel  $\chi^2$  test was used for comparison of proportions between groups. Actuarial patient and graft survivals were calculated using the Kaplan-Meier product-limit estimate with statistical comparisons between groups done via the log-rank test. Stepwise Cox regression multivariate analysis was used to test the statistical strength of independent association between the defined pretransplant and pertransplant covariates and patient survival. Statistical calculations were performed using the SPSS advanced statistics module (SPSS Inc, Chicago, Ill).

unsuccessful in those patients with clinical parameters suggesting progressive disease, and liver replacement has become the cornerstone of treatment in this setting.<sup>4-7</sup>

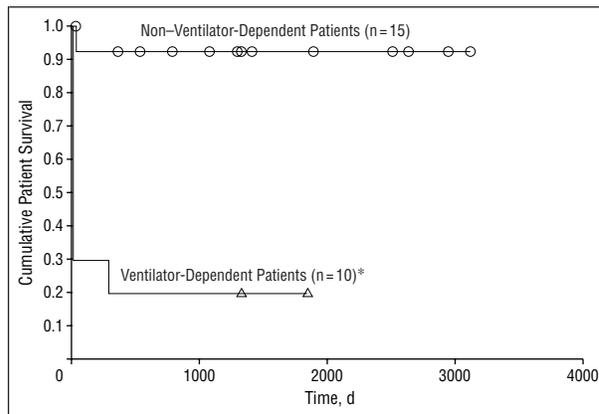
The overall success of pediatric liver transplantation has improved steadily to the point that patient and graft survival rates approach those achieved in adults.<sup>8</sup> Factors contributing to this success include refined surgical techniques and new immunosuppressive drug regimens, better anesthesia, and pediatric intensive care together with prompt recognition and treatment of medical and surgical complications.<sup>9-11</sup>

However, despite these advances, pediatric liver transplantation remains a challenging undertaking owing to ongoing and ever-increasing donor organ

shortage as well as the inherent technical demands. These factors are particularly germane in the setting of FHF, as the procedure must be undertaken on an urgent or emergent basis. Thus, the reported survival following liver transplantation in infants and children suffering from FHF has been inferior to that achieved with other disease processes that lead to liver failure.<sup>12</sup> With these considerations in mind, as well as an awareness of the relative paucity of reported series specifically devoted to it, we reviewed the University of California, Los Angeles (UCLA), experience with liver transplantation for FHF in pediatric subjects with an effort to determine overall outcomes as well as to identify independent risk factors affecting patient survival.



**Figure 1.** Kaplan-Meier survival curve demonstrating 1-, 3-, and 5-year actuarial patient and liver allograft survival.



**Figure 2.** Kaplan-Meier 1-, 3-, and 5-year actuarial patient survival curves for fulminant hepatic failure liver transplant recipients younger than 4 years. In comparison with patients younger than 4 years and not ventilator dependent, ventilator-dependent liver transplant recipients younger than 4 years had a significantly decreased ( $P < .001$ ) survival rate.

## RESULTS

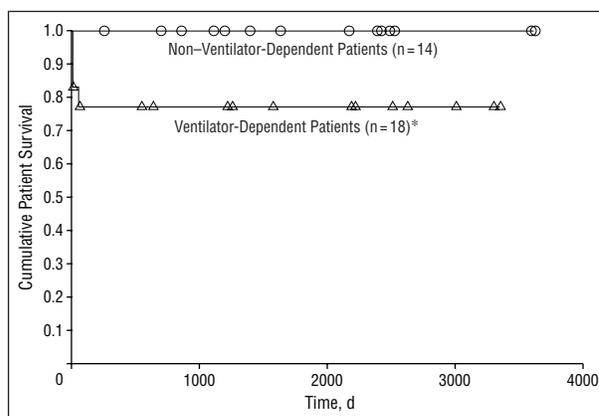
### PATIENT AND ALLOGRAFT SURVIVAL AND MULTIVARIATE ANALYSIS

Overall patient survival was 77% at 1, 3, and 5 years after transplantation (**Figure 1**). Graft survivals at these same time points were 73%, 65%, and 65% (Figure 1). Patient survival was not significantly different from that achieved in 383 children undergoing liver replacement for other indications at UCLA.<sup>13-15</sup> Covariates entered and the results obtained from stepwise Cox regression multivariate analysis are presented below.

Covariate	P
Age	.02
Weight	.61
Previous intra-abdominal surgery	.94
Allograft type	.84
Pretransplantation total bilirubin level	.78
Pretransplantation prothrombin time	.66
Pretransplantation ventilatory status	.003
Hepatic encephalopathy grade	.78
ABO match	.54
Peak posttransplantation aspartate aminotransferase level	.63
Hepatic artery thrombosis	.61

Of the 11 covariates entered only pretransplantation ventilator status ( $P = .003$ ) and recipient age ( $P = .02$ ) were found to be independently and significantly correlated with patient survival. No significant relationship was found between pretransplantation patient weight, prior intra-abdominal surgery, pretransplantation values for bilirubin concentration or prothrombin time, hepatic encephalopathy grade, ABO match, allograft type, peak posttransplantation aspartate aminotransferase concentration, or the presence of posttransplantation hepatic artery thrombosis.

Twenty-eight (49%) of 57 patients were ventilator dependent prior to transplantation and, of these, 21 (75%) were in grade 4 hepatic encephalopathy as compared with 0 (0%) of 29 patients who were ventilator independent ( $P < .001$ ). Survival at 1, 3, and 5 years was significantly inferior in these recipients as compared with that achieved in the 29 (51%) who remained ventilator independent pretransplant (56% vs 96%,  $P < .001$ ). Five-year survival for the 32 (56%) of 57

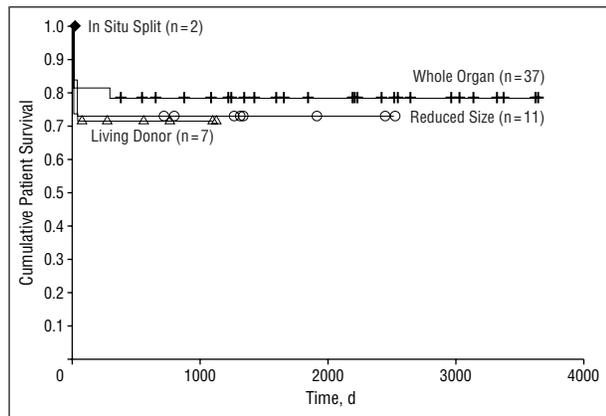


**Figure 3.** Kaplan-Meier 1-, 3-, and 5-year actuarial patient survival curves for fulminant hepatic failure liver transplant recipients older than 4. In comparison with patients older than 4 years and not ventilator dependent, recipients who were ventilator dependent at the time of transplantation and older than 4 years had a significantly decreased ( $P < .001$ ) survival rate.

patients who were 4 years or older at the time of transplantation was 87%, as compared with only 64% for those younger than 4 years ( $P = .03$ ).

The effect of ventilator dependence was more pronounced for younger recipients. As shown in **Figure 2**, patient survival was decreased by 70% in ventilator-dependent recipients younger than 4 years. Additionally, 8 of the 10 recipients younger than 4 years who received ventilation prior to transplantation died within their index hospitalization. In contrast the decrease in cumulative survival was less than 30% in those 4 years or older who required ventilator support prior to transplantation (**Figure 3**). Moreover, among 14 patients 4 years or older and who were ventilator independent, there were no deaths during the course of follow-up. Although 5-year survival in the 6 (10%) of 57 recipients weighing less than 10 kg was only 50% as compared with 80% in those weighing 10 kg or more, this difference was of marginal statistical significance ( $P = .07$ ).

**Figure 4** illustrates actuarial patient survival by liver allograft type. While no statistically significant differences were found, it is noteworthy that there were no early



**Figure 4.** Kaplan-Meier survival curves for recipient groups based on liver allograft type. The 1-, 3- and 5-year patient actuarial survival rates are not affected by allograft type.

mortalities associated with the use of in situ split-liver allografts, although there were only 2 such cases.

At the date of most recent follow-up, mean values for aspartate aminotransferase and total bilirubin concentration were 56 U/L and 10.3  $\mu$ mol/L (0.6 mg/dL), respectively, in the 40 surviving patients.

#### COMPLICATIONS AND MORTALITY AFTER ORTHOTOPIC LIVER TRANSPLANTATION FOR FHF IN THE PEDIATRIC PATIENT

During the 13-year period of follow-up, hepatic artery thrombosis occurred in 2 patients (3.5%), both of whom underwent transplantation prior to 1993. Portal vein thrombosis occurred in 1 patient (2%), necessitating retransplantation. Three children (5%) developed biliary strictures and all were treated with radiological intervention. One patient (2%) required exploratory laparotomy for bowel perforation. Five children (9%) developed neurological disturbances, which seemed to be unrelated to immunosuppressive medications. Four patients (7%) developed posttransplantation lymphoproliferative disorder; at the date of latest follow-up, all had been managed successfully by a reduction in immunosuppressive therapy. Two patients (4%) developed aplastic anemia in the post-transplantation period and both spontaneously recovered bone marrow function 21 and 92 days after diagnosis without specific intervention. In addition, the incidence of culture-proven bacterial, viral, and fungal infections per case were 0.76, 0.31, and 0.12, respectively.

Seventeen of the patients died following liver transplantation; 14 of the 17 died within 1 month of transplantation, 5 of brain herniation and brain death and 9 of a variety of infectious complications leading to multisystem organ failure. The remaining 3 patients had prolonged hospital courses and subsequently died following multiple infectious complications.

#### COMMENT

Fulminant hepatic failure in the pediatric patient is a rare but often fatal event. After unsuccessful attempts to treat such patients with a variety of modalities including plasma exchange,<sup>16</sup> steroids,<sup>17</sup> charcoal hemofiltration,<sup>18</sup> pros-

taglandins,<sup>19</sup> and N-acetylcysteine,<sup>20</sup> liver transplantation has emerged as a major breakthrough. However, 20% to 25% of the patients with FHF will recover without transplantation, making the decision to proceed with liver replacement most critical. While a clear set of indications for liver transplantation have not been outlined in the pediatric patient, 2 sets of criteria have been developed in the adult patient: one by the Paris, France, group at Villejuif<sup>21</sup> and the other by the group at King's College Hospital, London, England.<sup>22</sup> At Villejuif, selection is made on the basis of serum factor V levels. A level of less than 20% in patients who are younger than 30 years, or less than 30% in patients who are 30 years or older, if associated with hepatic encephalopathy, is the indication for transplant listing.<sup>23</sup> At King's College Hospital, the criteria used are dependent on the cause of FHF. In patients with paracetamol-induced FHF, a pH of less than 7.3 at 24 hours or more after overdose, assuming appropriate volume loading, or the concurrent presence of a serum creatinine level of greater than 300  $\mu$ mol/L (>3.4 mg/dL), hepatic encephalopathy of grade 3 or 4, and a prothrombin time of greater than 100 seconds are considered indications for liver transplantation.<sup>22</sup> In non-paracetamol-induced FHF, the decision is based on the occurrence of 3 of the following: a prothrombin time greater than 50 seconds; a jaundice-to-encephalopathy time of more than 7 days; non-A, non-B hepatitis or drug-induced hepatitis; age younger than 10 years or older than 40 years; bilirubin level greater than 300  $\mu$ mol/L (>17.5 mg/dL); or the finding of a prothrombin time of greater than 100 seconds in isolation.<sup>22</sup> Two other groups in North America have also suggested other criteria incorporating encephalopathy, course of illness, coagulopathy, and cerebral edema in addition to the results of transjugular hepatic biopsy and hepatic volume assessed by computed tomography or ultrasound techniques.<sup>24,25</sup> However, none of these criteria have been subjected to rigorous statistical analysis with large patient numbers.

The cause of FHF in the pediatric patient is dependent on the age of the child. In the perinatal period, the most likely cause is herpesvirus, echovirus, adenovirus,<sup>26</sup> or neonatal hepatitis B.<sup>27</sup> Following the perinatal period, hepatitis A, B, and sporadic cases of non-A, non-B, non-C hepatitis account for the majority of cases.<sup>28</sup> With the exception of Wilson disease, most children with FHF caused by metabolic disease present in infancy. An accurate diagnosis of metabolic disease is essential because some of these disease processes, such as galactosemia and fructosemia, will improve with appropriate dietary intervention. Infiltrative causes of FHF, such as leukemia and hemophagocytic lymphohistiocytosis, also require early diagnosis to allow the institution of appropriate chemotherapy and the avoidance of liver replacement. Autoimmune hepatitis may present with FHF, rarely responds to immunosuppression, and frequently requires liver transplantation.<sup>29</sup>

While the management of children with FHF is complex, the goal is to focus on preventing irreversible neurological injury until a suitable liver allograft is found. Cerebral edema occurs in 60% to 80% of patients dying of FHF and results in increased intracranial pressure.<sup>30</sup> Failure to maintain a mean cerebral perfusion pressure

of greater than 50 mm Hg results in irreversible neurological injury or death. Thus, previous literature has emphasized the value of aggressive monitoring of intracranial pressures in patients with grade 4 hepatic encephalopathy.<sup>30</sup> In our early experience, prior to 1992, we managed children with FHF without intracranial pressure monitoring, and 5 children had irreversible neurological sequelae after liver transplantation. Since 1993, we have taken an aggressive approach to the application of intracranial pressure monitoring and use it in all children with grade 3 to 4 hepatic encephalopathy, irrespective of severe coagulation disorders. Intracranial pressure monitoring not only directs management of intracranial pressure with the use of controlled hypotension and intravenous mannitol, but also provides prognostic information on suitability of transplant candidacy. While we do not have absolute contraindications, based on intracranial pressures, for liver replacement in children with FHF at our center, it is now generally accepted that liver transplantation is contraindicated if the cerebral perfusion pressure is less than 50 mm Hg for more than 2 hours.<sup>31</sup> These prognostic data are most important today when we are capable of pursuing multiple options for liver transplantation, including living-related liver donation.

Liver transplantation has revolutionized the treatment of FHF and now has 1-year survival rates ranging from 55% to 75%.<sup>5,32,33</sup> Our study extends this observation to children and demonstrates the achievement of a survival rate exceeding 75%. However, this milestone is counterbalanced with serious challenges and pitfalls. The selection of patients and the timing of liver replacement are certainly the most important; however, no pediatric studies have been published to date identifying definitive clinical parameters for liver transplantation and its timing. The decision to proceed with emergency liver transplantation in the pediatric patient with FHF at our center has been based on the evolution of hepatic encephalopathy, progressive synthetic dysfunction, and the presence of extrahepatic organ failure in the setting of a disease process that is not expected to spontaneously resolve. However, in many situations the progression of FHF and the need for liver transplantation has to be based on a constellation of clinical parameters including cerebral edema, patient age, origin of disease, serum total bilirubin level, and duration between the onset of jaundice and encephalopathy. Thus, the precise indication for liver transplantation may vary among patients and transplant centers, emphasizing the need for additional refined prognostic indicators to facilitate the selection of patients. On the other hand, the identification of absolute contraindications to liver transplantation in FHF is crucial, owing to the ongoing shortage of donor organs.

Organ availability continues to be the rate-limiting step governing liver transplantation in children with FHF. In many cases, ABO-mismatched and/or marginal allografts are used, which present their own set of risks, including the need for retransplantation. In a few patients, ABO-nonidentical and ABO-incompatible allografts were used in children with FHF and did not seem to affect the posttransplantation course. The lack of sufficient donors, coupled with the use of nonidentical or in-

compatible ABO-matched allografts, adds further support to the use of split-liver transplantation. In our series, patient survival was not affected by allograft type, and we as well as others have demonstrated that split-liver transplantation can be safely and effectively performed, especially with the application of in situ techniques.<sup>34,35</sup> Based on our accumulated experience, we believe that the split-liver technique is the preferred method of transplantation in the pediatric patient with FHF. Furthermore, if it were possible to organize a cooperative system in which all livers that were suitable for split-liver transplantation were shared, even at a regional level, the number of pediatric patients awaiting liver transplantation would be significantly reduced.

The present study demonstrates that, despite the continuing challenges facing pediatric liver transplantation, patient survival in children with FHF can exceed 75% and approach that of children undergoing transplantation for other disease processes. Our study also demonstrates that ventilator dependency prior to liver transplantation is the strongest predictor of patient survival, especially in those patients younger than 4 years. In conclusion, these data indicate that to achieve optimal outcomes in children with FHF, prompt referral to a center with special expertise in the management of pediatric FHF that can provide all the surgical options necessary for emergent liver transplantation is essential.

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## REFERENCES

1. Bhaduri BR, Mieli-Vergani G. Fulminant hepatic failure: pediatric aspects. *Semin Liver Dis.* 1996;16:782-794.
2. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definition and causes. *Semin Liver Dis.* 1986;6:97-106.
3. Ware AJ, D'Agostino A, Combes B. Cerebral edema: a major complication of massive hepatic necrosis. *Gastroenterology.* 1971;61:877-884.
4. Vickers C, Neuberger J, Buckels J, et al. Transplantation of the liver in adults and children with fulminant hepatic failure. *J Hepatology.* 1988;7:143-150.
5. Devictor D, Desplanques L, Debray D, et al. Emergency liver transplantation for fulminant liver failure in infants and children. *Hepatology.* 1992;16:1156-1162.
6. Ascher N, Lake JR, Emond JC, et al. Liver transplantation for fulminant hepatic failure. *Arch Surg.* 1993;128:677-682.
7. Brems JJ, Hiatt JR, Ramming KP, et al. Fulminant hepatic failure: the role of liver transplantation as primary therapy. *Am J Surg.* 1987;154:137-141.
8. *Annual Report of the US Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data, 1988-1993.* Richmond, Va: United Network for Organ Sharing; 1994.
9. De Ville de Goyet J, Hausleithner V, Reding R, et al. Impact of innovative techniques on the waiting list and results in pediatric liver transplantation. *Transplantation.* 1993;56:1130-1136.
10. McDiarmid SV, Busuttil RW, Ascher NL, et al. FK506 (tacrolimus) compared with cyclosporine for primary immunosuppression after pediatric liver transplantation: results from the US multicenter trial. *Transplantation.* 1995;59:530-535.
11. George DL, Arnow PM, Fox A, et al. Patterns of infection after pediatric liver transplantation. *AJDC.* 1992;146:924-927.
12. Hoofnagel JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. *Hepatology.* 1995;21:240-252.
13. Busuttil RW, Seu P, Millis JM, et al. Liver transplantation in children. *Ann Surg.* 1991;213:48-57.

14. Goss JA, Shackleton CR, Swenson K, et al. Orthotopic liver transplantation for congenital biliary atresia: an 11-year single center experience. *Ann Surg.* 1996; 224:276-286.
15. Goss JA, McDiarmid SV, Shackleton CR, et al. Long-term results of pediatric liver transplantation: an analysis of 569 transplants. *Ann Surg.* In press.
16. Kondrop J, Almadal T, Vilstrup H, Tygstrup N. High-volume plasma exchange in fulminant hepatic failure. *Int J Artif Organs.* 1992;15:669-676.
17. European Association for the Study of the Liver (EASL). Randomized trial of steroid therapy in acute liver failure. *Gut.* 1979;20:620-623.
18. Gimson AES, Braude S, Mellon PJ, Canalese J, Williams R. Earlier charcoal hemoperfusion in fulminant hepatic failure. *Lancet.* 1982;2:681-683.
19. Sinclair SB, Greig PD, Blendis LM, et al. Biochemical and clinical response of fulminant viral hepatitis to administration of prostaglandin E: a preliminary report. *J Clin Invest.* 1989;84:1063-1069.
20. Prescott LF, Illington RN, Critchley KL, et al. Intravenous *N*-acetylcysteine: the treatment of choice for paracetamol poisoning. *BMJ.* 1979;2:1097.
21. Bernuau J, Goudeau A, Poinard T, et al. Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology.* 1986;6:648-651.
22. O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology.* 1989;97:439-445.
23. Bernuau J, Samuel D, Durand R, et al. Criteria for emergency liver transplantation in patients with acute viral hepatitis and factor V below 50% of normal: a prospective study. *Hepatology.* 1991;14:49-55.
24. Schafer D, Shaw B. Fulminant hepatic failure and orthotopic liver transplantation. *Semin Liver Dis.* 1989;9:189-194.
25. Van Thiel DH. When should a decision to proceed with transplantation actually be made in cases of fulminant or subfulminant hepatic failure: at admission to hospital or when a donor organ is made available? *J Hepatol.* 1993;17:1-2.
26. Russell GJ, Fitzgerald JF, Clark JH. Fulminant hepatic failure. *J Pediatr.* 1987;111:313-319.
27. Okuda K. Is fulminant B hepatitis more common among infants born to e antigen-negative carrier mothers? *Hepatology.* 1987;7:974-976.
28. Yohannan MD, Arif M, Ramia S. Aetiology of icteric hepatitis and fulminant hepatic failure in children and the possible predisposition to hepatic failure by sickle cell disease. *Acta Paediatr Scand.* 1990;79:201-205.
29. Maggiore G, Bernard O, Hadchouel M, Alagille D. Life-saving immunosuppression treatment in severe autoimmune chronic active hepatitis. *J Pediatr Gastroenterol Nutr.* 1985;4:655-658.
30. Pappas SC. Fulminant hepatic failure. In: Gitwick G, LeBrecque DR, Moody FG, eds. *Diseases of the Liver and Biliary Tract.* St Louis, Mo: Mosby-Year Book Inc; 1992:615-629.
31. Lidofski SD, Bass NM, Prager MC, et al. Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. *Hepatology.* 1992;16:1-7.
32. Mondragon R, Mieli-Vergani G, Heaton ND, et al. Liver transplantation for fulminant liver failure in children. *Transplant Int.* 1992;5:206-208.
33. Ryckman FC, Fisher RA, Pedersen SH, et al. Liver transplantation in children. *Semin Pediatr Surg.* 1992;1:162-172.
34. Rogiers X, Malago M, Gawad K, et al. In situ splitting of cadaveric livers: the ultimate expansion of the donor pool. *Ann Surg.* 1996;224:331-336.
35. Goss JA, Yersiz H, Shackleton CR, et al. In situ splitting of the cadaveric liver for transplantation. *Transplantation.* 1997;64:871-877.

## DISCUSSION

**Carlos O. Esquivel, MD, Palo Alto, Calif:** Dr Goss and coauthors conducted a retrospective review of the UCLA experience with liver transplantation for fulminant hepatic failure in children. Fulminant hepatic failure is somewhat uncommon, but it is associated with an 80% mortality with medical management. Liver transplantation has reversed these results as eloquently described by Dr Goss.

The objective of this investigation was to identify perioperative factors that would predict outcome in children undergoing liver transplantation for fulminant hepatic failure. The authors identified 2 factors that were associated with posttransplant mortality—young age and need for mechanical ventilation. It is not clear to me why young age was found to be a risk factor since other parameters studied, such as thrombosis of the hepatic artery, primary graft nonfunction, and encephalopathy, which have been associated with high mortality in other reports in the literature, were not found to be good predictors of outcome in the present study. Did the small children have to wait longer for a donor and became much sicker in the pro-

cess? Unfortunately, the waiting time for transplantation was not considered during this analysis.

The other risk factor associated with high mortality was the need for mechanical ventilation. The indications for mechanical ventilation were not described in this paper; thus, it is unknown whether mechanical ventilation was used to protect the airway in comatose children, to treat respiratory insufficiency from pulmonary infections or ARDS, or both.

The other pitfall in the analysis was that the impact of the etiology of the liver failure on the clinical course of these patients was not investigated. Small children are prone to viral infections such as echovirus and adenovirus, and I wonder whether the hepatitis was more aggressive in small children than in older patients. This could have led to the rapid onset of multiple organ system failure, the need for mechanical ventilation rendering them poor candidates for transplantation.

But the main problem is that the authors did not properly address the issue of timing for transplantation. If prematurely done, a liver transplant will subject a child to life-long immunosuppression with all of its side effects. On the other hand, a late decision for transplantation may result in permanent neurologic damage or death due to herniation. Although the decision to proceed with transplantation is easy when patients have stage 3 or stage 4 encephalopathy, it can be extremely difficult in patients with stage 1 or 2 encephalopathy, since there is always the possibility for recovery without a transplant.

To illustrate my point, I would like to briefly describe the case of a 4-year-old who was recently referred to Stanford for hepatic transplantation for fulminant hepatic failure. The child had severe coagulopathy and hypoglycemia. She was comatose, requiring endotracheal intubation for protection of the airway. The mother, who was recovering from childbirth, was willing to be a donor. Meanwhile, a cadaveric liver became available and the child was brought to the operating room. The patient's liver was found to have a yellowish discoloration and a consistency firmer than normal. Ascites was also present, but because of concerns with the quality of the donor liver, a frozen-section biopsy of the patient's liver was performed. This biopsy showed extensive areas of necrosis (approximately 60%) with islands of what appeared to be viable hepatocytes, albeit abnormal since most of those hepatocytes showed significant vacuolization. There were also a few scattered mitoses present. I made the decision of not proceeding with the transplant, knowing that I was possibly committing the mother to the risk of an operation should the child not improve. The patient recovered and was discharged 10 days later.

This prompted a quick analysis of our experience. In a period of 9 years, a total of 54 children with fulminant hepatic failure were referred to us for transplantation. Three patients died before transplantation. Of the 51, 25 underwent urgent transplantation and the 5-year actuarial survival for this group is 73%. More importantly, 26 patients (almost 50%) recovered without transplantation.

With this I have a few questions for the authors. (1) During the study period, how many patients recovered without transplantation? (2) At the time of transplantation, are liver biopsies being performed to assess the potential for recovery without a transplant? (3) If biopsies were not performed, what were the clinical and diagnostic indications for transplantation? (4) And lastly, considering UCLA's large experience, would you comment on the use of auxiliary liver transplantation for fulminant hepatic failure?

**Nancy L. Ascher, MD, San Francisco, Calif:** The analysis of this paper raises several interesting questions that are not directly related to the results. There is increasing evidence that *N*-acetylcysteine is useful in all forms of fulminant liver failure, not just acetaminophen overdose; I was wondering whether

you have now changed your protocol and use it in all children who present with fulminant liver failure.

You also presented interesting data on 2 patients who had aplastic anemia. This is a well-recognized complication following liver transplantation in patients with fulminant liver failure based on non-A, non-B, non-C hepatitis. I was wondering whether you have undertaken bone marrow retrieval at the time of cadaveric donation in the event that aplastic anemia appears after transplantation and is problematic.

**John P. Roberts, MD, San Francisco:** One of the things that Dr Esquivel brought up was that it is difficult in these children to decide what is the right timing for transplantation because if you wait too long, you end up having neurologic impairment. If you pull the trigger too quickly, you may end up transplanting a child who didn't need it. This is a problem where a biopsy may help, but it is also one of clinical judgment.

The question that I wanted to ask was about the young children under the age of 4, who were ventilatory-dependent and died. I was wondering what the causes of death were. Were they progressive pulmonary sepsis or were they neurologic injury? It is important to try to understand when this group did poorly so we can do better in this population, which obviously is troublesome.

**Dr Shackleton:** At the outset it must be emphasized that this series spans the entire history of the UCLA Liver Transplant Program since its inception in 1984 and that over this period, both the technical conduct of the procedure, as well as overall patient management, have evolved considerably. Thus, while the conclusions we derived from the present study are valid for its population, they cannot be universally applied to cases done in the current era, but rather they serve as guidelines. For example, we know from our review of the entire UCLA pediatric liver transplant experience, which encompasses some 570 transplants in 440 recipients, that outcome has improved over time. These improvements have been most dramatic for the smallest children, particularly those under 1 year of age. This reflects, in addition to other factors, the introduction of a number of technical refinements, particularly microsurgical arterial reconstruction and partial liver grafting techniques.

These limitations are inherent to any retrospective review but fulminant hepatic failure in children, by virtue of its relative rarity, chronology, and devastating consequences in the majority of cases without liver replacement, defines a set of clinical circumstances that do not lend themselves to prospective evaluation. As such, prudent clinical decision making, including the optimal use of the finite donor resource, must be based on thoughtful reflection of past experience.

Dr Esquivel asked why our findings of predictive factors were unique as compared to those identified by other authors and did not include encephalopathy grade, hepatic artery thrombosis, or waiting time. In our study, pretransplant ventilatory status behaved as a surrogate for the depth of encephalopathy as well as a marker of overall clinical status. In fact, within the Cox regression model, pretransplant ventilator status confounded with encephalopathy grade. We chose to emphasize the former as it represents a more definable clinical milestone in its being less subject to observer variation than is depth of encephalopathy. This characteristic is especially germane to the collection of retrospective data.

With respect to hepatic artery thrombosis, there were only 2 instances in our series, both of whom were successfully retransplanted. Thus, while this factor impacted graft survival, it exerted no significant influence on patient outcome.

Dr Esquivel also asked about the specific etiologies of fulminant hepatic failure, and I regret that we were unable to accurately define the cause in many instances. The inference that specific disease entities may have a differential impact on the time course, severity, and ultimate outcome of disease is clearly

intuitive. Regrettably we cannot, from our current analysis, make such a prognostic distinction. However, it is unlikely, by virtue of the size of the study sample and the spectrum of etiologic agents causing fulminant hepatic failure in children, that statistically significant results would have been generated.

Further, the lack of this data in no way invalidates our conclusion that clinical deterioration to the point that mechanical support of ventilation is required pretransplant portends a markedly inferior outcome irrespective of the specific indications for its use. Granted, it may well be that a child whose pulmonary function has deteriorated as a result of adenoviral pneumonia has somewhat distinct prognostic characteristics as compared to one requiring intubation and ventilation for airway protection as a consequence of grade 4 hepatic coma, but our study is unable to define this distinction. Rather it tells us simply, but with considerable statistical power and irrespective of the specific indications for its introduction, that the need for ventilatory support adversely affects outcome, especially in those under 4 years of age.

The question of the timing of liver replacement in fulminant hepatic failure is, of course, paramount. Undertaken when spontaneous recovery would have occurred it condemns the recipient to life-long immunosuppression whereas waiting too long risks either nonsurvival or permanent neurologic impairment. Further impacting on this decision are the uncertainties of donor organ availability. Dr Esquivel has observed that our failure to provide a set of parameters with which to identify transplant candidates early in the course of their disease, similar to the King's College criteria for adults, is the principal deficiency of our report.

However, such information could only be generated by following the natural history of a large cohort of children with fulminant hepatic failure while withholding liver replacement to determine which constellation of clinical and laboratory characteristics distinguish survivors from nonsurvivors. I submit that the time has long passed when such a study could be done for a disease with an 85% mortality if left untreated and for which a lifesaving therapy already exists. I must reiterate that the purpose of our study was not to review all children with fulminant hepatic failure treated at UCLA but rather the outcome and risk factors of children with fulminant hepatic failure who were transplanted.

At UCLA, the decision to intervene with liver transplantation in these cases is based on considerations of disease etiology, clinical course, and laboratory tests of liver function which collectively strongly suggest an inexorable course together with the potential donor organ options which exist for the individual case. These considerations underscore our belief that optimal outcomes can only be realized through prompt referral to a center that can offer the full spectrum of transplant options.

We do not routinely perform liver biopsy in attempts to garner potentially prognostic information. Even if evidence of hepatic regeneration is seen on biopsy, in some cases the toll already extracted by the cumulative effects of liver failure may have rendered the patient too ill to survive long enough without liver replacement for the liver to regenerate adequately. As such, the decision to transplant must still rest upon clinical and functional characteristics in each individual case as opposed to relying too greatly on morphologic information. One wonders if, in the case described by Dr Esquivel, he mightn't have been prepared to wait as long as he did had he not had a potential living donor available for his patient.

With respect to the question of auxiliary liver transplantation for fulminant hepatic failure, it has indeed been used successfully in small numbers of patients by other groups, notably Dr Bismuth, and it does offer some advantages in allowing time for native hepatic regeneration and subsequent freedom

from immunosuppression should sufficient regeneration occur. We have not, to date, employed this technique at UCLA.

Dr Ascher asked about the wider use of *N*-acetylcysteine for nonacetaminophen-induced cases, and we acknowledge that it may offer some protection from oxidative injury. As it is relatively innocuous from the point of view of toxicity, broader application seems justifiable even if the potential therapeutic yield is small.

Aplastic anemia is a real and serious complication following liver transplantation for fulminant hepatic failure, as pointed out by Dr Ascher. It developed in 2 patients in the present series, both of whom recovered spontaneously following a period of supportive care. We do not routinely obtain bone marrow at the time of transplantation in anticipation of this complication.

Dr Roberts asked about the timing of transplantation, and I have already provided some of our thoughts about this most important issue. I can only reiterate my view of the substantial ethical difficulties that would shroud the undertaking of the

type of study that would be required to obtain reliable data on which to objectively base such decisions. I acknowledge that while clinical judgment based on experience is of considerable value and remains as our best option for the time being, it is more subjective and potentially influenced by bias than would be ideal for a condition in which the stakes are so high.

Finally, we agree with Dr Roberts that the identification of the specific causes of death may have further helped to discriminate distinguishing characteristics between survivors and nonsurvivors. I would submit that the numbers of cases in our series would likely have proved too small to draw statistically meaningful conclusions. While we were unable to stratify cases on the basis of indications for mechanical ventilation, specific etiology, or cause of death, these deficiencies in no way detract from the validity of our conclusion that the need for mechanical ventilation pretransplant portends poorer ultimate survival, especially in small children, and underscores the need for early referral and timely intervention if optimal outcomes are to be realized.

#### IN OTHER AMA JOURNALS

##### ARCHIVES OF PEDIATRICS & ADOLESCENT MEDICINE

##### Shared Management of Children With Cancer

C. Thomas Kisker, MD; Carol C. Fethke, PhD; Raymond Tannous, MD

**Objective:** To determine the risks and benefits of university-based pediatric oncologists and community-based primary care physicians sharing the management of children with cancer.

**Design:** Physicians participating in shared management of children with cancer were surveyed, and the outcomes of the children were measured.

**Setting and Participants:** One hundred thirty-seven community-based primary care physicians participated in the management of the 226 children with cancer in Iowa and western Illinois during the past 15 years. The survival of the 226 children was compared with that of 240 randomly selected children treated using the identical treatment protocols but treated only by pediatric oncologists.

**Intervention:** A 7-point Likert scale questionnaire was completed by 97 (71%) of the participating primary care physicians.

**Results and Outcome Measures:** There were no differences in the survival of children using shared management compared with those treated only by pediatric oncologists. Primary care physicians believed that shared management is of economic and psychosocial benefit to patients, improves the treatment choices available to patients, does not require excessive time, and does not result in loss of practice income. The system strengthens the primary care physicians' relationships with oncologists and results in additional referrals to the university-based pediatric oncologists. It is of educational value, is personally satisfying, and provides relief from the stress associated with caring for these families. Primary care physicians would like to see this system expanded to include other children with special health care needs.

**Conclusion:** The shared-management approach to care is a viable, attractive option of health care provision for children. *Arch Pediatr Adolesc Med.* 1997;151:1008-1013

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