Causes of Late Mortality in Pediatric Liver Transplant Recipients

Debra L. Sudan, M.D., Byers W. Shaw Jr., M.D., Alan N. Langnas, M.D.

From the Department of Surgery, University of Nebraska Medical Center, Omaha, NE

Objective
This study was undertaken to review the incidence and causes of death in children who have survived long-term (more than 1 year) after liver transplantation (LT).

Summary Background Data
No studies of the causes of late mortality in pediatric LT recipients are currently available in the literature.

Methods
The study group consists of 212 pediatric patients who survived more than 1 year after LT. Twenty-three of these patients subsequently died (mean follow-up = 5.3 yr). Hospital records, office charts, and autopsy records were reviewed retrospectively to identify the causes of death. The patients who died were further evaluated by age, gender, length of survival, primary diagnosis, immunosuppression, and retransplantation.

Results
The most common cause of death was graft failure, followed closely by infection. In patients dying from graft failure, eight of the nine patients underwent retransplantation and no child survived more than three liver transplants. Overwhelming infections occurred suddenly in eight children who had been previously healthy. Noncompliance was the third most common cause of death, primarily in older children. One child died from a posttransplant lymphoproliferative disorder (PTLD). Actuarial survival at 10 years is 83.7% (based on 100% survival at 1 year). There was no difference in survival based on primary disease. Retransplantation was far more prevalent in the nonsurvivors (47.8%) compared with survivors (13.7%) (p < 0.05). There were no significant differences in survival based on age, gender, or immunosuppression.

Conclusions
Late mortality in children continues to be directly related to complications of LT and immunosuppression, even after the first year of transplantation. This is in contrast to adult liver transplant recipients, where approximately 50% of late deaths were related to LT and the remainder were because of unrelated illnesses.
Overall survival after liver transplants (LT) has improved dramatically during the past 15 years. One year survival as reported by Kilpe et al. was 35% in 1982 and increased to approximately 85% in 1991. This improvement in survival is multifactorial. Experience with and standardization of operative techniques, the introduction of University of Wisconsin solution, experience in the care of these very ill patients, the introduction of cyclosporine and OKT3, the development of effective antiviral therapies, and an understanding of the infectious risks have all contributed to this improvement in survival. The early posttransplant period is the time with the greatest incidence of death. Shaw et al. found that 43% of deaths occurred in the first month after LT. Likewise, Mora et al. found that 47% of all deaths after LT occurred in the first 3 months. This is further demonstrated by the slopes of the survival curves, which are steep in the first few months and thereafter have a steady but less negative decline. Interestingly, the marked improvement in survival reported by Kilpe et al., was primarily in the early posttransplant period. That is, the slopes of the survival curves of each of the years examined remain parallel, beyond the first year posttransplant. This would indicate that further improvements in the long-term outcome of LT will likely need to be directed at the causes of these late deaths. A knowledge of the causes of late mortality would therefore be helpful in directing these future efforts.

A study of late mortality in adult LT recipients revealed recurrent diseases, including hepatitis and malignancy, to be the most common cause of death beyond the first year. Furthermore, approximately half of the late deaths were because of nontransplant related diseases, which included myocardial infarctions (MI), cerebrovascular accidents (CVA), nonlymphoid de novo malignancies, and trauma. Abu-Elmagd et al. have shown that pediatric recipients of LT, who survive the first year after transplants, have a lower mortality rate than adult LT recipients. Nevertheless, the death rate beyond one year after LT is greater than the general population. Identifying the causes of late mortality, may decrease this risk, by identifying high risk patients or conditions that could be altered in the future. The causes of late mortality in pediatric LT recipients are examined here.

**MATERIALS AND METHODS**

From 1985 to 1995, 263 pediatric patients less than 18 years old underwent LT at the University of Nebraska Medical Center. Fifty-one patients who died during the first year after transplantation were excluded from the analysis. The 212 remaining patients formed the study group of long-term survivors to be examined. Immunosuppression routinely consisted of cyclosporine and prednisone. Antilymphocyte therapy was reserved for the treatment of refractory rejection and rarely was used for induction. The causes of death and demographic characteristics were collected retrospectively from chart review and autopsy reports, where available.

Statistical analyses were performed with Student's t test or Chi square analyses and statistical significance was defined as p < 0.05. Actuarial survival curves were calculated by the Kaplan-Meier method and survival curves were compared using the log rank test.

**RESULTS**

From the study group of 212 LT recipients who survived more than one year, 23 late deaths occurred from 1.1 to 8.3 years after transplantation (mean follow-up of 5.3 years). The causes of late mortality in the 23 pediatric patients include graft failure, infection, noncompliance, post transplant lymphoproliferative disease (PTLD) and complications of cerebral edema. Ten year actuarial survival was 84% in this group of long-term survivors (based on 100% survival at 1 year; Fig. 1 and 65.4% overall (i.e. all 263 pediatric patients). The timing of late deaths is examined in Fig. 2. The two most common causes of late death, graft failure and infection, occurred predominantly in the second and third years. Noncompliance continued to be a serious problem even 5 to 8 years after LT. For LT recipients between the ages of 10 and 17, noncompliance was the leading cause of late mortality.

Deaths from graft failure (n = 9) can be further subdivided into those retransplanted for chronic rejection (n =
Figure 2. Timing of late deaths after pediatric liver transplant.

4), those with late biliary tract complications (n = 3), and those with recurrent diseases (n = 2; hepatitis B and hepatoblastoma). Table 1 summarizes patient characteristics and patient and graft survival times. Four of these nine patients had undergone retransplantation in the early posttransplant period (i.e., days 8 and 35 in patient 2, day 2 in patient 5, days 83 and 110 in patient 7, and day 21 in patient 8). No patient in this series had long-term survival after a fourth liver transplant. Three patients developed severe biliary complications that ultimately led to their graft failure and death. One had been retransplanted on day 2 for primary nonfunction, then developed a late hepatic artery thrombosis in the second allograft and multiple biliary strictures. These strictures were managed for many months with percutaneous biliary catheters. The strictures did not improve, however, and a third liver transplant was performed 605 days after the initial LT. She again developed poor initial graft function and received a fourth allograft eight days later. She died with multiple organ system failure 2 weeks after the fourth transplant. Patient 6 had an anastomotic biliary stricture treated with a metallic stent in the first year after LT. In the fourth year after transplant she developed recurrent cholangitis from stones and sludge that blocked the stent. Surgical removal of the stent was performed, but was complicated by the chronic erosion of the stent through

Table 1. CHARACTERISTICS OF NINE PEDIATRIC LIVER TRANSPLANT RECIPIENTS WITH LATE MORTALITY SECONDARY TO GRAFT FAILURE

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Primary Diagnosis</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Number of Rejection Episodes</th>
<th>Antilymphocyte Therapy</th>
<th>Diagnosis at Retransplant</th>
<th>Graft Survival (days)</th>
<th>Patient Survival (days)</th>
<th>Etiology of Graft Failure</th>
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<tr>
<td>1</td>
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<td>CC</td>
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<td>M</td>
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<td>Yes</td>
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<td>CR</td>
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<td>F</td>
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<td>BS</td>
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<td>1.4</td>
<td>M</td>
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<td>550</td>
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<td></td>
<td>459</td>
<td>459</td>
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</table>

BA = biliary atresia; FHF = fulminant hepatic failure; PNF = primary nonfunction; PIF = poor initial function; HAT = hepatic artery thrombosis; CR = chronic rejection; RD = recurrent disease; CC = cryptogenic cirrhosis; CA = malignancy; BS = biliary stricture; RC = recurrent cholangitis; IN = ischemic necrosis; BHVF = biliary hepatic vein fistula.
the anterior wall of the portal vein. Postoperatively she developed hepatic necrosis, was urgently retransplanted, but died 16 days later. Patient 7 developed cholangitis and was found to have a biliary stricture 22 months after her first LT. After percutaneous dilatation and catheter placement, she developed severe hemobilia from a biliary hepatic vein fistula and underwent retransplantation. She subsequently developed multiple organ system failure and died 81 days after her fourth LT. Interestingly, she had evidence of PTLD involvement of the right lung, stomach, and left ovary on autopsy, although this was not thought to have contributed to her death.

Of the eight children who died from infection later after LT, five were essentially well and at home at the time of sudden onset of sepsis. The other three died periprocedurally; two after percutaneous cholangiography (patients 13 and 17) and one after appendectomy (patient 16). Only two of these eight had ever received antilymphocyte therapy, none of these eight had been treated for a rejection episode within the 12 months before their death, and two had been retransplanted. Additionally, two of these eight patients underwent splenectomy around the time of transplantation for marked thrombocytopenia. Patient 17 received the pneumococcal vaccine, but patient 10 underwent transplantation and splenectomy before the availability of the vaccine. Enteric organisms grew in blood cultures in two of the patients with spontaneous septic episodes (Enterobacter cloacae, Enterococcus faecalis). Patient 10 grew Hemophilus influenza in blood and sputum cultures postmortem. This patient had undergone splenectomy. Table 2 summarizes many of the characteristics of these children who died from infection.

Four patients died due to noncompliance. Three of these four were teenagers at the time of transplant (14.7, 14.8, and 17 years, respectively). All three stopped taking their immunosuppression 2 to 8 years after LT. One patient, who was transplanted at age 4.6 years, died 5.5 years later when her mother refused to allow medical care. She had recovered from a significant infection, but was severely malnourished and debilitated. Against the recommendations of her local physician the patient was taken home where she died approximately 4 weeks later.

The patient who died secondary to PTLD was 11 months old at the time of LT for giant cell hepatitis and cirrhosis. He required retransplantation on Day 6 for hepatic artery thrombosis. Eighteen months after initial LT he developed a sepsis like syndrome and was admitted to a local hospital. No focus of infection was found after extensive workup, however, moderate rejection of his liver allograft was demonstrated on biopsy. He was treated initially with corticosteroids and then OKT3. He had improvement of his liver function tests, however, he continued to have fevers and developed progressive multisystem organ failure and died 581 days after initial LT. On autopsy he was found to have generalized lymphadenopathy and a polyclonal lymphocytic infiltrate of lungs, liver, spleen, kidneys, bone marrow, brain, spinal cord, bladder, prostate, pancreas, esophagus, and adrenal glands. In situ, DNA hybridization for Epstein-Barr virus was negative.

One patient suffered severe neurologic injury second-
ary to cerebral edema at the time of LT for fulminant hepatic failure (FHF), and although he had prolonged survival, he eventually died from complications related to this injury.

The study group was analyzed by age, weight, and gender. No difference in survival was found with age as a continuous variable ($p = 0.17$). Furthermore there was no difference in survival in children greater than 1 year old at the time of transplant compared to children less than 1 year old (92.5% vs. 87.2%, respectively $p = 0.37$). Weight of the recipient (greater or less than 12 kg at the time of transplant) was not a risk factor for survival in this series (86.4% vs. 91.3%, respectively; $p = 0.27$). Likewise, gender did not affect long term survival (male = 91.3%, female = 87%; $p = 0.26$).

Figure 3 reveals the primary diagnoses causing liver failure for the 212 LT recipients. There were no significant differences in the rates of these diagnoses among either long-term survivors or those who died more than 1 year after LT.

Other potential risk factors examined include number of rejection episodes, use of antilymphocyte therapy, and retransplantation (see Tables 3, 4, 5, and 6). Although approximately 80% of these LT recipients experienced at least one episode of rejection, this did not increase their risk of late mortality (1 or more rejection, survival = 87.2% vs. no rejection, survival = 92.5%; $p = 0.45$). The use of antilymphocyte therapy also did not affect long-term survival ($p = 0.72$). Retransplantation, however, was a significant risk factor for late mortality. Actual survival in LT recipients who underwent retransplantation was 70% compared with 93% in recipients with a primary liver allograft ($p < 0.05$). Of the 37 patients retransplanted 29 underwent a total of 2 allografts, (19 during the first year postLT, and 10 more than 1 year after initial LT), 4 patients underwent 3 liver allografts, and 4 patients underwent a total of 4 allografts (Timing of retransplantation in Table 6 is based on the second allograft in patients with more than 2 LT). There was no difference in survival based on the timing of retransplantation, whether it occurred in the early posttransplant period or beyond the first year. However, only three of the eight patients who received more than two allografts remain alive.

## DISCUSSION

This study of long-term survivors after pediatric LT reveals that most late deaths in pediatric LT recipients are related to complications of the allograft and immunosuppression. Infection and graft failure accounted for 74% of late deaths in this series. Furthermore, deaths from infection occurred at a time when immunosuppression was relatively low, leading to a false sense that infection rates would more nearly approximate the general population. A review of the causes and incidence of deaths in the United States in 1991 revealed 40% of deaths in children ages 1 to 14 were related to accidents. Interestingly, this study of pediatric LT recipients identified no late deaths related to accident or trauma. Additionally, cancer,
congenital anomalies, homicide, heart disease, and suicide were all more frequent causes of death in children in the general population than the most common infectious cause. Pneumonia/influenza accounted for only 2% of pediatric deaths in the general population.7 Despite chronic immunosuppression after LT, with a regimen including steroids, there were no deaths in this study group from cardiac disease. Clearly, causes of death in children differ after LT when compared with the general population.

Penn reported that 53% of de novo malignancies in all pediatric organ transplant recipients were lymphomas.8 In this study, only one death was the direct result of malignancy, a de novo lymphoma, leading to death of the recipient 18 months after LT. Penn also reported that the incidence of melanomas, lip cancers, and carcinomas of the vulva, perineum and/or anus were increased in pediatric organ transplant recipients when compared with non-immunocompromised children.8 There was a notable absence of nonlymphoid malignancies in this study, which may be due in part to the length of follow-up of 5.3 years or to a lower level of chronic immunosuppression in these LT recipients compared with other solid organ transplants.

The causes of late death after pediatric LT, also differ from the causes of late death after adult LT. In adults, infection was a relatively uncommon cause of late death after LT (9%).3 In this study of pediatric LT recipients infection was responsible for 35% of late deaths. Recurrent disease, on the other hand, was a relatively rare cause of late death in pediatric LT recipients, and the most common cause of late mortality in adults. Late deaths from graft failure secondary to chronic rejection, occurred at a similar rate in both adults and pediatric LT recipients (3.1% vs. 3.4%, respectively). Despite improvements in immunosuppression over the last 15 years, graft failure is still the most common cause of death in the pediatric LT recipients long-term. Retransplantation may be an option for patients with late graft failure, however, retransplantation yields significantly lower survival than primary grafts.

Belani, et al. suggested that infants less than 1 year of age are a high risk group for LT, whereas, Dunn, et al. found that age was not a risk factor for survival after LT.9,10 The results reported here are consistent with Dunn’s findings that age less than 1 year does not pose increased risk for LT. Similarly, Vazquez examined recipient weight as a risk factor for survival after LT, and as in this series, there was no increased risk for mortality based on recipient weight.11

It is widely accepted that splenectomy causes an increased risk of overwhelming infection, perhaps as high as 40 times the risk of the general population.12 The reported incidence of these infections ranges from 1% to 5%, and is greater in children than adults.13 The mortality rate reported for patients developing postsplenectomy sepsis is approximately 50%.13 In this series, only two patients with late mortality had undergone splenectomy, both of whom died from infection. In patient 10 Hemophilus influenza was indeed cultured from the blood and lung at autopsy, and his death occurred within 2 years of transplantation and splenectomy. The postsplenectomy sepsis syndrome is strikingly similar to the septic episodes described for several of the other patients who died from infection.

It is not yet clear what increased risk LT recipients will experience, because of lifelong immunosuppression, for other age related causes of mortality such as MI, CVA, and nonlymphoid malignancy. The results of this study would seem to indicate that in the first 5 years after liver transplant there does not appear to be an increased risk of vascular disease or nonlymphoid malignancy in children. This will need to be examined, however, as these children become adults.

CONCLUSIONS

Overall actuarial survival is excellent (84% at 10 years) in those patients who survive more than 1 year post LT. Nevertheless, late deaths continue to be related to complications of immunosuppression. Deaths from infection appear to be unpredictable, therefore every febrile illness should be evaluated early and antibiotic therapy instituted as soon as a bacterial infection is suspected. Protocols for postsplenectomy infection prophylaxis are likewise important, since these spontaneous septic episodes are primarily from gram negative bacteria. Chronic rejection is a common cause of late mortality, that may respond to newer immunosuppressives, but can lead to graft failure requiring retransplantation with its attendant risks. Unlike adults, recurrent disease is not a significant risk factor for late mortality in children after LT, but noncompliance continues to be a critical issue in teenage LT recipients.

References

2. Harrison JD, Mirza DF, Gunson BK, et al. Development of indications and results during 10 years of orthotopic liver transplantation. Clinical Transplants 1993;153–160. (Figure 1)