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Original article

Renal transplantation in children and adolescents: the 1992 Annual Report of the North American Pediatric Renal Transplant Cooperative Study*

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Abstract. From January 1987 to January 1992 the North American Pediatric Renal Transplant Cooperative Study registered and followed 2,037 children and adolescents 17 years of age or less who received 2,197 renal transplants at 75 participating centers in the United States and Canada. The cumulative experience over 5 years of data collection demonstrated trends in renal transplantation practice for pediatric patients. The percentage of live donor organ recipients receiving donor-specific blood transfusions decreased from 40% in 1987 to less than 12% in 1991; random blood transfusions also were used less frequently during the most recent 2 years of the study. Immunosuppressive therapy on posttransplant day 0 or 1 with polyclonal and monoclonal antilymphocyte agents was used in over 40% of transplants. There was also a notable preference for the combined use of prednisone, azathioprine and cyclosporine as maintenance immunosuppression. The percentage of live donor source graft recipients receiving cyclosporine increased from 78% in 1987 to 90% in the most recent year, and considered together, nearly 90% of live donor and cadaver organ recipients received cyclosporine. The observed graft survival probabilities for live donor grafts were 88%, 83%, 81% and 76% at years 1–4 post transplantation, respectively. The 1st through 4th year graft survival probabilities for cadaver grafts were 74%, 68%, 63% and 58%, respectively. The five most common causes of pediatric end-stage renal disease have remained as: hypoplastic-dysplastic kidney, obstructive uropathy, focal segmental glomerulosclerosis, reflux nephropathy and systemic immunological diseases throughout the 5 years of this study. There has been a decrease in children 2 years of age or less undergoing transplant surgery. On average, 50% of graft failures were due to the various forms of rejection. Vascular thrombosis (14%) and recurrence of primary renal disease (7%) were the next most frequently encountered causes of graft failure. Poor linear growth was identified as a problem affecting the majority of children both before and after transplantation. Post transplant linear growth was best among recipients less than 6 years of age at transplantation and recipients of all ages who received alternate-day prednisone. A total of 16 malignancies were reported during the 5 years of study. A total of 105 deaths were reported, with infection (41%) the most common primary cause of death. The 2-year patient survival probabilities were 95.5% and 93% for recipients of live donor and cadaver grafts, respectively.

Key words: Renal transplant – Malignancy – Growth – Immunosuppression – End-stage renal disease – Graft survival – Patient survival

Introduction

Since 1987, through the voluntary participation of pediatric nephrologists, renal transplant surgeons, transplant coordinators and others, the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has studied renal transplantation in children and adolescents in the United States and Canada [1, 2]. The 1992 NAPRTCS Annual Report summarizes data contributed by 75 participating centers on 2,037 pediatric patients who received 2,197 transplants during the period January 1987 through January 1992. In this report cumulative experience has been analyzed to examine trends in transplantation practices over the 5 years of the study and to identify factors that have affected the outcome of renal transplantation in these pediatric patients.

Methods

The NAPRTCS is made up of a clinical coordinating center, a data coordinating center (DCC) and 75 medical centers treating children with end-stage renal disease (ESRD) in the United States and Canada. The data for this report, compiled in February 1992, include transplants reported during the 5 preceding years. Since January 1987, each renal allograft received at participating centers by a child or adolescent 17 years of age or less has been reported to the DCC, along with information on graft function and therapy 1 month after transplantation and every 6 months thereafter, as previously described [1, 2].

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 was the exponentiated parameter.

Results

Patient characteristics

A total of 2,033 patients from 75 centers were registered between January 1987 and January 1992. Data were com-

Table 1. Characteristics of pediatric renal transplant recipients according to year of transplantation

Year	Patients			Transplants	
	Number	% Male	% Nonwhite	Number	% Live donors
1987	490	60	27	499	44
1988	439	62	31	467	41
1989	411	62	36	446	47
1990	397	60	30	443	41
1991	296	58	34	338	58
Total 1987–1991	2,033	60	31	2,193	45

Table 2. Age distribution of pediatric renal transplant recipients (%) according to year of transplantation

Year of transplant	*n*	Age group (years)			
		0–1	2–5	6–12	13–17
1987	490	6.4	18.4	36.3	38.9
1988	439	7.5	16.9	36.2	39.4
1989	411	7.2	17.3	38.1	37.4
1990	397	3.8	17.2	40.0	39.1
1991	296	4.7	16.3	39.9	39.1
Total 1987–1991	2,033	6.0	17.3	37.9	38.8

Table 3. Sex, race and biopsy distributions by primary renal disease diagnosis

Diagnosis	*n*	Male (%)	White (%)	Not biopsied (%)
Aplastic/hypoplastic/dysplastic kidneys	344	62	72	66
Obstructive uropathy	343	87	73	55
Focal segmental glomerulosclerosis	241	62	56	3
Reflux nephropathy	102	43	74	56
Systemic immunological disease	96	29	52	7
Chronic glomerulonephritis	82	39	55	28
Congenital nephrotic syndrome	73	52	68	5
Syndrome of agenesis of abdominal musculature	62	98	74	48
Medullary cystic disease/ juvenile nephronophthisis	60	57	85	27
Hemolytic uremic syndrome	58	59	90	33
Polycystic kidney disease	53	42	87	36
Cystinosis	46	56	87	48
Membranoproliferative glomerulonephritis type I	44	48	73	2
Pyelonephritis/interstitial nephritis	43	40	73	28
Renal infarct	43	53	86	47
Familial nephritis	42	76	67	2
Idiopathic crescentic glomerulonephritis	38	34	68	0
Membranoproliferative glomerulonephritis type II	21	43	71	0
Oxalosis	16	69	88	25
Wilms' tumor	11	45	82	0
Drasch syndrome	11	45	64	0
Membranous nephropathy	9	89	67	0
Sickle cell nephropathy	2	0	0	50
Diabetic glomerulonephritis	1	100	0	0
Other	110	69	60	30
Unknown	82	49	39	62

piled on 2,193 transplant procedures: 2,033 index transplants (i.e., transplants performed at the time of study enrolment) and 160 additional transplants performed in previously registered patients (Table 1). Due to characteristic reporting lags, it is anticipated that the total number of transplants will increase for the 1991 reporting period. Over the 5 years of the study, males consistently received about 60% of registered transplants, and the proportion of non-white recipients averaged 31%. Living donors provided 45% of transplanted kidneys over the 5 study years, but in 1991 live donors were the source for 58% of reported transplants (Table 1).

The age distribution of recipients according to year of index transplantation is shown in Table 2, using age groups defined as 0–1, 2–5, 6–12 and 13–17 years at time of transplantation. Since 1987, only minor changes in age distribution have been seen among the three oldest age groups. However, the number of recipients in the youngest age group (0–1 year) decreased from an average of 33 per year during 1987–1989 to 16 per year in 1990–1991 (Table 2).

The five most common primary renal disease diagnoses in transplanted children were hypoplastic-dysplastic kidneys, obstructive uropathy, focal segmental glomerulosclerosis, reflux nephropathy and systemic immunological disease (Table 3), together accounting for 56% of the patients enrolled in the study. Renal dysplasia and obstructive malformations were responsible for adding an average of 170 new patients to the study each year. Among children 5 years of age or less, congenital lesions accounted for about 50% of the causes of ESRD, while acquired forms of glomerulonephritis made up more than 50% of the causes of ESRD among older age groups.

Two hundred and fifty-eight patients received at least one transplant prior to enrolment in the study. Thus, 87.4% of index transplants (i.e., transplants performed at time of study enrolment) were first transplants. For patients with prior transplants, a median of 51 months (quartiles 35 months and 70 months) elapsed between their prior transplants and their index transplants.

Transplantation without prior dialysis (i.e., "preemptive" transplantation) was used as initial renal replacement therapy in 22.0% of patients. The rate of preemptive transplantation differed for males (25%) and females (18%) and across the age groups, with rates of 18%, 24%, 25% and 19% in the 0–1, 2–5, 6–12 and 13–17 years age groups, respectively. For those with prior maintenance dialysis, the median time of dialysis initiation was 12 months (mean 21 months) prior to the index transplant. During the month prior to the index transplant, 25% of patients were not receiving maintenance dialysis, 28% were on hemodialysis (HD), 42% were on peritoneal dialysis (PD) and 5% received both HD an PD. The proportional distribution of pretransplant maintenance therapies was consistent throughout the 5 years of the study. All native renal tissue was removed before or at the time of the index transplant in 28.6% of recipients, while 67% of patients with a prior

transplant had all prior grafts removed. Donor-specific transfusions (DST) have been performed in 22% of living donor grafts, but DST have decreased from 40% to less than 12% over the 5 years of reports.

Donor history and antigen match

Living donors (parents 38.8%, siblings 3.4%, other related 2.5%, unrelated 0.6%) provided 45% of transplanted organs over the 5 years of the study. A total of 75 sibling transplants were performed. Fifty live donor grafts were from donors under the age of 21 years, 5 donors were under 18 years of age and there were 3 transplants between identical twins, the youngest pair being 13 years of age. Cadaver source organs were used in 55% of the transplants. Thirty-eight (3.2%) cadaver grafts were from donors less than 24 months of age. The number of donors 0–10 years of age decreased from 110 (39.5%) per year in 1987–1988 to 84 (34.3%) per year in 1989–1990. Only 23 (16%) cadaver donors 0–10 years of age have been reported in the 1991 cohort. Fifty-six (8.6%) cadaver and 29 (2.9%) living donors were greater than 50 years of age. The oldest cadaver donor was 64 years and the oldest living donor was 66 years. Seventeen percent of cadaver allografts were preserved by machine perfusion. Forty-six percent of cadaver grafts had cold ischemia times of greater than 24 h, with 9 (0.8%) exceeding 48 h. The maximum cold ischemia time was 56 h.

There were 5 confirmed transplants across ABO blood group compatibility barriers (4 with 0 recipients and A donors and 1 with a B recipient and an AB donor). In 2, graft failure occurred within 30 days, the others are functioning more than 1 year post transplantation. Blood group 0 occurred in 52% of the donor cohort and 46% of the recipients. The reporting system considers histocompatibility antigen alleles as matching only if identical known alleles are reported for both donor and recipient. Among living donor recipient pairs, 85% had at least a single haplotype match, while in 11% only one of the four possible HLA-B and HLA-DR matches occurred. No matches in both the B and DR loci occurred in 28% of the transplants from cadaver source donors; a single B or DR locus match occurred in 37% of cadaver transplants. Known matches of all six A, B and DR alleles occurred in 2.3% of cadaver transplants.

Therapy

Preoperative immunotherapy was employed during the period immediately prior to the day of transplantation in 67% of live donor transplants; however, the details of this preoperative therapy are not collected in the NAPRTCS data base. The use of DST in living donor transplants decreased from 39.6% in 1987 to 11.5% in 1991. The use of more than five prior random blood transfusions in cadaver donor transplants decreased from 45.9% in 1987 to 29.5% in 1991. Over the initial posttransplant month, median doses of prednisone in both live donor and cadaver source grafts decreased to approximately one-third of the initial amount

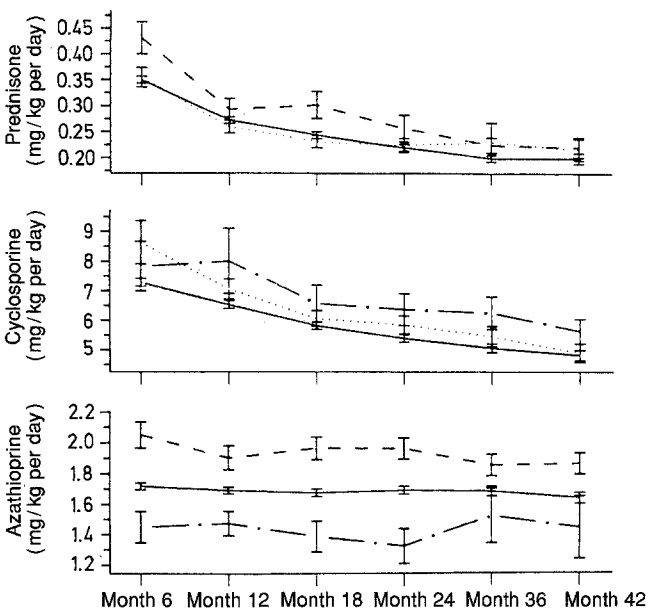


Fig. 1. Mean (±SE) daily maintenance immunosuppressive drug dosages by drug combination and time post transplant. Triple (———) prednisone, azathioprine and cyclosporine; ..., prednisone and cyclosporine; – – – –, prednisone and azathioprine, – · – · –, cyclosporine and azathioprine

(1.8 mg/kg per day to 0.62 mg/kg per day), while median doses of cyclosporine and azathioprine remained nearly constant (8.2 mg/kg per day and 2.2 mg/kg per day, respectively). Polyclonal antilymphocyte preparations (ATG or ALG) were employed from day 0 or 1 post transplant for a median course of 10 days in 42% of transplants (live donor 37%, cadaver 46%). Orthoclone OKT3 was used similarly in 10% of patients (live donor 6%, cadaver 13%). Cyclosporine was used during the 1st month post transplant in 87% of patients (live donor 85%, cadaver 89%) and of those, 22% began cyclosproine by day 0, 21% on day 1 and 23% during days 2 through 7 post transplant.

Median daily prednisone doses decreased from 0.31 mg/kg per day at month 6 to 0.17 mg/kg per day at month 36; the percentage of patients receiving alternate-day prednisone therapy increased from 12% at month 6 to 21%, 27% and 31% at the 12th, 24th and 36th month, respectively. The median azathioprine dose was relatively constant at each follow-up time. A decrease in the median dose of cyclosporine was observed, from 9 mg/kg per day at day 30 to 6.23 mg/kg per day at month 6, with dose attenuation continuing over the following report periods. Mean daily cyclosporine doses were 7.4, 6.6 and 5.5 mg/kg at 6, 12 and 24 months, respectively. Through the initial 2 post transplant years, over 70% of recipients (live donor 69%, cadaver donor 80%) received combination immunosuppressives with three agents: prednisone, cyclosporine and azathioprine. Dual therapy with prednisone and cyclosporine was received by equivalent percentages of recipients of grafts from live and cadaver donors, while dual therapy with prednisone and azathioprine was used three to four times more often in living-related donor graft recipients than in cadaver donor graft recipients. The trend to use single immunosuppressive drug therapy, initially noted

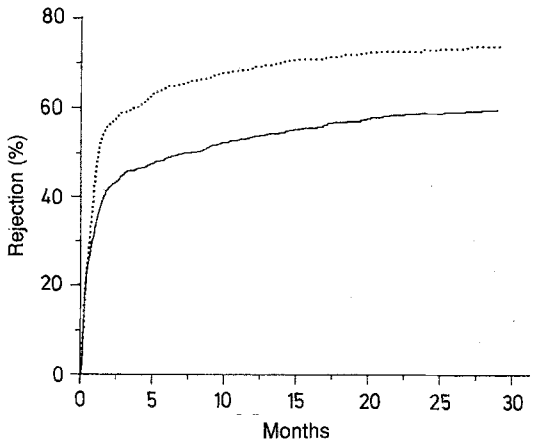


Fig. 2. Times to first rejection episode by allograft donor source. – – – –, Cadaver; ———, live donor

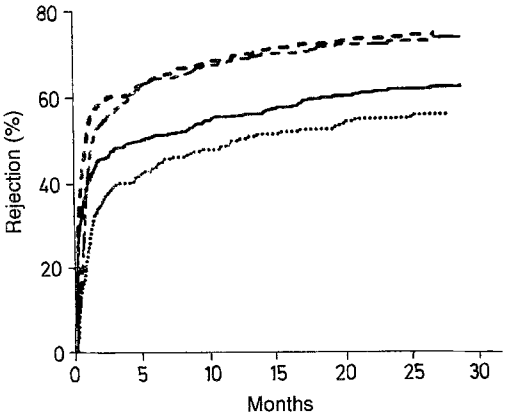


Fig. 3. Times to first rejection episode by allograft donor source and administration of antilymphocyte preparations (ATG/ALG or OKT3) on posttransplant day 0 or 1. – – –, Cadaver no antilymphocyte therapy; – – – –, cadaver with antilymphocyte therapy; ———, live donor no antilymphocyte therapy; ..., live donor antilymphocyte therapy

in 1990, has not continued. Mean dosages for individual agents employed in dual and triple combination therapies were generally equivalent, with very little dose reduction seen when agents were used in combinations involving additional immunosuppressive drugs (Fig. 1). The dose of azathioprine used in dual therapy was less in patients receiving azathioprine and cyclosporine compared with patients receiving azathioprine with prednisone.

The proportion of patients receiving antihypertensives decreased from 74% to 52% of recipients at months 1 and 36 post transplant, respectively. Anticonvulsant medication was given to 10% of transplant recipients, with a greater frequency among recipients of cadaver organs. Prophylactic antibiotics were used in 36% of patients at 1 year post transplant, with minimal decreases thereafter. Patients with ESRD due to congenital renal lesions were more likely to be on prophylactic antibiotic medications than those with acquired causes for ESRD.

Rejection

Using the decision to initiate specific antirejection therapy as the definition of a rejection episode, a total of 2,370 incidents of rejection occurring in 1,268 transplants were reported. Two or more rejection episodes occurred in recipients of 533 transplants. The incidence of rejection did not decrease over the 5 years of this study. During the first 4 weeks post transplant, rejection patterns for living and cadaver donor groups were nearly identical, but there was an increased first rejection risk for cadaver source grafts during the following 2 months (Fig. 2). At days 15, 30 and 45 post transplant, 25%, 33% and 39% of live donor transplant recipients and 27%, 44% and 54% of cadaver graft recipients had been treated for at least one rejection episode, respectively. By 2 years post transplant, 59% of live donor graft recipients and 73% of cadaver source recipients had experienced at lease one rejection episode (Fig. 2). Younger recipients (i.e., those less than 24 months of age at time of transplantation) were not observed to be at a disadvantage with respect to time to first rejection episode. Recipients of grafts from cadaver donors aged 0–5 years had an increased instantaneous relative risk (RR) of experiencing at least one rejection episode (RR = 1.5, $P < 0.001$) compared with recipients of grafts from older cadaver donors. Only 19% of recipients of cadaver grafts from donors aged 0–5 years were rejection free at 1 year post transplant versus 41% for recipients of grafts from older cadaver donors. Use of ATG/ALG or OKT3 on day 0 or 1 post transplant substantially increased the length of time to first rejection episode in live donor, and to a lesser degree in cadaver source transplants (Fig. 3). The time to first rejection episode among live donor graft recipients was unaffected by preoperative immunotherapy.

Allograft rejection episodes had higher reversal rates if they were not biopsied, suggesting an association between the severity of rejection episode and the decision to biopsy. Overall, 55% of rejection episodes were completely reversed (i.e., returned to baseline serum creatinine levels), 38% were partially reversed (i.e., sustained subsequent graft function without return to baseline creatinine), while 7% ended in graft failure and/or patient death. Complete rejection reversal rates declined with increasing number of rejections (63% complete reversal of first rejection episodes vs. 32% of fourth or greater). The maximum number of rejection episodes reported to have occurred in a single patient with a single graft was ten. OKT3 was used in the treatment of 624 (27%) rejection episodes and intravenous methylprednisolone in 1,598 (69%). Dialysis was required during 13% of rejection episodes.

Of 483 patients who were rejection free for a minimum of 365 days post transplantation, 75 experienced at least one subsequent rejection episode, considered a "late" rejection episode for the purposes of this report. The median time elapsed between transplantation and late rejection episodes was 591 days (with upper and lower quartiles of 450 and 878 days, respectively). Graft loss associated with a first rejection episode occurring after day 365 was uncommon, with 51% of such episodes completely and 47% at least partially reversed. A proportional hazards regression analysis which considered recipient race, sex and age, donor source and cyclosporine dose simultaneously, indi-

Table 4. Causes of graft failure

Cause	Index graft failures ($n = 475$)	Second[a] graft failures ($n = 49$)	Total (%) ($n = 524$)
Primary nonfunction	14	0	14 (3)
Vascular thromboses	57	14	71 (14)
Miscellaneous technical	7	0	7 (1)
Hyperacute rejection, <24 h	7	1	8 (2)
Accelerated acute rejection, 2–7 days	17	4	21 (4)
Acute rejection	113	10	123 (23)
Chronic rejection	113	6	119 (23)
Recurrence of original disease	31	4	35 (7)
Death	41	5	46 (9)
Other	75	5	80 (15)

[a] One patient had 3 graft failures

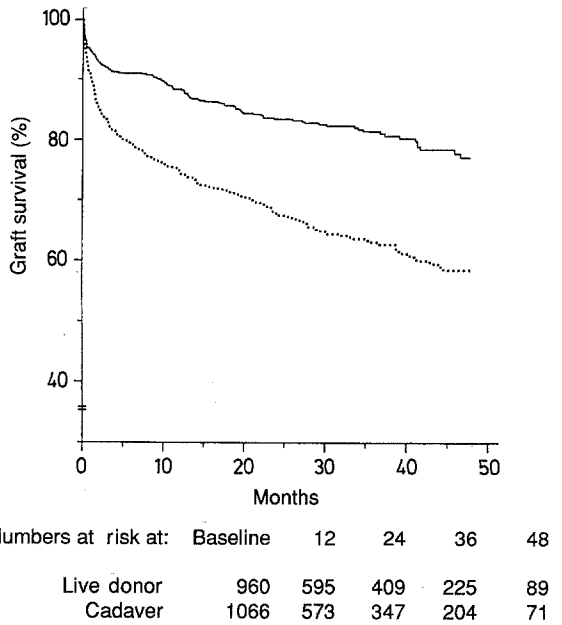


Fig. 4. Graft survival probability distribution (plotted from 40% to 100%) by allograft donor source. ———, Live donor; ..., cadaver

cated that non-white patients (RR = 2.1, $P < 0.01$) and patients over 6 years of age (RR = 2.4, $P = 0.03$) were at increased risk of experiencing a late rejection episode. Lower doses of cyclosporine were associated with a higher rate of rejection than higher doses (RR = 0.90, $P = 0.02$). Late rejection rates were 22%, 17%, 17% and 10% for patients receiving mean cyclosporine doses of less than 3.8, 3.8–5.5, 5.6–8.3 and greater than 8.3 mg/kg per day, respectively. The potential contribution of immunosuppressive regimen noncompliance to the incidence of late rejection was not examined.

Graft survival

Since the start of this study, 524 (24%) of 2,191 allografts have failed. Forty-seven patients have lost 2 grafts and 1 subject has had 3 graft failures. Following graft failure, 435 patients (83%) were treated with dialysis, 22 (4%) were retransplanted at the time of graft failure, 17 had adequate residual native kidney function and 4 had adequate residual prior graft function. Thirty seven (7%) patients died with functioning grafts which were considered graft failures. The causes of graft failure reported during the 5 years of the study are shown in Table 4. Acute and chronic rejection together accounted for 46% of graft failures over all. Primary nonfunction, vascular thrombosis and miscellaneous technical problems comprised a total of 92 graft failures, with vascular thrombosis the most frequent cause of graft failure after rejection (Table 4). Thirty-five patients had recurrence of original disease as the cause of graft failure: focal segmental glomerulosclerosis in 16, recurrent systemic immunological disease in 6, membranoproliferative glomerulonephritis type II in 5, oxalosis in 4 and hemolytic uremic syndrome in 4.

Overall median follow-up of subjects with functioning grafts was 23 months. For live donor source allografts, the estimated graft survival probabilities [standard error (SE)] at years 1 through 4 post transplant were 0.883 (±0.011), 0.833 (±0.014), 0.813 (±0.015) and 0.761 (±0.022), respectively. Comparable estimates for cadaver source organs were 0.744 (±0.014), 0.676 (±0.016), 0.629 (±0.018) and 0.583 (±0.022), respectively (Fig. 4). At 1 year post renal transplantation, cadaver allograft survival has increased from 72% in the 1987 cohort to 79% in the 1991 cohort. There has been no change in graft survival of living donor allografts.

Table 5. Risks factors associated with increased relative risks of graft failure based on a proportional hazards model

	Relative risk	P
Living donor graft recipients		
Recipient <24 months of age	1.8	0.01
Black race	2.1	<0.005
>5 prior transfusions	1.81	0.001
Cadaver donor graft recipients		
Recipient <24 months of age	2.73	<0.001
Donor <6 years of age	1.46	0.003
Prior transplant	1.44	0.007
No early ATG/ALG/OKT3	1.34	0.01
Cold ischemia time >24 h	1.30	0.02

The risk factors found to be associated with graft failure in a proportional hazards analysis are presented in Table 5. For recipients of living donor grafts, the most influential prognostic variables of index graft failure were young recipient age (recipient age = 0–1 year, RR = 1.8, $P = 0.01$) black race (RR = 2.1, $P < 0.005$) and more than five prior transfusions (RR = 1.81, $P = 0.001$). Treatment with OKT3 or ALG/ATG on day 0 or 1 was not associated with increased living donor graft survival. However, serum creatinine level among surviving living donor graft recipients at 6 months post transplant was significantly lower (mean 0.87 mg/dl, SE = 0.032) for early ATG/ALG/OKT3 therapy versus nontreated subjects (mean 1.14, SE = 0.056).

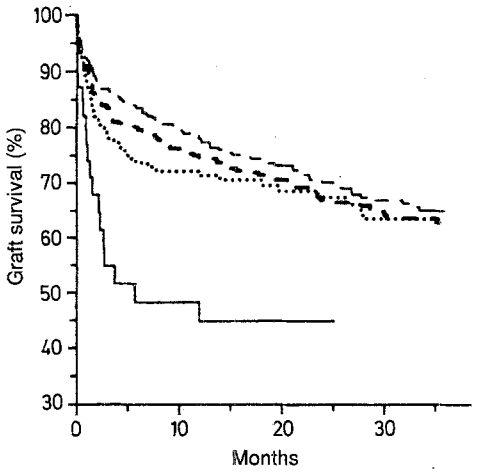
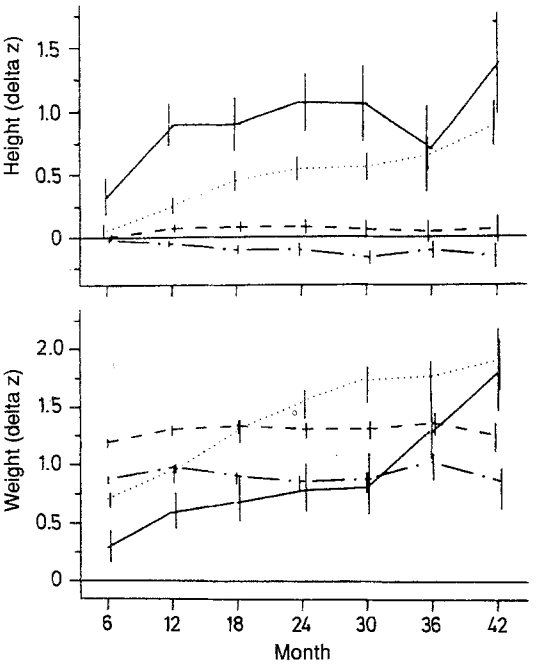


Fig. 5. Graft survival probability distribution for cadaver source renal transplants by recipient age group (years) at transplantation. ———, 0–1 year; ..., 2–5 years; – –, 6–12 years; – –, 13–17 years

For recipients of cadaver source organs, recipient age, donor age and cold ischemia time were found to be significant factors affecting graft outcome (Table 5). The relationship between recipient age and cadaver graft survival probability is shown in Fig. 5. Prior transplantation and the lack of ATG/ALG/OKT3 on day 0 or 1 were additional simultaneous significant contributors to the risk of cadaver graft failure (Table 5). Race, sex, prior dialysis, native nephrectomy, prior transfusion, HLA-A, -B and -DR matches and allograft preservation methods did not contribute significantly to cadaver graft survival when adjustment was made for recipient and donor age, cold ischemia time, prior transplants and lack of early ATG/ALG/OKT3.

Delayed graft function, defined as the use of dialysis during the initial post transplant week, was reported in 6% of living donor graft and in 20.3% of cadaver grafts. Living donor transplant recipients aged 0–1 years had a significantly higher rate of delayed function (12.5%) than did those with more than five prior transfusions (12.1%) and native nephrectomy (8.4%). The lowest rate of delayed function was seen in subjects transplanted with living donor grafts without prior dialysis (2.1%). Among cadaver graft recipients delayed function rates were highest for black recipients (27.2%), cold ischemia times more than 24 h (25.8%), more than five prior transfusions (28.7%), prior transplants (30.0%) and native nephrectomy (27.3%). The use of cyclosporine on day 0 was associated with delayed function in 4.2% and 23.6% of live donor and cadaver grafts, respectively. Donor and recipient ages and HLA antigen matching were not predictive of delayed function risk among cadaver graft recipients. In a logistic regression analysis, prior dialysis, race, transfusion history and cold ischemia time were jointly predictive of delayed cadaver graft function risk.

Graft survival beyond the 1st week was significantly worse in the presence of delayed function in both donor source groups. In the living donor group, black race (RR = 2.5), more than five prior transfusion (RR = 1.5) and delayed function (RR = 4.1) were associated with a simultaneous significant increase in the risk of graft failure. Seventy percent of subjects without 1st week dialysis were estimated to have functioning cadaver grafts at 3 years post transplant, whereas only 45% of recipients who required dialysis during the 1st week had functioning grafts at 3 years. For cadaver grafts that survived beyond 1 week, young donor age (RR = 1.4), young recipient age (RR = 2.3) and delayed function (RR = 2.2) were simultaneous significant risk factors for subsequent graft failure.



Sample size for height change at (months):

Age group (years)	6	18	30
0-1	78	57	37
2-5	228	159	97
6-12	515	340	222
13-17	518	340	186

Fig. 6. Mean change from baseline (with SE) in standardized height and weight scores (delta z scores) in pediatric subjects with graft function at each follow-up time by age group (years) at transplantation. ———, 0–1 year; ..., 2–5 years; – – – –, 6–12 years; – · – · –, 13–17 years

Growth

Characterization of growth following renal transplantation has been a major goal of this study. Normative data from the National Center for Health Statistics on United States children were used to determine standardized z scores for various patient groups. At transplantation, the mean height deficit (standardized z score) observed for all patients was –2.21 standard deviations (SD) below the appropriate age-sex-adjusted mean level. Mean height z scores (SE) were –2.69 (0.15), –2.70 (0.08), –2.29 (0.06) and –1.84 (0.06) for patients 0–1, 2–5, 6–12 and 13–17 years at transplantation, respectively. Subjects with prior transplants had substantially greater height deficits at the time of transplantation (mean height z scores = –3.26 vs. –2.06 without

prior transplants). For patients less than 24 months old at time of transplantation, an increase in height of 0.32 SD was observed in the first 6 months post transplant and of 0.90 SD by 12 months post transplant (Fig. 6). Subjects 2–5 years of age achieved acceleration in linear growth more slowly [mean (SE) increase in height z score of 0.54 (±0.09) at 2 years]. For subjects aged 6–12 years, linear growth was stable and consistent with that of the normal population, while older subjects demonstrated a slight non-significant decrease in z scores for height (Fig. 6).

Subjects not receiving antihypertensive therapy during the 1st posttransplant month had better growth in the initial 2 posttransplant years (mean difference in z score = 0.35, $P = <0.001$), a difference that was maintained at 3 years and persisted after age adjustment. Alternate-day prednisone use was associated with an additional 0.25 SD increase in height at 3 years, after adjustment for age and antihypertensive therapy status. A rapid increase in standardized weight scores was observed for all age groups (Fig. 6).

Morbidity and mortality

Length of hospital stay for transplantation surgery was negatively correlated with patient age. Median initial post-transplant hospital stays were 25, 21, 18 and 17 days for age groups 0–1, 2–5, 6–12 and 13–17 years, respectively. Recipients of cadaver donor grafts had a median initial hospital stay of 20 days, and those who received grafts from living donors stayed a median of 17 days. The longest initial hospitalization was 144 days with lower and upper quartiles of 12 and 24 days, respectively.

During posttransplant months 1–5, 59% of the patients were rehospitalized. The most common single reason for rehospitalization during this period was for treatment of rejection (33.1% of rehospitalized patients). Bacterial (12.7%) and viral (14.1%) infections and hypertension (8.0%) were other major causes of rehospitalization. Hospital stays decreased in both frequency and length beyond month 5, with treatment of rejection episodes remaining the primary reason for rehospitalization. Four malignancies were reported in 1991, yielding a total of 16 malignancies reported during the 5-year study period. Lymphoproliferative disorders occurred in 9 patients, 5 patients had sarcomas and 2 had carcinomas. Of 16 patients with malignancies 4 had more than 1 renal allograft. Of 16 patients with malignancies 8 had died at the time this report was compiled.

A total of 105 deaths have been reported since the study start. Infection was the most common primary cause of death (43 patients). Dialysis-related complications were the cause of death in 3 patients; 5 deaths were attributed to disease recurrence and 8 to malignancies. In 37 (35%) deaths, the graft was reported to be functioning at the time of the patient's death. Ten deaths occurred during the 1st week post transplant and 22 during the 1st month.

At the time this report was compiled, median follow-up time for surviving recipients was 24 months. The 2-year patient survival rates (SE) for recipients of living donor and cadaver source grafts were 0.955 (±0.008) and 0.930 (±0.009), respectively. The mortality rate for cadaver graft recipients was significantly greater than the mortality rate for live donor graft recipients (6.4% vs. 3.8%, $P = 0.006$). Among 127 infant recipients 0–1 years old, 23 died (11 with functioning grafts) for a mortality rate of 18%. This was significantly greater than the 3.5%–6.7% mortality rates observed in the three older age categories ($P < 0.001$).

Discussion

Since its inception in 1987, the NAPRTCS has grown from 45 to 75 contributing pediatric renal transplant centers located throughout the United States and Canada. Participation in the NAPRTCS is voluntary with only a token honorarium paid to transplant centers for each registered patient at the time of patient enrolment. Still it was hoped that all renal transplant centers in which 4 or more pediatric renal transplants were performed each year would join the study and that in this way the NAPRTCS would register and follow more than 80% of the children and adolescents receiving renal allografts in the United States and Canada.

During the first 5 years of the study, data have been collected on 2,037 pediatric patients who have received 2,197 renal transplants. Whether this level of participation meets the objectives cited above is unknown. Data on pediatric renal transplant recipients in the United States are available from the United States Renal Data System (USRDS) and can be used to estimate the completeness of the NAPRTCS data base [3]. Unfortunately, different age criteria were used by the two registries to report pediatric data (NAPRTCS 0–17 years, USRDS 0–19 years). However, with a few assumptions a rough estimate of the completeness of the NAPRTCS data base can be obtained from a comparison of USRDS and NAPRTCS pediatric transplant totals reported for the period 1987–1989. During this period, a total of 1,412 transplants were recorded by the NAPRTCS, 1,324 of which were performed in United States centers. For the same period the USRDS reported 2,154 transplants in patients 0–19 years of age, 1,038 of which were performed in patients 15–19 years of age. By assuming an even distribution of transplants over the 5 years of the 15–19 years age group and then reducing that age group's total by 40%, the total number of transplants registered by the USRDS for patients 0–17 years old can be roughly estimated to be 1,739 transplants. Comparing this estimate with the 1987–1989 NAPRTCS total of 1,324 United States transplants suggests that the NAPRTCS data base contains at least 75% of the eligible pediatric transplants recorded by the USRDS. While this estimate comes close to the NAPRTCS goal of registering 80% of pediatric transplants, only a direct year by year and patient by patient comparison of the data bases can properly assess the completeness of the two registries.

Over the 5 years of the NAPRTCS study, living donors were the source for 45% of transplanted kidneys and in 1991 reliance on living donors increased to 58%. Whether the increased emphasis on live donors reflects a decreasing availability of cadaver source organs for pediatric recipients is not clear. In contrast to the NAPRTCS experi-

ence, the European Dialysis and Transplant Association – European Renal Association (EDTA) has reported that only about 20% of pediatric renal transplants performed in the member countries of the EDTA are from living donors [4].

A marked decline in the number of transplants performed in infant recipients (those <24 months of age) occurred between 1989 and 1990. Recipient age less than 24 months was associated with a significantly increased RR of graft failure in both living and cadaver donor transplant recipients. While better results have been reported from small series of infants transplanted at single centers [5–7], findings similar to those of the present NAPRTCS study were recently reported by the EDTA for a large cohort of European infants transplanted before the age of 2 years [8]. The present report also described an increased relative risk of graft failure in recipients of grafts from cadaver donors less than 6 years of age and noted an apparent trend away from the use of young cadaver donors. Recipients of cadaver grafts from donors less than 6 years of age had an increased RR of experiencing at least one rejection episode and were less than half as likely to remain rejection free at 1 year compared with recipients of grafts from older cadaver donors. A detailed examination of the influence of donor age on cadaver graft outcome in pediatric recipients was recently reported by the NAPRTCS [9]. An increasing RR of graft failure was found to be associated with decreasing donor age. However, among pediatric donors there was no discrete donor age level below which graft failure was dramatically increased. Rather, the data described a steadily increasing RR of graft failure as donor age decreased [9].

PD appeared to be the favored dialytic modality for pediatric ESRD patients awaiting transplantation in participating NAPRTCS centers. Similar findings have been reported separately for both Canada [10] and the United States [3], and have been reviewed in detail elsewhere [11]. A consistent finding of the present study was the emphasis on preemptive transplantation; almost one-quarter of these patients received transplants without prior maintenance dialysis. Prior maintenance dialysis had no independent effect on graft outcome, but patients without prior dialysis appeared to have a lower rate of delayed graft function. This finding is obviously an artifact of the study design, which defines delayed graft function as the need for dialysis during the 1st posttransplant week. However, a previous NAPRTCS report described an association between the lack of prior dialysis and an increased risk of graft thrombosis in recipients less than 6 years of age [12]. It has been suggested that the polyuria that permits some of these children to come to transplantation without prior dialysis may predispose them to graft thrombosis as a consequence of relative volume depletion [12]. The present study did not further examine the relationship between prior dialysis and graft thrombosis.

Trends in immunotherapy have been observed during the 5 years of this study. The use of DST decreased from nearly 40% to only 11.5% of live donor graft recipients, and the number of cadaver graft recipients who received more than five random prior transfusions dropped by more than one-third. This figure is likely to decline even further in future reports as a consequence of more widespread use of erythropoietin therapy in pediatric ESRD patients. The present report is the first to describe the association of multiple prior transfusions with decreased living donor graft survival rates. A similar effect was not seen in cadaver grafts. The relationship between prior transfusions and graft outcome in pediatric patients deserves further study.

Immunotherapy among NAPRTCS centers can be characterized *in general* from the present report as follows: (1) nearly all patients receive cyclosporine; (2) nearly three-quarters of patients receive triple therapy with cyclosporine, prednisone and azathioprine; (3) nearly one-half of patients receive quadruple therapy with the added early use of ALG/ATG or OKT3. Several observations on the effectiveness of various immunotherapy regimens are included in the present report. For example, the early use of ATG/ALG or OKT3 significantly increased the time to first rejection episode in both live donor and cadaver source grafts, reduced the risk of cadaver graft failure, had no effect on live donor graft outcome, but was associated with lower mean serum creatinine levels at month 6. Similarly, the use of preoperative immunotherapy had no effect on time to first rejection episode. These observations must be interpreted with caution. Selective factors motivating the use of specific immunotherapy regimens are unknown and thus the size and direction of these potential biases cannot be quantified. Controlled prospective studies of immunotherapy regimens are needed to properly assess the effectiveness of these drugs in pediatric renal transplant recipients.

Rejection episodes were common occurrences among pediatric renal transplant recipients followed by the NAPRTCS. By the end of year 2, nearly 60% of live donor graft recipients and over 70% of cadaver graft recipients had experienced at least one rejection episode. Most rejection episodes occurred during the first 45 days post transplant, and almost all occurred before the end of year 1. Fortunately, over 80% of rejection episodes were at least partially reversible, and although the likelihood of complete reversal declined with increasing numbers of rejection episodes, over 30% of fourth and greater rejections were still completely reversed. A cohort of 75 patients whose first rejection episode occurred after day 365 was identified. These patients were more likely to be nonwhite, over 6 years of age and receiving relatively lower mean daily doses of cyclosporine. The role of noncompliance in these late rejections was not examined.

Nearly one-quarter of the transplants enrolled in this study since 1987 have failed, the majority due to acute or chronic rejection. A striking number of grafts were lost to vascular thrombosis, an observation that has been examined in a previous report from the NAPRTCS [12]. The living donor source graft survival rate was 88% at 1 year and declined to 83% at 2 years and to 76% at 4 years post transplant. Survival rates for cadaver source grafts were 74%, 68% and 58% at 1, 2 and 4 years post transplant, respectively. Similar live donor graft survival rates at 1 and 2 years post transplant have been reported by the Scientific Renal Transplant Registry of the United Network for Organ Sharing (UNOS) for patients of all ages receiving

transplants in the United States between 1 October 1987 and 1 October 1990 [13]. First cadaver graft survival rates were reported by the UNOS registry to be 78% and 70% at 1 and 2 years post transplant, respectively. Pediatric recipients (1–15 years of age) had consistently lower graft survival rates compared with patients 16–60 years old in the UNOS cohort [13]. But the overall 1-year cadaver allograft survival of the NAPRTCS cohorts has improved from 72% in 1987 to 79% in 1991.

The reasons for the lower cadaver graft survival rates observed in pediatric compared with adult recipients have not been defined. The present NAPRTCS report has attempted to identify those factors associated with increased RR of graft loss within a large cohort of pediatric renal transplant recipients. For pediatric recipients of live donor grafts, recipient age less than 24 months, black race and more than five prior transfusions independently increased the risk of graft failure. For recipients of cadaver source grafts, recipient age less than 24 months, donor age less than 6 years, cold ischemia time more than 24 h, prior transplantation and the lack of ATG/ALG or OKT3 on day 0 or 1 were associated with increased RR of graft loss. Risk factors do not of themselves rule out the use of higher risk donor-recipients pairs, but do provide potentially valuable information.

Observed linear growth following renal transplantation was disappointing. Most children were more than two SD below the mean for height at the time of transplantation, and only recipients less than 6 years of age demonstrated accelerated linear growth after transplantation. The use of alternate-day prednisone was associated with better linear growth compared with daily prednisone therapy, and patients who did not receive antihypertensive therapy during the 1st posttransplant month grew better than those who did. The latter finding is not readily explained.

Overall mortality rate was relatively low at 3.8% for live donor and 6.4% for cadaver donor source graft recipients. However, 18% of infants less than 24 months old at time of transplantation subsequently died, nearly half with functioning grafts. Infections were the predominant cause of death, and malignancies remained an uncommon but persistent occurrence. Treatment of acute rejection episodes, bacterial and viral infections and hypertension continue to dominate posttransplant inpatient management of pediatric patients. Future NAPRTCS reports will address additional characteristics of this expanding patient cohort in an effort to better describe pediatric renal transplantation practices in the United States and Canada and to identify those factors associated with improved outcomes.

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