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Steady improvement in renal allograft survival among North American children: A five year appraisal by the North American Pediatric Renal Transplant Cooperative Study

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Steady improvement in renal allograft survival among North American children. From 1987 through 1994, the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has enrolled 1641 cadaver donor transplants. For this study, we have analyzed one and two year graft survival by annual cohorts for the years 1987 through 1991. For the 1987 cohort one and two year graft survival was 72% and 65%, respectively, and for the 1991 cohort it was 83% and 78%, respectively. Using a proportional hazards model, and comparing the 1987 cohort to the 1991 cohort, the relative risk for graft failure was 1.40 ($P = 0.02$). Analysis of practice patterns revealed the following changes which may have been associated with this improved graft survival: (1) use of T cell induction antibody, 38% in 1987 and 67% in 1991 ($P \leq 0.001$); (2) the increased use of cyclosporine (CsA) post-transplant: in 1987, 87% were maintained on CsA at day 30 compared to 97% in 1991 ($P < 0.001$); (3) the mean higher daily maintenance CsA dose at 12 months post-transplant which in 1987 was 6.5 mg/kg compared to 7.5 mg/kg in 1991 ($P = 0.03$); (4) the decreased use of random transfusions, 54% receiving >5 transfusions in 1987 compared to 37% in 1991 ($P < 0.001$); and (5) decreased use of younger cadaver donors between 1987 and 1991 ($P < 0.001$).

Renal transplantation is considered the optimal replacement therapy for children with end-stage renal disease (ESRD). More than 25% of the pediatric ESRD population in the United States and Canada never undergoes dialysis but receives a renal transplant preemptively [1]. Unfortunately, the outcome of renal transplantation in children has been inferior to the results observed in adults. The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) was organized in 1987 to register and follow children up to 17 years of age who receive renal allografts in the United States and Canada. Since its inception, the 83 participating Centers have registered 3438 transplants. This report analyzes data from the first five years of the registry (1987-1991) to define trends in cadaver graft outcome and identify the practice patterns which may have been contributory to changes in that outcome. There has been a secular trend to steady improvement in transplant outcome in children in the study group felt to be a consequence of alterations in clinical practice identified by the North American Pediatric Renal Transplant Cooperative Study.

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Methods

The NAPRTCS is made up of a Clinical Coordinating Center, a Data Coordinating Center and 83 participating centers treating children with renal disease in the United States and Canada. Methods of data collection have been reported previously [2]. Briefly these methods consist of collecting information at 30 days following a transplant, then additional status information at each six month interval post-transplantation. The data collected include information regarding immunosuppression therapy, episodes of graft rejection and patient morbidity as determined by hospitalization post-transplantation. Separate data are also collected for each graft failure and for patient death.

Statistical analysis

Standard univariate and multivariate statistical methods, including product-limit estimates of survival distributions, were used to analyze the data. Proportional-hazards survival models were constructed that equated an individual patient's hazard to an underlying hazard multiplied by an estimated exponentiated linear combination of risk factors. Multivariate models were scaled so that risk increased with larger values of the covariates; the relative risk for a single dichotomous risk factor is the exponentiated parameter.

Results

From January 1987 through December 1991, 1410 cadaver donor transplants were performed, of which 1258 were index transplants. (An index transplant is the first transplant reported to the NAPRTCS for a patient since the study began in January 1987.) Plots of graft survival distributions of index transplants, by annual cohort, are shown in Figure 1. The one year graft survival percentages for the annual cohorts are 72% ($N = 202$) for 1987, 70% ($N = 190$) for 1988, 77% ($N = 169$) for 1989, 80% ($N = 200$) for 1990, and 83% ($N = 157$) for 1991. Two year graft survival percentages are 65% ($N = 175$), 62% ($N = 160$), 73% ($N = 148$), 76% ($N = 172$), and 78% ($N = 86$), respectively, for 1987 through 1991.

Since there are multiple variables that influence cadaver graft survival, proportional hazards regression models were used to determine if transplant year was a significant concomitant risk factor. The risk factors of graft failure are shown in Table 1, with the relative risk increases and P values. In order to remove any bias associated with technical graft losses, Table 1 also presents

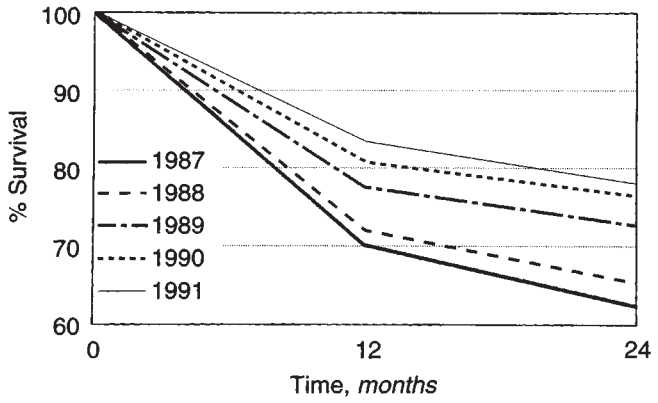

Fig. 1. *Two years graft survival distribution for years 1987 through 1991.*

Table 1. Risk of graft failure based on a proportional hazards model

	All CD transplants		CD transplants lasting ≥ 30 days	
	RR	*P* value	RR	*P* value
Recipient age (<2)	2.35	<0.001	1.89	0.012
Donor age (<6)	1.48	<0.001	1.35	0.020
Prior transplant	1.44	0.001	1.28	0.075
ATG/ALG/OKT3 early administration (none)	1.42	<0.001	1.28	0.030
>5 Lifetime transfusions	1.30	0.006	1.42	0.002
Annual cohort (1987 vs. 1991)	1.40	0.023	1.50	0.037
Recipient race (black)	1.27	0.034	1.26	0.091
No DR matches	1.25	0.015	1.31	0.014

estimates of relative risk for these variables conditional on the graft having survived for at least 30 days.

In addition, we reviewed changes in clinical practice patterns over the five year period, especially changes in the use of immunosuppressive therapy, both at the time of grafting and during the maintenance phase that may account for the improvement in graft outcome. We observed that in 1987 only 38% of cadaver donor transplant recipients received anti-T cell induction therapy in the form of either ATG, ALG, or OKT3, whereas in 1991 67% of all cadaver donor transplant recipients were treated with anti-T cell induction therapy ($P < 0.001$).

Analysis of cyclosporine dosing showed that in 1987 87% of all cadaver donor transplant recipients were being maintained on cyclosporine at day 30 post-transplantation, compared to 97% of all cadaver donor transplant recipients in 1991 ($P < 0.001$). We also noted that the mean daily maintenance dose of cyclosporine at 12 months post-transplantation in 1991 was higher at 7.5 mg/kg (SD = 4.6) compared to 6.5 mg/kg (SD = 4.2) in 1987 ($P = 0.033$). To determine the relationship of cyclosporine dose to changes in graft survival, the conditional analysis of graft survival was repeated in a model that included a time dependent term for cyclosporine dose (Table 2). Introduction of the cyclosporine dose into the hazard model diminished the significance of the year of transplant, suggesting a correlation between higher cyclosporine doses and improved graft survival. An analysis that included only cyclosporine dose (RR = 0.95, $P < 0.001$) and year of transplants (1987 vs. 1991, RR = 1.76, $P = 0.002$) indicates that cyclosporine dose alone does not remove the significance of transplant year.

Changes in clinical practice patterns were also examined regarding transfusion therapy and the use of young cadaver donors. Whereas 54% of all cadaver donor recipients in 1987 received >5 random transfusions, only 37% of cadaver donor recipients in 1991 received >5 random transfusions ($P < 0.001$).

Tabel 2. Risk of post-day 30 graft failure with time dependent term for cyclosporine dose

	Relative risk increase	*P* value
Recipient age (<2)	2.02	0.006
Donor age (<6)	1.37	0.014
Prior transplant	1.28	0.068
ATG/ALG/OKT3 early administration (none)	1.26	0.039
>5 Lifetime transfusions	1.44	0.004
Annual cohort (1987 vs 1991)	1.41	0.075
Recipient race (black)	1.31	0.045
No DR matches	1.34	0.008
Cyclosporine dose *mg/kg*[a]	0.95	<0.001

[a] At day 30, 6 months, and every 6 months thereafter

There were also significant changes in the distribution of cadaver donor ages between 1987 and 1991 ($P < 0.001$). In 1987 4% (12 of 299) of cadaver donors were less than two years of age and 18% (53 of 299) were between the ages of 2 and 5. Comparatively, there were no cadaver donors less than two years of age and only 11% (28 of 248) were between the ages of 2 and 5 in 1991. While 58% of cadaver donors in 1987 were older than 12 years, 75% in 1991 were of similar age.

Discussion

The NAPRTCS is a research effort organized in 1987 with a specific aim of capturing information about current practices and trends in immunosuppression therapy with an ultimate goal of improving care of pediatric renal allograft recipients in North America. The initial analysis of 390 children receiving a renal allograft was presented in 1988 [3]. Since then, factors which impact on graft survival have been regularly evaluated [2, 4, 5]. Under the aegis of NAPRTCS, changes in practice have steadily improved outcome in children from those described by the registry and from the first cohort of the group.

Antibody induction introduced in the study group may have contributed to the improvement in graft outcome in children. Antibody based induction protocols have been utilized for more than two decades, but the results of their use have been controversial. Sequential therapy using Minnesota Antilymphoblast Globulin (MALG) was first described in 1985 [6]. Since then it has been extensively used in adults with improved graft survival rates [7]. In a single center randomized study, Goldman et al [8] noted an improved early graft survival rate in OKT3 treated patients compared to those with conventional therapy. In a multicenter trial of adult CD transplant recipients, induction with OKT3 lead to a 8 to 9% increase in graft survival rate; however, the improvement was not statistically significant [9]. Available data on the use of sequential therapy with either MALG, ATG or OKT3 in pediatric allograft recipients are limited. The beneficial effect of anti-T cell induction in pediatric CD recipients with the use of antibody preparations was initially described in the NAPRTCS 1990 report [10] and the beneficial effect persists [2]. The most recent analysis [1] noted that the CD graft survival rate in 944 children not receiving anti-T cell induction was 60% compared to 70% in 698 children who received induction therapy. Additionally, NAPRTCS data indicated that the use of anti-T cell induction

therapy can obviate any adverse impact of poor HLA matching. No differences have been seen in the one and two years graft survival rate of poorly HLA matched, anti-T cell induced recipients, whereas HLA matching has been important in graft outcome in the non-anti-T cell induced recipient group ($P < 0.04$) [11].

A second factor in the improvement in graft outcome in children may be reduction in the use of transfusions. Data from the UCLA Transplant registry reveal that the proportion of transfused to nontransfused patients has decreased from a ratio of 10:1 in 1981 to 1:1 in 1990 [12]. Furthermore, the beneficial effect of transfusions first noted in 1981 has disappeared [13, 14]. Previously, we have not been able to document that >5 transfusions is detrimental to CD graft survival rates, but with a larger population and longer follow-up our data confirm the observation seen in adult recipients. Therefore, the decreasing frequency of 37% in 1991 compared to 54% in 1987 is a reflection of improved clinical practice and of the increasing use of erythropoietin, which was released for use in dialysis patients in 1990.

The dosing of cyclosporine A which takes into account the peculiar metabolism and immune systems of children culminating in the use of higher doses may also have contributed to the improved graft survival that we are exhibiting in this study. Previous data from NAPRTCS demonstrated that lower maintenance doses of CsA are associated with a higher frequency of rejection and graft failure [15]. This finding has been observed by Solomon [16] in adult recipients. More pertinent was the observation that the 1991 cohort is being maintained on a higher dose (7.5 mg/kg/day) compared to the 1987 cohort (6.5 mg/kg/day). When the cyclosporine dose is entered into the proportional hazards model as a time dependent variable as shown in Table 2 the annual cohort effect ceases to be significant. This finding points strongly to an important influence of cyclosporine dose in improving graft survival in 1991.

Lastly, the avoidance in later cohorts of transplantation between the youngest donor and youngest recipient may also be a contributing factor in the observed improved graft survival. We have previously noted that when there is a concordance between young recipient age and young cadaver donor age, graft survival is markedly inferior [17]. In a special analysis of cadaver donor transplants done from 1987 through 1990 [18], we noted that the risk of graft loss from a neonatal donor was 2.7-fold that of the ideal donor. We also noted that 10% of grafts from cadaver donors <5 years of age are lost due to vascular thrombosis, primary non-function and other technical causes. Obviously, the greater use of older cadaver donors, which reached 75% in 1991, has had a beneficial impact on graft survival.

Some factors that increase the relative risk of cadaver graft failure in children such as recipient age are integral to pediatrics, others such as recipient race, the degree of HLA matching, and prior transplantation are factors that cannot be easily manipulated. Improvement in cadaver allograft survival rates, however, can be achieved by judicious choice of donors, pretransplant management, manipulation of induction therapy, and by optimal maintenance immunosuppressive therapy. The observation that improvement in cadaver graft survival rates is correlated with changing practice patterns confirms the original intent of NAPRTCS. As our data base grows, it is anticipated that identification of various factors which impact on graft survival will lead to improved graft survival rates, thereby improving the quality of life in children following renal transplantation.

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