

# CAUSES OF MORTALITY BEYOND 1 YEAR AFTER PRIMARY PEDIATRIC LIVER TRANSPLANT UNDER TACROLIMUS<sup>1</sup>

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**Background.** Success of pediatric liver transplantation has improved significantly. Most posttransplant deaths occur early and are related to surgical complications or recipient status at the time of transplantation. The causes of mortality beyond the first year have not been well described.

**Methods.** Three hundred twenty-six pediatric liver transplants were performed between November 1989 and April 1998 using tacrolimus-based immunosuppression. Patients were followed until March 2002. Mean follow-up was  $9.2 \pm 2.4$  years.

**Results.** At 1 year, 279 patients (85.5%) were alive. In the subsequent 12.5 years, 10 of the remaining children died (3.58%) at a mean interval of  $3.68 \pm 1.69$  years after transplant. The mean age at transplant was  $5.62 \pm 6.3$  years. Six patients had infections as a major contributor to mortality, including two patients with posttransplant lymphoproliferative disorder (PTLD) and one patient that died after retransplantation for hepatitis. Two patients had recurrent malignancy. Other deaths were attributable to chronic rejection, liver failure after being lost to follow-up, and complications of cystic fibrosis.

**Conclusions.** Pediatric liver transplantation using tacrolimus-based immunosuppression has demonstrated excellent success, with 1- and 10-year survival rates of 85.5% and 82.9%, respectively. Late mortality after pediatric liver transplantation overall remains low, with a rate of 0.32% per year. The most common cause of death was infection (60%), including PTLD-related disease (20%). However, in the recent cohort of patients who underwent transplantation after September 1995, there were no fatal cases of Epstein-Barr virus or PTLD or late mortality thus far, suggesting a benefit from improved infectious disease surveillance using currently available modalities. Mortality from chronic rejection and noncompliance under tacrolimus has been exceedingly rare.

Liver transplantation is the procedure of choice for progressive, irreversible hepatic insufficiency. Outcomes after liver transplantation, particularly in children, have improved significantly over the past two decades because of improvements in operative technique and organ preservation, improved perioperative management, and advances in immunosuppressive medication protocols (1, 2). The majority of posttransplant deaths occur early and are related to infection; surgical complications; recipient age, size, and status at the time of transplantation; and primary graft nonfunction (3, 4). Late mortality in adults is related primarily to infection, chronic rejection, recurrent or de novo malignancy, recurrent disease (especially hepatitis), and age-related complications (5–7). Late outcome after pediatric transplantation has been reported to differ from that of adults (1, 8–10). These previous reports highlight infectious complications and posttransplant lymphoproliferative disease (PTLD) as the primary causes of death in the late postoperative period with several reported late deaths from chronic graft dysfunction. These reports focused primarily on transplants performed in an earlier era of pediatric hepatic transplantation under cyclosporine-based immunosuppression. This article examines the mortality rate and the various causes of death beyond the first posttransplant year in children receiving tacrolimus-based immunosuppression.

## MATERIALS AND METHODS

Three hundred twenty-six pediatric liver transplants were performed at the Children's Hospital of Pittsburgh between November 1989 and April 1998. The indications for transplantation are listed in Table 1. Initial immunosuppression management was with steroids and tacrolimus as described previously (11). Target tacrolimus whole blood trough levels at 1 month, 2 to 3 months, and 3 to 12 months were 15, 12, and 8 to 10 ng/mL, respectively. Thereafter, tacrolimus levels were maintained between 5 and 8 ng/mL in those patients with a documented history of rejection or at high risk for rejection. In all others, tacrolimus dosage was not routinely adjusted to maintain a target level as long as liver function remained normal. In a previously reported cohort of these patients, mean tacrolimus dose per day (in milligrams) and mean whole blood trough levels (in nanograms per milliliter) at 1, 2, 4, and 7 years were 4.3 mg and 7.3 ng/mL, 3.9 mg and 8.2 ng/mL, 3.4 mg and 6.6 ng/mL, and 3.0 mg and 5.0 ng/mL, respectively (11).

Steroids were administered as a solumedrol bolus (10 mg/kg intravenously) followed by a rapid taper and conversion to oral prednisone within the first week. Attempts at steroid weaning were typically initiated at 3 months. Patients received prophylaxis against *Pneumocystis carinii* and received intravenous ganciclovir prophylaxis. Acute rejection was treated with intravenous steroids, reserving OKT3 or antilymphocyte globulin for steroid-resistant rejection. Third-agent immunosuppression with azathioprine or mycophenolate mofetil was introduced only in cases of resistant or recurrent rejection or for tacrolimus-related nephrotoxicity.

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**TABLE 1. Indication for liver transplantation in 326 pediatric recipients treated with primary tacrolimus immunosuppression**

Indication for liver transplantation	No. (%)
Biliary atresia	153 (46.9)
Metabolic	46 (14.1)
ALF	25 (7.6)
NANB hepatitis	9 (2.7)
Cryptogenic	15 (4.6)
Familial cholestasis	10 (3.0)
Primary hepatic malignancy	12 (3.6)
Neonatal hepatitis	7 (2.1)
Secondary biliary cirrhosis	6 (1.8)
Congenital hepatic fibrosis	10 (3.1)
Autoimmune hepatitis	4 (1.2)
PSC	3 (0.9)
HCV	2 (0.6)
Budd-Chiari	3 (0.9)
HBV	1 (0.3)
Others	20 (6.1)
Cystic fibrosis	7
TPN liver failure	3
Nodular regenerative hyperplasia	3
Hemangioma	1
Indian childhood cirrhosis	2
Adrenoleukodystrophy	1
Histiocytosis X	1
Biliary dysgenesis	1
Unknown	1
Total	326

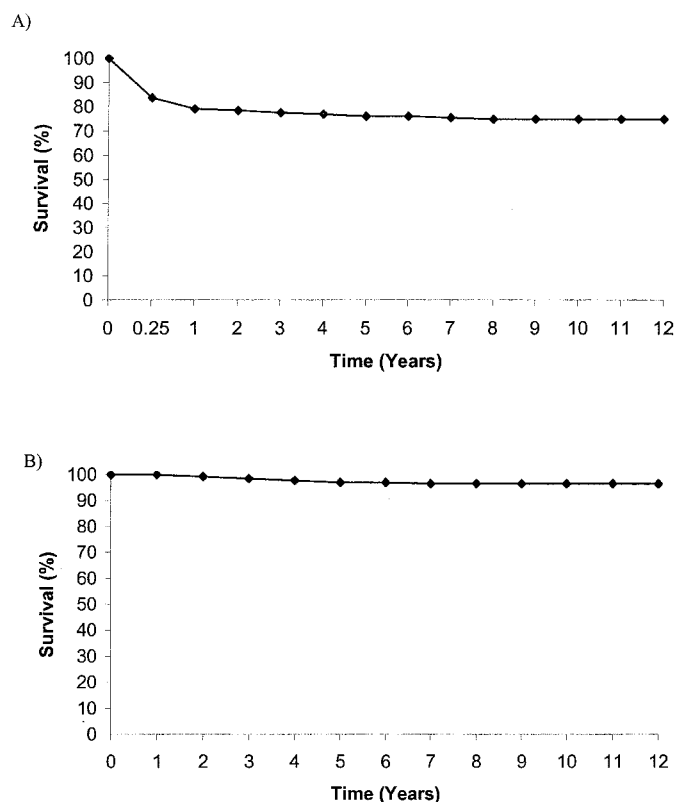
ALF, acute liver failure; NANB, non-A, non-B hepatitis; PSC, primary sclerosing cholangitis; HCV, hepatitis C virus; HBV, hepatitis B virus.

Study patients were followed until March 2002. The mean follow-up was  $9.2 \pm 2.4$  years (range, 1.74–12.5 years). There were 178 boys (55%) and 148 girls (45%), with a mean age at transplant of  $5.33 \pm 5.3$  years. Actuarial survival curves were generated using Kaplan-Meier estimates (SPSS for Windows, Version, 10.1, SPSS, Inc., Chicago, IL).

## RESULTS

At 1 year, 279 patients (85.5%) were alive. In the subsequent 2 to 12.5 years, 10 of the remaining children died (3.58%) at a mean interval of  $3.68 \pm 1.69$  years. The patient survival curves for all pediatric liver transplant recipients and for recipients who survived beyond the first posttransplant year are presented in Figure 1. One- and 10-year survival rates are 85.5% and 82.9%, respectively. Patient demographics and causes of death after 1 year are depicted in Table 2. Of these patients, there were six boys (60%) and four girls (40%), with a mean age at transplant of  $5.62 \pm 6.3$  years. Of these 10 patients who died beyond the first posttransplant year, infection was a major contributor to mortality in the majority (six of ten). Two patients died from recurrent malignancy. One patient (patient 10) died of pulmonary complications from his preexisting cystic fibrosis. One patient died of liver failure after being lost to follow-up and with known compliance issues.

In patients with infectious mortality, two died because of Epstein-Barr virus (EBV) and PTL. One patient (patient 7) died within a month after retransplantation for hepatitis (hepatitis C virus–negative, EBV–negative) performed 2.18 years after his initial transplant for biliary atresia. The re-



**FIGURE 1. Patient survival (A) and survival beyond first post-transplant year (B) in 326 pediatric liver recipients who underwent transplantation between November 1989 and April 1998 under tacrolimus-based immunosuppression.**

maining three patients had pneumonia (patient 1), candida sepsis (patient 3), and sepsis-like syndrome of unknown origin (patient 9). Of these six patients, three had had prior rejection episodes (50%), one of which was treated with antilymphocyte therapy. This one patient (patient 4) received a course of OKT3 (three doses of 5 mL) more than 3 years before his death.

Two of the patients who underwent transplantation for primary hepatic malignancies died from diffuse metastatic disease. Patient 2 developed recurrent hepatocellular carcinoma more than 4 years after transplant for a stage IVA (T4N1M0) lesion. Patient 8 had a liver transplant for a  $20 \times 15 \times 10$ -cm lesion involving approximately 90% of the liver, with two smaller nodules included with the resected liver specimen. Pathologic examination demonstrated an infantile multicentric epithelioid hemangioendothelioma confined to the liver; this patient developed recurrent angiosarcoma 2 years after transplant. Both of these patients had received chemotherapy after transplant. Patient 6 underwent transplantation for liver failure resulting from a Budd-Chiari syndrome complicating resection of an epithelioid hemangioendothelioma. This patient survived without recurrent malignancy, but died of disseminated PTL 2.27 years after transplant.

## DISCUSSION

Our data demonstrate that pediatric liver transplantation using tacrolimus-based immunosuppression has resulted in

**TABLE 2. Patient demographics and causes of death**

Patient	Age at transplant (yr)	Gender	Indication	Interval of death from transplant (yr)	Cause of death
1	9.19	Female	Familial cholestasis	7.03	Sepsis, pneumonia
2	15.69	Female	Fibrolamellar HCC	4.86	Recurrent malignancy
3	0.53	Male	Biliary atresia	4.78	Chronic rejection, candida sepsis and pancreatitis
4	10.61	Male	Congenital hepatic fibrosis	3.47	Disseminated gastrointestinal PTLD, pancytopenia
5	0.56	Male	Cryptogenic cirrhosis	3.45	Liver failure, noncompliance
6	0.43	Male	Epithelioid hemangioendothelioma, Budd-Chiari	2.27	Disseminated PTLD, pseudomonas pneumonia
7	1.51	Male	Biliary atresia	2.27	Early complications after retransplantation for hepatitis
8	1.94	Female	Angiosarcoma	2.04	Recurrent malignancy
9	0.85	Female	Biliary atresia	1.74	Sepsis syndrome
10	14.93	Male	Cystic fibrosis	4.89	Pulmonary events secondary to cystic fibrosis

excellent success, with 1- and 10-year survival rates of 85.5% and 82.9%, respectively. Late mortality beyond 1 year after pediatric liver transplantation overall remains low, with a rate of 0.32% per year.

The majority of previous reports describing late pediatric mortality after liver transplantation are based on primary cyclosporine immunosuppression. These reports are summarized in Table 3. Of the 577 patients studied in all of these reports, there were 49 late deaths (8.5%). The most common cause of mortality beyond the first year in all of these studies was infection, accounting for 29 of the 48 deaths (60%), of which PTLD accounted for 6 of the 48 (12.5%) deaths. Recurrent primary hepatic disease was also common, accounting for 6 of 48 (12.5%) late deaths. The largest study to date in the cyclosporine era was by Sudan et al. (8, 9), who also found a particularly high incidence of late mortality secondary to chronic rejection and noncompliance, both of which accounted for 4 of 24 (17%) of their late mortalities.

**TABLE 3. Causes of late mortality after pediatric liver transplantation: literature review**

Author	No. of patients	No. of deaths (%)	Causes of death
Sudan et al. (8, 9)	212	23 (10.8)	8 infections 4 noncompliance 1 PTLD 4 chronic rejection 3 biliary complications 1 recurrent HBV 1 recurrent malignancy (hepatoblastoma) 1 cerebral edema
Ryckman et al. (20)	132	15 (11.1)	11 infections 3 PTLD 1 recurrent hepatitis
Migliazza et al. (10)	158	9 (5.69)	3 infections 3 complications of the primary disease 2 PTLD 1 variceal bleeding
Asfar et al. (7)	75	1 (1.3)	CMV sepsis after third transplant

We have recently reported the 20-year experience with pediatric liver transplantation at our institution (2). Of 808 pediatric recipients of liver allografts, 326 patients (40.3%) were treated with tacrolimus-based immunosuppression. A significant difference in survival between children treated primarily with cyclosporine-based immunosuppression versus tacrolimus-based immunosuppression became evident: 71.2%, 68.1%, 65.4%, and 61% versus 85.8%, 84.7%, 83.3%, and 82.9% at 1, 3, 5, and 10 years, cyclosporine versus tacrolimus, respectively ( $P=0.0001$ ). This improvement in survival is most likely multifactorial and reflects earlier patient referral, improvements in operative and perioperative patient management, and an increased understanding of immunosuppressive agents. However, in terms of impact on survival beyond 1 year and quality of life, the immunosuppressive regimen becomes the most critical determinant. In fact, in this group of patients, death directly related to either acute or chronic rejection was not seen under tacrolimus-based immunosuppression. Because late survival after transplantation is inherently related to immunologic phenomena vis-à-vis the balance between acute or chronic rejection and infection, understanding the impact from the type of immunosuppressive therapy is critical. Consequently, it may be inferred from this that steroid-free regimens and the ability to maintain drug monotherapy free of rejection are reasonable long-term goals.

Our data highlight several important issues that add to the experience previously reported. Significantly, infections remain a frequent cause of death in these children experiencing late mortality after liver transplantation. One of these patients had a documented pneumonia, another one had candida sepsis in the background of chronic rejection and pancreatitis, and yet another presented with fulminant systemic inflammatory response syndrome without actual documentation of a micro-organism. We have made the assumption that these deaths were attributable to an infectious cause, perhaps as an altered presentation of a community-acquired viral illness in the background of an immunosuppressed individual, although this was not confirmed by culture. Although the incidence of late infection is significantly decreased over prior reports, it remains an important issue.

Several factors may explain this and require further study. One explanation may be an unnecessarily high maintenance level of immunosuppression before the onset of illness. Alternatively, patients who reject late after transplant may be recalcitrant to therapy and therefore prone to require more intensive therapy with subsequent increased risk for infectious morbidity and mortality. Our data support the continued need to tailor long-term posttransplant immunosuppression as much as possible to specific patient needs and, when possible, to consider weaning or withdrawing immunosuppression (11–14).

EBV-related disease accounted for 2 of the 10 late deaths observed in this series. Of interest, both of these deaths occurred in the early cohort of patients treated with tacrolimus-based immunosuppression followed through June 1995. The two deaths appeared to be related to complications of disseminated PTLD and not to acute or chronic rejection episodes developing as sequelae of withdrawal of immunosuppression. In the group of patients followed since 1995, there has been no EBV-related late mortality. This may be in part because of the availability of EBV polymerase chain reaction monitoring introduced in 1997 (15–17), which allows for earlier diagnosis of EBV disease and even preemptive treatment of subclinical elevations in the EBV viral load. The availability of EBV viral load monitoring may also contribute to improved outcome of EBV-associated PTLD by providing a marker of a patient's response to therapy (18), identifying those who might benefit from the use of more aggressive, second-line treatments such as rituximab or chemotherapy.

Malignancy, although uncommon as an indication for transplant, certainly has had good long-term results. Two patients in our study survived beyond the first year and subsequently died from recurrent primary malignancy. A third child, who underwent transplantation for complications after resection of his malignancy, died of PTLD-related disease. The remainder of the 12 patients who underwent transplantation for hepatic malignancies did not die from recurrent malignancy by the end of our study period and are reported elsewhere (19).

Chronic rejection has also become rare as a cause of late liver failure and mortality in our series. This is distinct from the incidence of mortality from chronic rejection reported under cyclosporine (8, 9). Only one child developed chronic rejection under tacrolimus-based immunosuppression. His progressive liver failure was complicated by pancreatitis and candida sepsis before the availability of a suitable organ for retransplantation. Noncompliance as a cause of late mortality in this group also appears to be less of an issue with tacrolimus-treated children. Only one patient was lost to noncompliance issues, and this was related more to familial noncompliance.

#### CONCLUSION

Liver transplantation in pediatric recipients remains the procedure of choice for children with end-stage liver failure. Survival of children undergoing transplantation during the tacrolimus era in our hospital that survive beyond the first year is excellent, with a cumulative mortality rate of 3.58% beyond this time point and an annual mortality rate of 0.32% per year. The late deaths in our institution have been primarily related to infections. PTLD, which was originally a

significant contributor to late mortality, has become an exceedingly rare cause of death more recently. Similarly, mortalities from chronic rejection and noncompliance under tacrolimus have become unusual as well. This suggests a benefit from recent improvements in immunosuppressive regimens, infectious disease surveillance, and minimization of long-term immunosuppressive drug therapy, which culminate in an improved quality of life and improved survival. Continued improvement, however, must be made to individualize immunosuppressive therapy in order to further minimize long-term morbidity and mortality.

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