Registry of the International Society for Heart and Lung Transplantation: Ninth Official Pediatric Heart Transplantation Report—2006

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The ninth official pediatric report of the International Society for Heart and Lung Transplantation (ISHLT) covers the pediatric heart transplant experience from 1982 through 2005. This worldwide experience in pediatric heart transplantation represents a unique documentary in an ongoing effort to help children with lethal cardiac disease. Some aspects of pediatric heart transplantation have been remarkably stable, such as the number of transplants each year, whereas other aspects show continuing evolution in the care of these patients and their outcomes. The indications for pediatric heart transplantation have settled into a pattern that is reflective of structural congenital heart disease leading to heart transplantation in infancy, and of cardiomyopathy in the majority of adolescents. Re-transplantation has been slowly but steadily increasing as an indication in the adolescent age group, and this year we present data evaluating the inter-transplant interval and outcomes of re-transplantation. All figures and tables from this report and a more comprehensive set of registry slides are available from the ISHLT website (http://www.ishlt.org/registries/).

Overall survival continues to improve and the spectrum of immunosuppressive regimens has broadened. In this large registry experience it is still difficult to see distinct differences in outcomes based on the immunosuppressive regimen used, and we have not observed a difference between outcomes with cyclosporine vs tacrolimus as primary T-cell activation inhibitor therapy. Risk factors for short-term survival are related to the indication for transplant, and also to the severity of illness at the time of transplant. Late survival continues to be affected by early rejection, as well as the severity of illness at the time of transplant. Coronary vasculopathy also remains a threat to long-term survival.

We continue to update the most recent experience in an attempt to capture what is presently occurring in the pediatric heart transplant community. The current data, when compared with previous registry reports,[1] allow us to evaluate trends in patient management and outcomes over time. The long-term survivors of pediatric heart transplantation continue to demonstrate excellent recovery and rehabilitation, but there remains an ongoing risk of late graft loss due to graft failure and vasculopathy. Fortunately, the youngest recipients with a lifelong need for graft survival seem to be at less risk for these problems.

STATISTICAL METHODS

Survival rates were calculated using the Kaplan-Meier method and compared using the log rank test as described previously.[2,3] The predicted survival curves were computed for specified patient/donor/transplant profiles as outlined elsewhere.[1]

PEDIATRIC HEART TRANSPLANTATION

Volumes and Indications

The total number of pediatric heart transplant procedures, including re-transplants, has decreased slightly from its peak in the early 1990s (Figure 1). The age distribution of pediatric heart recipients has remained unchanged from previous years, and the distribution of donor ages is also similar (http://www.ishlt.org/registries/). However, the number of heart transplant centers reporting to the registry has shown a steadily decreasing trend from its peak in the mid-1990s, and this has, in effect, created a concentration of transplant experience. Almost 40% of patients are now being transplanted by a center with a volume of between 10 and 19 procedures per year (Figure 2). During the same period, the percent of transplants done at centers performing ≤4 each year has decreased from 33% to 25%.

The most common indication for transplantation in the infant age group remains congenital heart disease, and the trend toward an increasing percentage of patients with cardiomyopathy has reached a plateau over the last several years. Re-transplantation is

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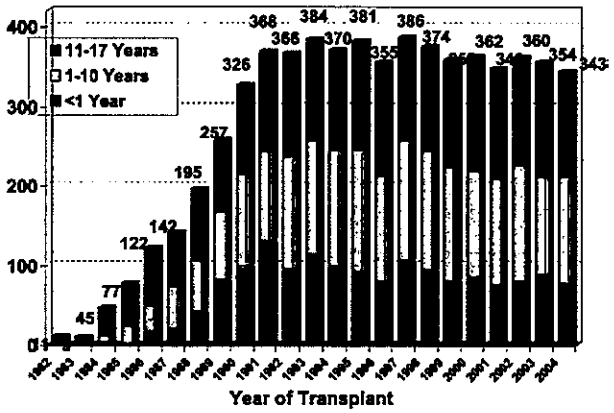

Figure 1. Age distribution of pediatric heart recipients by year of transplant.

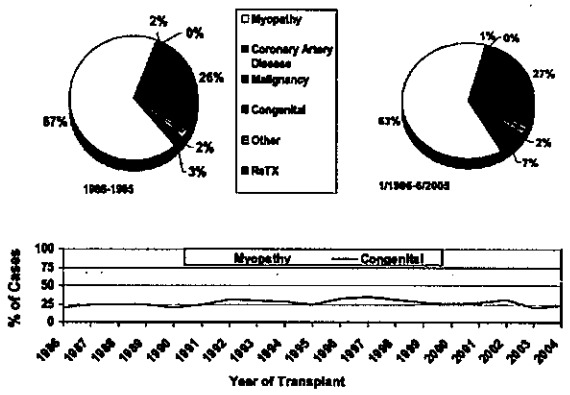

Figure 3. Pre-transplant diagnosis in 11- to 17-year-old heart transplant recipients.

infrequent in the infant age group (http://www.ishlt.org/registries/). Among the child recipients, the percent of patients with congenital heart disease and cardiomyopathy is more closely balanced. This proportion has been stable for approximately 5 years, whereas the percent of patients with a diagnosis of re-transplantation has been creeping upward in recent years (http://www.ishlt.org/registries/). The diagnosis leading to transplantation for adolescent recipients (11 to 17 years) has remained stable and is dominated by myopathic disease (Figure 3). As seen in child recipients, re-transplantation is slowly increasing, and reflects the large number of patients transplanted in infancy and childhood who reach adolescence and then require re-transplantation. There is a small, but constant, need for re-transplantation within the first 5 years of the primary transplant (Figure 4). However, the majority of these patients underwent re-transplantation >5 years after their original transplant. The effect of inter-transplant interval on outcome was evaluated, and is presented later in this report (see Survival section).

Immunosuppression

Compared with recent registry reports[2] there has been little change in immunosuppressive agents taken by pediatric heart recipients (Figure 5). A slight preponderance of patients are on tacrolimus as their calcineurin inhibitor, and rapamycin use remains infrequent at both 1 year and 5 years after transplant. The proportion of patients on mycophenolate mofetil (MMF) has remained stable, as has the proportion of patients on prednisone. The proportion of patients receiving azathioprine continues to decrease compared with previous reports, and now only about 25% of patients take azathioprine at 1-year post-transplant. The most common combinations of therapies include tacrolimus or cyclosporine as the primary calcineurin inhibitor, and MMF. A smaller percent of patients are taking a calcineurin inhibitor combined with azathioprine. Even smaller still is the proportion receiving either cyclosporine or tacrolimus alone as maintenance immunosuppression (http://www.ishlt.org/registries/). There has been a recent trend toward decreased use of induction therapy (Figure 6). In 2003, >50% of patients were receiving induction

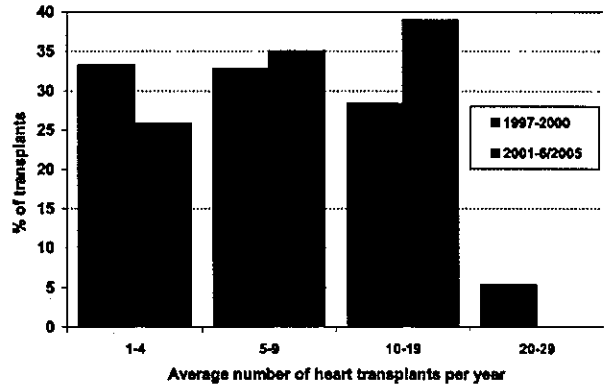

Figure 2. Distribution of pediatric heart transplants by center volume (transplants: January 1, 1997 to June 30, 2005).

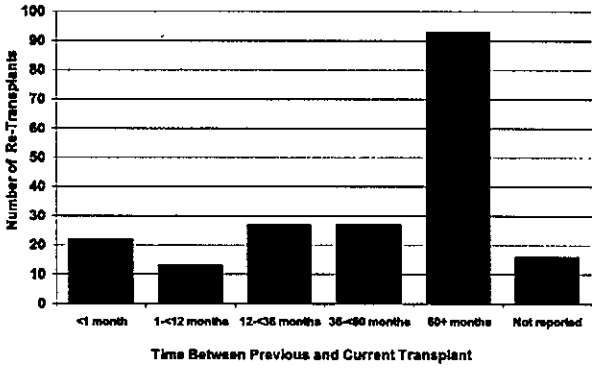

Figure 4. Number of pediatric heart re-transplants stratified by inter-transplant interval (re-transplants: January 1994 to June 2005). Note: Different patients analyzed between Year 1 and Year 5.

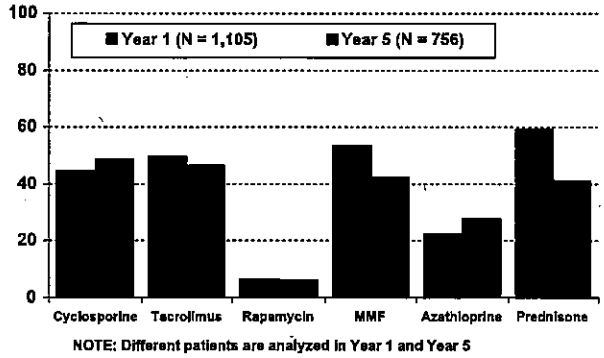

Figure 5. Pediatric heart recipients: maintenance immunosuppression (follow-ups: January 2001 to June 2005).

immunosuppression, but this has decreased to just over 40%; this reduction has affected all of the various induction agents.

The effect of maintenance immunosuppressive therapy on acute rejection in the first year post-transplant is displayed in Figure 7. Combinations of cyclosporine with either MMF or azathioprine are associated with a higher frequency of rejection in the first year, as compared to combinations of tacrolimus with either MMF or azathioprine. This trend is observed regardless of age group or gender. Figure 8 displays the influence of induction therapy, with either maintenance cyclosporine or tacrolimus, on subsequent rejection within the first year after transplant. Again, tacrolimus was associated with a lower percentage of patients treated for rejection within the first year, and induction therapy did not seem to have any consistent effect across age groups or by gender. In fact, if one looks at induction therapy alone, there is no real effect on the proportion of patients treated for rejection with either the polyclonal or the interleukin-2 receptor (IL-2R) antagonist. However, with OKT3 there was an increase in the percentage of patients treated for rejection within 1 year (http://www.ishlt.org/registries).

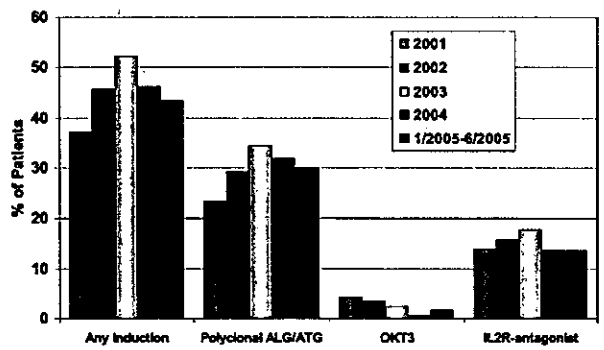

Figure 6. Pediatric heart recipients: induction immunosuppression (transplants: January 2001 to June 2004).

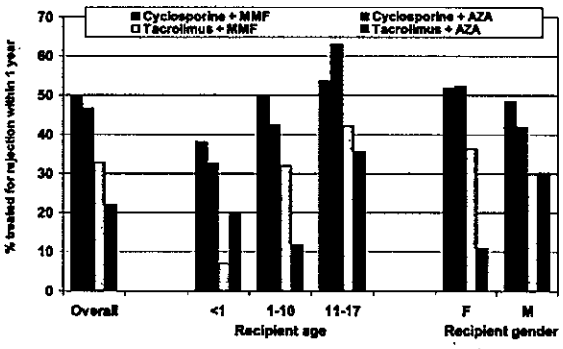

Figure 7. Pediatric heart transplant recipients treated for rejection in the first year stratified by maintenance immunosuppression (transplants: January 2000 to June 2004). Statistical comparisons: overall: CyA + MMF vs TAC + MMF ($p = 0.0011$), CyA + MMF vs TAC + AZA ($p = 0.0011$), CyA + AZA vs TAC + MMF ($p = 0.009$), CyA + AZA vs TAC + AZA ($p = 0.009$); <1 year: CyA + MMF vs TAC + MMF ($p = 0.004$), CyA + AZA vs TAC + MMF ($p = 0.01$); 1 to 10 years: CyA + MMF vs TAC + MMF ($p = 0.4$), CyA + MMF vs TAC + AZA ($p = 0.004$), CyA + AZA vs TAC + AZA ($p = 0.019$); 11 to 17 years: CyA + AZA vs TAC + MMF ($p = 0.012$). Female: CyA + MMF vs TAC + AZA ($p = 0.002$), CyA + AZA vs TAC + MMF ($p = 0.045$), CyA + AZA vs TAC + AZA ($p = 0.001$), TAC + MMF vs TAC + AZA ($p = 0.038$). Male: CyA + MMF vs TAC + MMF ($p = 0.007$).

Outcomes

Survival. Improved survival is evident over the two decades of pediatric experience (Figure 9). Most of this improvement occurred during the 1990s, with the most

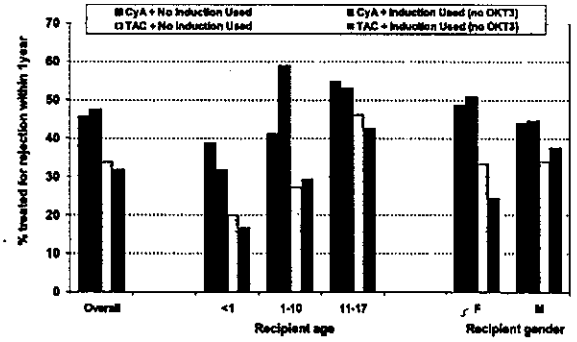

Figure 8. Pediatric heart transplant recipients treated for rejection in first year stratified by calcineurin inhibitor and induction (transplants: January 2000 to June 2004). Statistical comparisons: overall: CyA + no induction vs TAC + no induction ($p = 0.0076$), CyA + induction vs TAC + induction ($p = 0.012$), CyA + induction vs TAC + no induction ($p = 0.0025$), CyA + no induction vs TAC + induction ($p = 0.024$); <1 year: CyA + no induction vs TAC + no induction ($p = 0.047$); 1 to 10 years: CyA + no induction vs TAC + no induction ($p = 0.047$), CyA + induction vs TAC + induction ($p = 0.036$), CyA + induction vs TAC + no induction ($p < 0.0001$), CyA + no induction vs CyA + induction ($p = 0.0143$). Female: CyA + no induction vs TAC + no induction ($p = 0.028$), CyA + induction vs TAC + induction ($p = 0.0049$), CyA + induction vs TAC + no induction ($p = 0.0097$), CyA + no induction vs TAC + induction ($p = 0.011$). No other age group or gender differences were statistically significant.

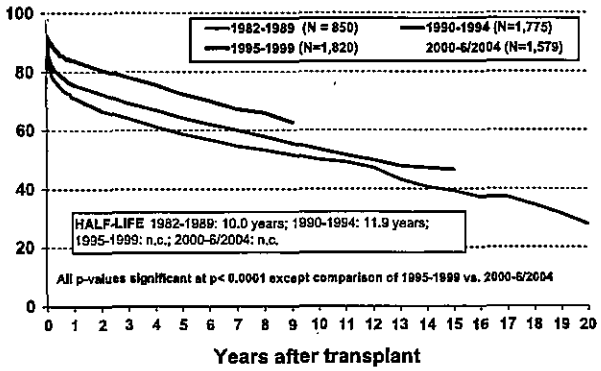

Figure 9. Kaplan–Meier survival stratified by era.

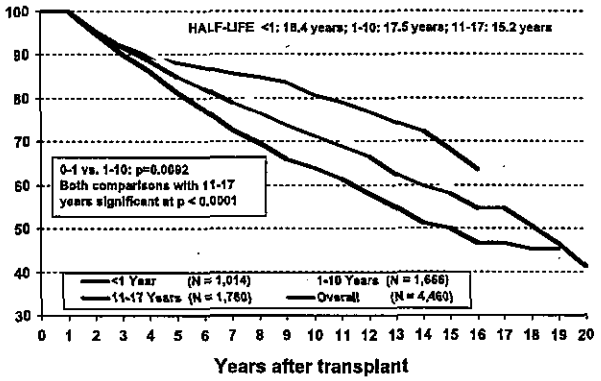

Figure 11. Kaplan–Meier survival conditional on survival to 1 year stratified by recipient age (transplants: 1982 to June 2004).

recent survival curve from 2002 to 2004 almost superimposable over the survival curve of 1995 to 1999. As noted in previous reports, the infant age group was associated with higher early mortality and adolescence with higher late mortality (Figure 10). When plotted over the almost 20 years of experience, the estimated half-life for infant recipients (<1 year of age) was 14.9 years, for child recipients 13.4 years, and for adolescent recipients 11.5 years. The improvement in survival noted over the last 20 years is most striking in the infant and child age groups (http://www.ishlt.org/registries/).

Analysis of conditional Kaplan–Meier survival for pediatric recipients, in which only patients who survive beyond the first year of transplant are considered, eliminates the relatively high early mortality (Figure 11). The late survival curve shows an ongoing risk of death with time since transplant. The late risk of death was lower for infant recipients (estimated conditional half-life: 18.4 years) vs adolescent recipients (estimated conditional half-life: 15.2 years). There is a significant difference in late survival for both infant and child recipients, as compared with the adolescent recipients. However, all age groups seem to share the ongoing risk of graft loss. This trend continued even if the conditional survival is extended to 5 years, to eliminate the impact of all early mortality. Still, there was an ongoing late graft loss, although this was less marked for infant vs adolescents recipients (http://www.ishlt.org/registries/). Even during the most recent era, from 1999 to 2004, the late survival conditional on survival to the first year was better for infant recipients (http://www.ishlt.org/registries/).

Survival after re-transplantation is shown in Figure 12. The survival curve for patients undergoing primary transplantation is also included for comparison. Patients with an inter-transplant interval <36 months appear to have reduced survival compared with patients undergoing primary transplant. However, for re-transplant recipients beyond 3 years after the date of their primary transplant, survival tracks very closely with the primary transplant survival curve.

Early rejection within the first year post-transplant continues to have an important impact on late survival (Figure 13). Patients free from rejection during the first year have significantly better survival at 10 years than those who undergo rejection therapy during the first year. Even when this analysis is restricted to the most recent era, from January 2000 to June 2003, a significant effect is still detected with early rejection associated with increase mortality (http://www.ishlt.org/registries/).

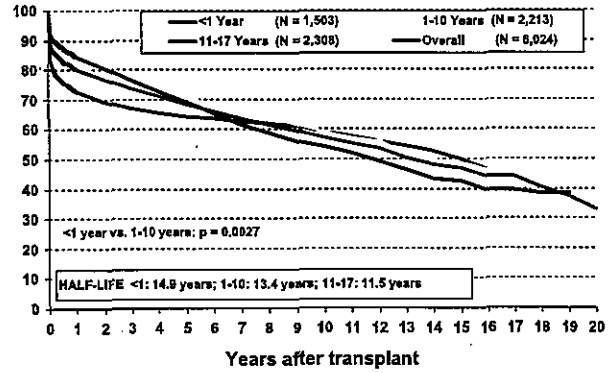

Figure 10. Kaplan–Meier survival stratified by recipient age (transplants: 1982 to June 2004).

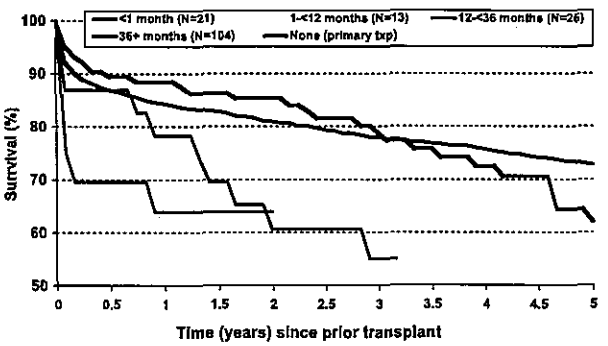

Figure 12. Kaplan–Meier survival after re-transplantation stratified by inter-transplant interval (transplants: 1994 to June 2004).

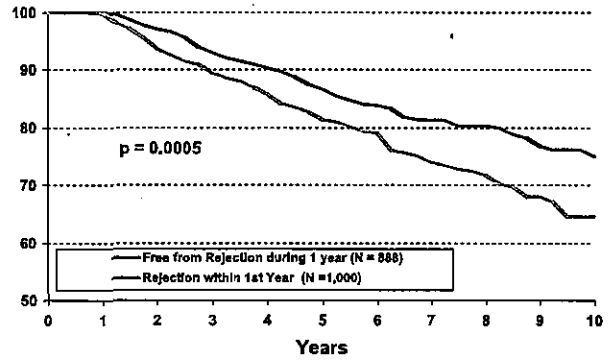

Figure 13. Kaplan–Meier survival conditional on survival to 1 year stratified by rejection within first year (transplants: April 1994 to June 2003).

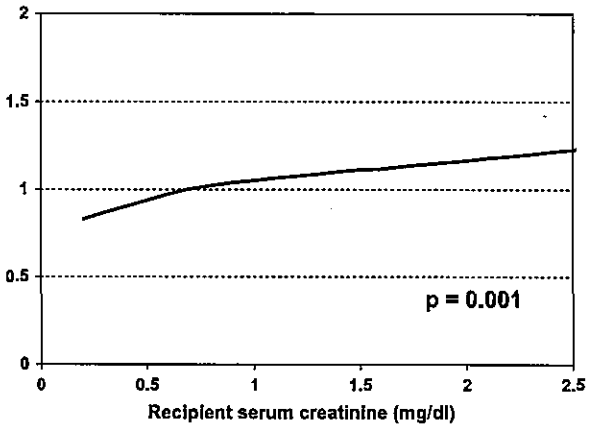

Figure 14. Impact of pre-transplant creatinine on mortality within 1 year (multivariate analysis of transplants between 1995 and June 2004).

Risk Factors for Mortality

Table 1 shows the factors associated with increased risk for 1-year mortality for all 3,341 registrations between 1995 and June 2004. The greatest relative risk was in the few patients who had a congenital diagnosis leading to transplant, and who also were on extracorporeal membrane oxygenation (ECMO) at the time of transplant. The next highest group was those with a congenital diagnosis but not requiring mechanical support, followed by re-transplantation, year of transplant, and whether the patient was hospitalized or on a ventilator. Several other factors did not reach the level of significance, but there was a trend toward increased mortality with mechanical support, either ECMO (with diagnosis other than congenital) or a ventricular assist device. Finally, female recipients were also at increased relative risk (RR = −1.2), but the *p*-value was marginally significant at 0.055. The continuous factors associated with 1-year mortality include donor age, bilirubin and creatinine at the time of transplant, and the donor:recipient weight ratio (http://www.ishlt.org/registries/). The factors not associated with 1-year mortality include previous sternotomy or thoracotomy, history of malignancy, age, pulmonary artery pressure, pulmonary vascular resistance and panel-reactive antibodies (PRA). Donor gender, history of donor infection, cytomegalovirus (CMV) mismatch, ischemic time, HLA mismatch and transplant center volume also were not related to 1-year mortality. There was a significant increase in the RR of 1-year mortality with increasing recipient creatinine at the time of transplant (Figure 14). This trend was similar to that observed with bilirubin, presumably because both reflect the adverse influence of an ill recipient with end-organ injury on subsequent outcome.

The risk factors for 5-year mortality were similar to the risk factors for 1-year mortality (Table 2). Interestingly, re-transplant (all inter-transplant intervals) was associated with the highest RR. The needs for dialysis or ECMO at the time of transplant, indicating increased illness severity, were important factors in 5-year mortality. Congenital diagnosis leading to transplant, and also the year of transplant, remain important risk factors for 5-year mortality. It is perhaps of greater interest to look at the factors not associated with 5-year mortality, specifically: age of recipient; history of recent infection; PRA; pulmonary vascular resistance; pulmonary artery (PA) pressure; donor cause of death; donor:recipient weight ratio; graft ischemic time; and human leuko-

Table 1. Pediatric Heart Transplants (January 1995 to June 2004): Risk Factors for 1-Year Mortality (N = 3,341)

Variable	N	Relative risk	p-value	95% confidence interval
Congenital diagnosis, on ECMO	81	4.57	<0.0001	3.03 to −6.89
Congenital diagnosis, no ECMO	1,025	2.11	<0.0001	1.68 to −2.65
Other diagnosis (not congenital, cardiomyopathy or re-transplant)	122	1.92	0.0072	1.19 to −3.10
Re-transplant	160	1.85	0.0043	1.21 to −2.83
Year of transplant: 1995 vs 1998	361	1.84	0.0016	1.26 to −2.68
Congenital diagnosis, age = 0 year, on PGE	189	1.73	0.0074	1.16 to −2.58
Year of transplant: 1996 vs 1998	341	1.6	0.0204	1.08 to −2.39
Hospitalized (including ICU)	2,384	1.38	0.0097	1.08 to −1.75
On ventilator	513	1.37	0.0132	1.07 to −1.75

ECMO, extracorporeal membrane oxygenation; PGE, prostaglandin E.

Table 2. Pediatric Heart Transplants (January 1995 to June 2000): Risk Factors for 5-Year Mortality (N = 1,953)

Variable	N	Relative risk	p-value	95% confidence interval
Re-transplant	79	2.22	0.0000	1.51 to −3.25
Recipient on dialysis	21	2.02	0.0292	1.07 to −3.79
ECMO	63	1.88	0.0040	1.22 to −2.90
Congenital diagnosis, no ECMO	595	1.55	0.0001	1.25 to −1.93
Congenital diagnosis, age = 0 year, PGE	144	1.53	0.0294	1.04 to −2.24
Year of transplant: 1995 vs 1998	361	1.40	0.0277	1.04 to −1.89
Year of transplant: 1996 vs 1998	341	1.36	0.0463	1.01 to −1.85
Hospitalized (including ICU)	1,388	1.26	0.0400	1.01 to −1.56
Female donor	836	1.25	0.0142	1.05 to −1.49
A locus HLA mismatches (0, 1 or 2 RR per mismatch)	1 MM, 752; 2 MM, 1,096	1.21	0.0157	1.04 to −1.42

ECMO, extracorporeal membrane oxygenation; PGE, prostaglandin E; ICU, intensive care unit; MM, mismatch; HLA, human leukocyte antigen.

cyte antigen (HLA) mismatch (http://www.ishlt.org/registries/). Because much of the power in an analysis of risk factors for 5-year mortality is derived from the large number of deaths that occur within the first year, it is useful to look at risk factors for 5-year mortality conditional on survival to 1 year after transplant (Table 3). ECMO performed for diagnoses other than congenital had the greatest risk in this analysis, but the number of patients was relatively small and was similar to the number of re-transplants. The largest group of patients at significantly increased risk included those who were treated for rejection within the first post-transplant year. Female recipients again were at increased risk for conditional 5-year mortality. Most other recipient and donor factors do not appear to predict 5-year mortality that is conditional on survival to the first year of post-transplant (http://www.ishlt.org/registries/).

Because rejection during the first post-transplant year was clearly associated with increased risk of late mortality, and there was a difference in early rejection based on the primary calcineurin inhibitor (i.e., tacrolimus vs cyclosporine), we evaluated the effect of tacrolimus and cyclosporine on survival, conditional on surviving the first 14 days. In this analysis, cyclosporine and tacrolimus use were defined by the reported agent used at the time of hospital discharge after transplantation. There was no significant effect on late survival regardless of whether tacrolimus or cyclosporine was used (Figure 15). This somewhat surprising observation was analyzed further by stratifying survival based on rejection within the first year and by calcineurin antagonist use at discharge (Figure 16). This analysis demonstrates that patients treated with cyclosporine who did not have rejection had significantly better survival than patients treated with cyclosporine who were also treated for rejection. However, patients treated with tacrolimus at discharge showed no difference in survival, regardless of whether or not they were treated for rejection during the first year. These data suggest the diagnosis of rejection may have different implications depending upon the maintenance immunosuppression. Alternatively, the patient populations treated with a different immunosuppressive regimen may have differing risks related to therapy, or it may be a surrogate for other characteristics of a transplant program.

There continues to be a significant association between prednisone use and mortality, as we have reported previously (Figure 17). These data assume that if prednisone was used at discharge and then reported at the 1-year follow-up, then use during the year was continuous; however, it is not possible to be certain that patients were not started and stopped on prednisone during the intervening year. Again, it is also not possible to make an etiologic link between drug use and outcome because it may be reflective of other characteristics of the transplant population or program. However, these data combined with the calcineurin inhibitor data do provide an opportunity to dissect events occurring early post-transplant that may be related to late mortality. Additional data regarding this analysis are available at the registry website (http://www.ishlt.org/registries/).

Table 3. Pediatric Heart Transplants (January 1995 to June 2000): Risk Factors for 5-Year Mortality Conditional on 1-Year Survival (N = 1,571)

Variable	N	Relative risk	p-value	95% confidence interval
ECMO, diagnosis other than congenital	23	2.71	0.018	1.19 to −6.2
Re-transplant	61	2.51	0.0004	1.51 to −4.17
Treated for rejection (after transplant hospitalization)	424	1.96	<0.0001	1.47 to −2.62
Female recipient	654	1.39	0.0261	1.04 to −1.85

ECMO, extracorporeal membrane oxygenation.

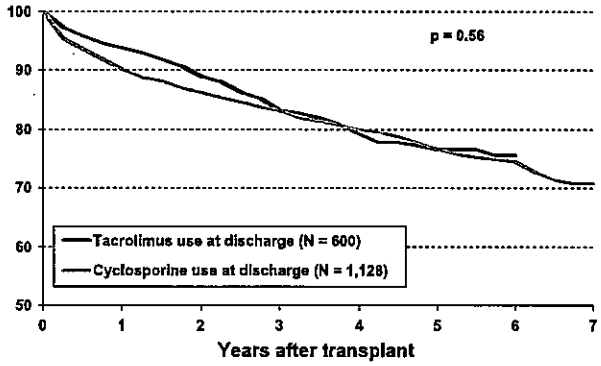

Figure 15. Kaplan–Meier survival stratified by calcineurin use at discharge conditional on survival to 14 days (transplants: 1998 to June 2004).

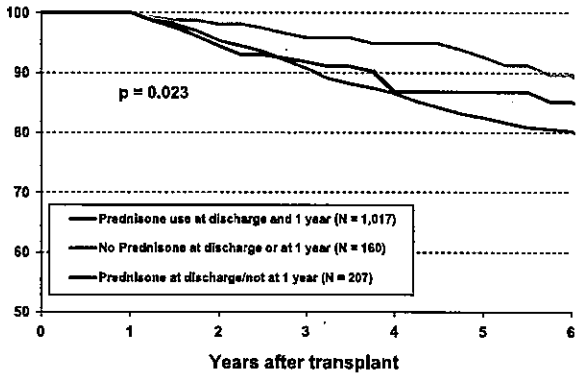

Figure 17. Kaplan–Meier survival stratified by prednisone use (transplants: 1998 to June 2004).

Cause of Death

Table 4 lists causes of death for pediatric heart recipients transplanted between January 1992 and June 2005. Within the first 30 days after transplant, graft failure, primary failure and infection were the leading causes of death. Between 1 month and 1 year, acute rejection emerged as the leading cause of death, followed by infection and graft failure. A report of "graft failure" at this stage post-transplant presumably represented some sequelae of rejection. Thus, about 33% of all deaths during the first year could be attributed to some immunologic process. Beyond the first year and up to 3 years the combination of acute rejection and graft failure accounted for up to 45% of deaths, with coronary artery disease responsible for an additional 20%. Thus, approximately 67% of deaths between 1 and 3 years were related to rejection in either its acute or chronic form. This pattern held true for the period from 3 to 5 years, during which about 70% of deaths appear to have been related to rejection. In patients >5 years post-transplant, coronary vasculopathy accounted for 28% of deaths, graft failure and acute rejection about 32% of deaths, lymphoma about 8.5% of deaths, and infections about 7.5% of deaths. These data continue to indicate that rejection-related phenomena are the predominant risks to pediatric heart transplant recipients throughout their entire post-transplant course. In very late follow-up, >5 years, our attempts to control rejection with immunosuppressive agents were associated with an increasing frequency of lethal, malignant disease.

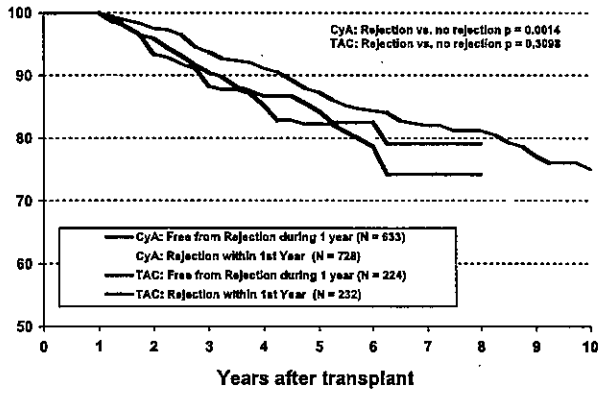

Figure 16. Kaplan–Meier survival conditional on survival to 1 year stratified by rejection within first year and calcineurin use (transplants: April 1994 to June 2003).

Although the overall risk of vasculopathy in pediatric heart recipients is lower than that of adults,[3] coronary artery vasculopathy is a more frequent cause of death in pediatric recipients. These data suggest that pediatric recipients who develop coronary vasculopathy have a more aggressive and lethal form than that seen in adult patients. It is also of interest to note that, in contrast to adult recipients, acute rejection continues to occur frequently up to and beyond 5 years post-transplant in pediatric patients. During late follow-up, lymphomas are more common in children than in adults. Presumably, the strong link between Epstein-Barr virus (EBV) infection and lymphoma places the EBV-naive pediatric recipient at greater risk for this particular malignancy.

Because rejection-related phenomena remain the greatest risks to long-term survival after pediatric heart transplantation, efforts to modify the immune environment at the time of transplant seem justified. However, data presented in this and previous registry reports indicate that induction therapy has no currently demonstrable effect on short- or long-term outcomes. Perhaps newer strategies to promote a tolerizing immune response will prove to have an impact on late acute and chronic rejection.

Specific Complications

Within 5 years after transplant, about 63% of patients had hypertension; almost 10% had some degree of renal dysfunction, and 10% had coronary vasculopathy (Table 5). Hyperlipidemia was also reported in 25% of patients. There was a large increase in the percent of patients with hyperlipidemia and coronary vasculopathy be-

Table 4. Pediatric Heart Transplant Recipients: Cause of Death (Deaths: January 1992 to June 2005)

Cause of death	0–30 days ($N = 358$)	31 days to 1 year ($N = 303$)	>1 year to 3 years ($N = 220$)	>3 years to 5 years ($N = 150$)	>5 years ($N = 281$)
Coronary artery vasculopathy	4 (1.1%)	26 (8.6%)	42 (19.1%)	55 (36.7%)	79 (28.1%)
Acute rejection	33 (9.2%)	80 (26.4%)	59 (26.8%)	19 (12.7%)	37 (13.2%)
Lymphoma		6 (2.0%)	10 (4.5%)	3 (2.0%)	24 (8.5%)
Malignancy, other		4 (1.3%)	2 (0.9%)	1 (0.7%)	10 (3.6%)
CMV	1 (0.3%)	7 (2.3%)	1 (0.5%)		
Infection, non-CMV	49 (13.7%)	49 (16.2%)	17 (7.7%)	7 (4.7%)	21 (7.5%)
Primary failure	62 (17.3%)	12 (4.0%)	7 (3.2%)	8 (5.3%)	12 (4.3%)
Graft failure	85 (23.7%)	35 (11.6%)	40 (18.2%)	34 (22.7%)	55 (19.6%)
Technical	22 (6.1%)	2 (0.7%)	2 (0.9%)	1 (0.7%)	1 (0.4%)
Other	18 (5.0%)	17 (5.6%)	18 (8.2%)	12 (8.0%)	19 (6.8%)
Multiple-organ failure	35 (9.8%)	36 (11.9%)	4 (1.8%)	3 (2.0%)	10 (3.6%)
Renal failure	1 (0.3%)	4 (1.3%)	1 (0.5%)		
Pulmonary	24 (6.7%)	18 (5.9%)	10 (4.5%)	6 (4.0%)	9 (3.2%)
Cerebrovascular	24 (6.7%)	7 (2.3%)	7 (3.2%)	1 (0.7%)	4 (1.4%)

CMV, cytomegalovirus.

tween 1 and 5 years of follow-up (http://www.ishlt.org/registries/). Renal dysfunction also doubled between 1 and 5 years.

In this ninth pediatric report from the registry of ISHLT, we tracked the cumulative incidence of post-transplant morbidities to 8 years after transplant (Table 6). The percent of patients with hypertension (68%) was increased only slightly relative to the 5-year follow-up data, and the incidence of diabetes was unchanged. The percent of patients with renal dysfunction was essentially stable at approximately 10%, but now 2% of patients are either on long-term dialysis or have required renal transplantation. It appears that there may be an at-risk population for progressive renal disease, because most patients did not have progressive renal dysfunction, at least through 8 years of follow-up. The incidence of hyperlipidemia between 5 and 8 years did not change, nor did the proportion of patients diagnosed with coronary artery vasculopathy.

The 8-year follow-up data clearly indicate an increasing incidence of coronary artery vasculopathy with recipient age (Figure 18). This effect was evident even when only the recent cohort from January 1999 to June 2005 was evaluated. The incidence of coronary artery vasculopathy for the entire pediatric population was not influenced by the use of induction therapy at the time of transplant. (http://www.ishlt.org/registries/). Survival after the report of coronary artery vasculopathy also showed age-related differences (Figure 19); specifically, adolescent recipients were significantly less likely to die from vasculopathy than were child or infant recipients.

Analysis of the risk factors for coronary artery vasculopathy indicates that ischemic time of the graft might be related to the subsequent development of vasculopathy (Figure 20). Perhaps surprisingly, a shorter ischemic time was significantly associated with increased risk of vasculopathy. Also, patients with ischemic times of >4 hours were not at greater risk than were patients in the standard time window of 2 to 4 hours. It is also of interest to note that about 35% all pediatric transplant procedures apparently were performed with an isch-

Table 5. Post–Heart Transplant Morbidity for Pediatrics: Cumulative Prevalence in Survivors Within 5 Years Post-transplant (Follow-ups: April 1994 to June 2005)

Outcome	Within 5 years	Total number with known response
Hypertension	62.7%	836
Renal dysfunction	9.9%	862
Abnormal creatinine <2.5 mg/dl	8.2%	
Creatinine >2.5 mg/dl	0.8%	
Long-term dialysis	0.6%	
Renal transplant	0.2%	
Hyperlipidemia	25.1%	902
Diabetes	5.2%	833
Coronary artery vasculopathy	10.9%	605

Table 6. Post–Heart Transplant Morbidity for Pediatrics: Cumulative Prevalence in Survivors Within 8 Years Post-transplant (Follow-ups: April 1994 to June 2005)

Outcome	Within 8 years	Total number with known response
Hypertension	68.3%	325
Renal dysfunction	10.3%	339
Abnormal creatinine <2.5 mg/dl	7.7%	
Creatinine >2.5 mg/dl	0.6%	
Long-term dialysis	1.5%	
Renal transplant	0.6%	
Hyperlipidemia	28.1%	356
Diabetes	4.0%	323
Coronary artery vasculopathy	12.8%	188

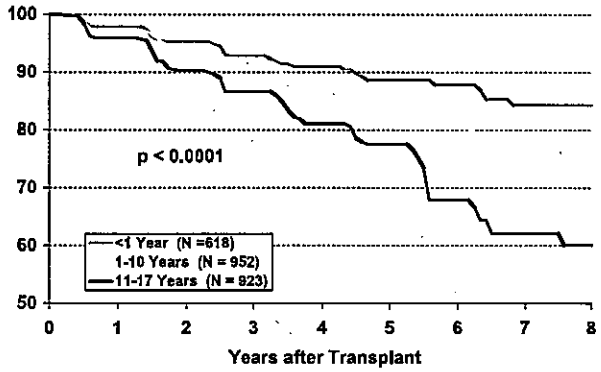

Figure 18. Freedom from coronary artery vasculopathy stratified by age groups (follow-ups: April 1994 to June 2005).

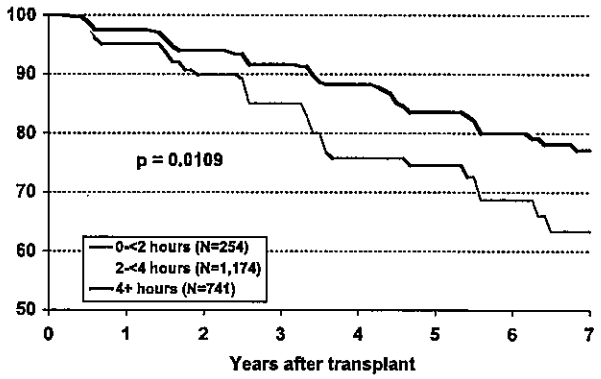

Figure 20. Freedom from coronary artery vasculopathy (CAV) stratified by ischemia time (follow-ups: 1999 to June 2005).

emic time of >4 hours. To further analyze the effect of ischemic time on vasculopathy, we repeated the analysis after stratifying by ischemic time and also by two age groups: 0 to 10 years and 11 to 17 years (Figure 21). The two age groups were not significantly different: adolescent recipients with ischemic times of <2 hours had the greatest risk of vasculopathy; and childhood recipients with short ischemic times also had the greatest within-group increased risk of vasculopathy. These data seem counterintuitive, because patients with an ischemic time of <2 hours likely represent the controlled environment of a local donor matched to a local recipient. Future reports will re-evaluate the relationship between ischemic time and vasculopathy, and also whether the vasculopathy data translate to risk of mortality in very late follow-up. At present, the biologic interpretation of this statistical observation is uncertain.

There was a highly significant increase in early-onset coronary vasculopathy for those patients who reported rejection during the first year (Table 7). There was also an association between acute rejection during the first year and death during the first 5 years. Analysis of the causes of death indicates that the various forms of rejection frequently led to mortality within the first 5 years (Table 4). However, if one looks only at vasculopathy reported between 3 and 5 years after transplant, there was no longer an association with rejection occurring within the first year. It is possible that later-onset vasculopathy will turn out to be related to acute rejection episodes occurring beyond the first year.

As mentioned earlier in this report, >90% of patients have remained free from severe renal dysfunction after 8 years of follow-up. However, the freedom from renal dysfunction has shown a steady decrease with time, suggesting that the population at large may still be at risk. These data will be followed in future reports to determine whether there is a plateau in the freedom from severe renal dysfunction in surviving recipients of pediatric heart transplantation (http://www.ishlt.org/registries/). Malignancy was an increasing cause of death in pediatric recipients, and freedom of malignancy also showed a steady decrease with time. The vast majority of malignancies were lymphatic in origin. However, the data indicate that >90% of pediatric recipients were free from malignancy at up to 8 years of follow-up (http://www.ishlt.org/registries/).

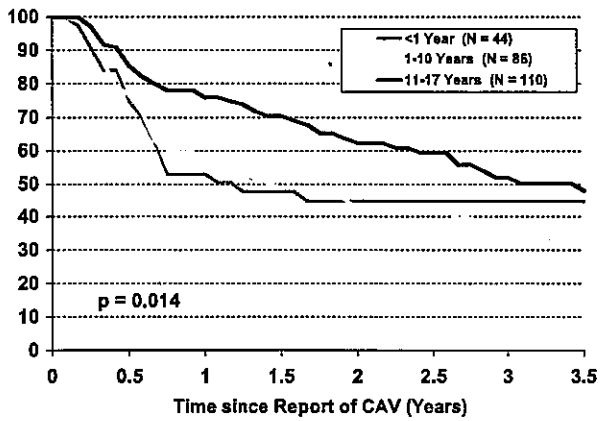

Figure 19. Graft survival following report of coronary artery vasculopathy (CAV) stratified by age group (follow-ups: April 1994 to June 2005).

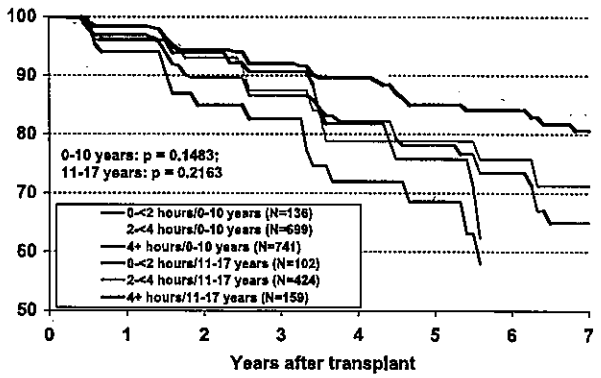

Figure 21. Freedom from coronary artery vasculopathy (CAV) stratified by ischemia time and age group (follow-ups: 1999 to June 2005).

Table 7. Pediatric Heart Recipients: Relationship of Rejection and Coronary Artery Vasculopathy (CAV) (Follow-ups: April 1994 to June 2005)

Rejection during Year 1	Reported CAV between Years 1 and 3 post-transplant			Reported CAV between Years 3 and 5 post-transplant		
	Yes	No	All	Yes	No	All
Yes	40 (7.8%)	473 (92.2%)	513 (100%)	19 (7.5%)	235 (92.5%)	254 (100%)
No	15 (2.9%)	504 (97.1%)	519 (100%)	10 (4.1%)	234 (95.9%)	244 (100%)
		$p = 0.0004$			$p = 0.1072$	

Only those recipients without CAV prior to 3 years were included in the analysis of CAV between 3 and 5 years.

As in previous pediatric reports, surviving pediatric heart recipients have excellent functional recovery, with >90% of patients reporting no activity limitation (http://www.ishlt.org/registries/). Furthermore, hospitalization becomes less common as time after transplant increases; between 7 and 8 years post-transplant <25% of patients reported hospitalization for any cause (http://www.ishlt.org/registries/). The data on functional status and re-hospitalization indicate that, with increasing follow-up, patients continue to demonstrate an excellent level of rehabilitation.

Predicted Pediatric Heart Transplant Survival

Projected patient survival curves based on hypothetical patient profiles were first presented in the eighth official pediatric report.[2] A number of recipient characteristics, including age, degree of illness and donor characteristics, can all be reflected in these hypothetical outcome graphs.

We compared several recipient scenarios, which could affect the outcome of hypothetical 12-year-old female recipients with different clinical characteristics (Figure 22). These curves assume the recipient has a weight of 30 kg and a serum creatinine of 1.4 mg/dl. Case 1 depicts data for a patient whose original diagnosis was congenital heart disease and who underwent transplantation at 4 years of age. She developed vasculopathy, and ultimately graft dysfunction, for which she required re-transplantation. She was receiving home milrinone therapy. Case 2 depicts data for a 12-year-old girl with a similar weight and creatinine level, who was undergoing primary transplantation. Her original problem was a congenital heart defect, managed with palliative reconstruction during several surgical procedures. Recently, she underwent Fontan revision in an attempt to improve protein-losing enteropathy. However, she required ECMO support after surgery and was listed for cardiac transplantation on an urgent basis. Both of these hypothetical recipients received a donor heart from a 16-year-old female, with a weight of 45 kg. The donor cause of death was a head injury in a motor vehicle accident. The ischemic time was 2.5 hours. The predicted survival curves display the important impact of congenital heart disease and mechanical support with ECMO on survival. In contrast, the recipient undergoing re-transplantation would appear to have a better outlook with this set of defining characteristics.

Figure 23 shows the projected survival curves to 5 years, conditional on survival to the first year, for 2 additional hypothetical recipients. Recipient characteristics are considered, but in this scenario the management and clinical course from the time of transplant

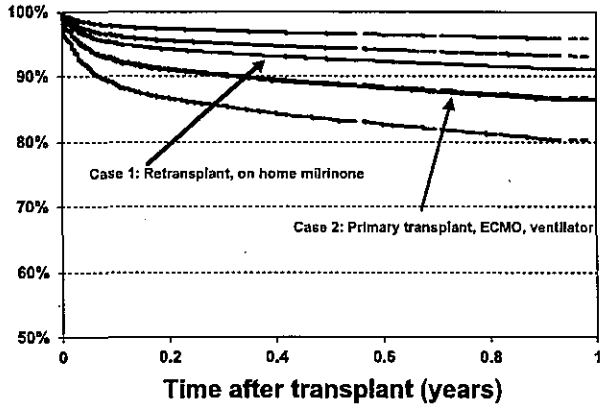

Figure 22. Predicted survival based on the multivariate Cox model of mortality within 1 year (transplants: 1995 to June 2004). Recipient: 12-year-old girl; weight: 30 kg; creatinine: 1.4 mg/dl. Donor: 16-year-old girl; cause of death: motor vehicle accident; weight: 64 kg; ischemia time: 3 hours.

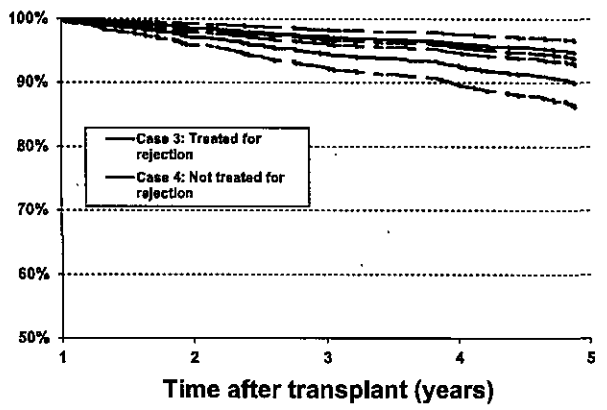

Figure 23. Predicted survival based on multivariate Cox model of mortality within 5 years (transplants: 1995 to June 2000). Recipient: 1-year-old boy with dilated cardiomyopathy; weight: 8 kg; creatinine: 0.8; not hospitalized at time of transplant. Donor: 2-year-old boy; weight 13 kg; cause of death: asphyxia; ischemia time: 3 hours.

were the variables that influence long-term survival. The recipient model in Figure 23 shows a 1-year-old, 8-kg boy with serum creatinine of 0.8 mg/dl and a diagnosis of dilated cardiomyopathy requiring transplant. The donor was a 2-year-old, 13-kg boy who suffered a closed-head injury leading to brain death and organ donation. The ischemic time was 2 hours. The two hypothetical patients with the same demographics were treated with different immunosuppressive regimens and had a different clinical course in the first year. Case 3 was treated with no induction therapy and received tacrolimus and prednisone as the primary immunosuppressive regimen at the time of transplant and throughout the first year. This individual suffered a rejection episode during this first year, resulting in hospitalization, but subsequently recovered with no apparent sequelae. Case 4 also did not receive induction therapy at the time of transplant, received only cyclosporine for calcineurin inhibition, but did not receive other concomitant immunosuppressive medications. Furthermore, this infant did not have any rejection episodes during the first year after transplant. The subsequent 5-year survival for these 2 hypothetical cases was then computed. In these scenarios the combination of rejection and immunosuppressive regimen led to different projected outcomes. Although it is understood that these projections are based on historic data in the registry, and there may still exist a real-time gap with current experience and outcomes, many of these issues have had a very stable influence for up to as long as 10 years.

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