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Occasional survey

The 1989 report of the North American Pediatric Renal Transplant Cooperative Study*

This report is prepared under the auspices of the scientific advisory committee of the North American Pediatric Renal Transplant Cooperative Study

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Abstract. This report of the North American Pediatric Transplant Cooperative Study summarizes data contributed by 57 participating centers on 754 children with 761 transplants from 1 January 1989 to 16 February 1989. Data collection was initiated in October 1987 and follow-up of all patients is ongoing. Transplant frequency increased with age; 24% of the patients were less than 5 years, with 7% being under 2 years. Common frequent diagnoses were: aplastic/dysplastic kidneys (18%), obstructive uropathy (16%), and focal segmental glomerulosclerosis (12%). Preemptive transplant, i.e., transplantation without prior maintenance dialysis, was performed in 21% of the patients. Dialytic modalities pretransplant were peritoneal dialysis in 42% and hemodialysis in 25%. Bilateral nephrectomy was reported in 29%. Live-donor sources accounted for 42% of the transplants. Among cadaveric donors, 41% of the donors were under 11 years old. During the first post-transplant month, maintenance therapy was used similarly for live-donor and cadaver source transplants, with prednisone, cyclosporine, and azathioprine used in 93%, 83%, and 81%, respectively. Triple therapy with prednisone, cyclosporine, and azathioprine was used in 78%, 75%, and 75% of functioning cadaver source transplants at 6 months, 12 months, and 18 months as opposed to 60%, 63%, and 54% for live-donor procedures, with single-drug therapy being uncommon. Rehospitalization during months 1–5 occurred in 62% of the patients, with treatment of rejection and infection being the main causes. Additionally, 9% were hospitalized for hypertension. During months 6–12 and 12–17, 30% and 28% of the patients with functioning grafts were rehospitalized. Times to first rejection differed significantly for cadaver and live-donor transplants. The median time to the first rejection was 36 days for cadaver transplants and 156 days for live-donor transplants. Overall, 57% of treated rejections were completely reversible although the complete reversal rate decreased to 37% for four or more rejections. One hundred and fifty-two graft failures had occurred at the time of writing, with a 1-year graft survival estimate of 0.88 for live-donor and 0.71 for cadaver source transplants. In addition to donor source, recipient age is a significant prognostic factor for graft survival. Among cadaver donors, decreasing donor age is associated with a decreasing probability of graft survival. Thirty-five deaths have occurred; 16 attributed to infection and 19 to other causes. The current 1-year survival estimate is 0.94. There have been 9 malignancies.

Key words: Renal transplants – Live donors – Cadaveric donors – Maintenance therapy – Rehospitalization – Rejection

Introduction

The North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS) is a research effort organized in 1987. The organizational structure of the NAPRTCS consists of: (1) the Clinical Coordinating Center (Dr. Tejani) located at the State University of New York Health Science Center at Brooklyn, (2) the Data Coordinating Center (EMMES Corporation, Drs. Novak and Stablein) located in Maryland, (3) a Scientific Advisory Committee of 13 members which has a geographic distribution across the United States and Canada, and (4) the participating clinic centers. (A listing of the centers appears at the end.) The objective of this group is to obtain the voluntary participation of all renal transplant centers in the United States and Canada in which multiple pediatric patients (>4) receive renal allografts annually. In so doing, we hope to register and follow greater than 80% of the children receiving renal allografts in the United States and Canada. For the purpose of this study, children are defined as patients

* A list of all participating centers and the names of the investigators is printed on pages 552–553

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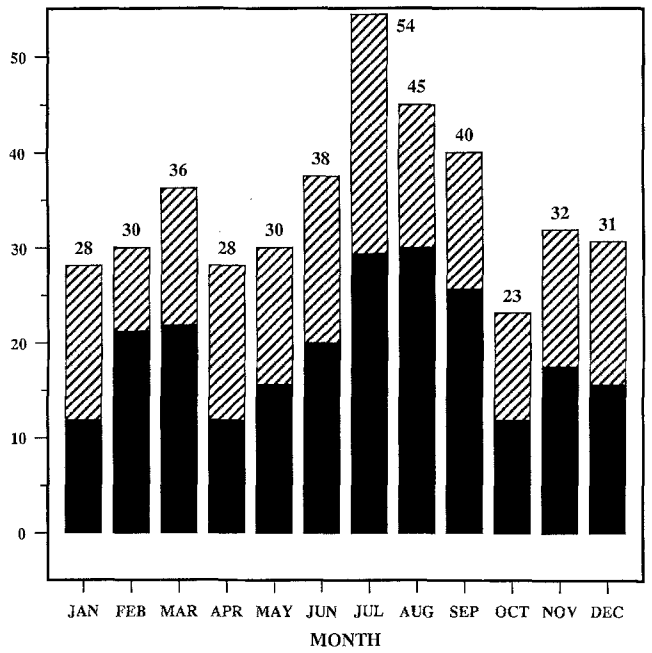

Fig. 1. Distribution of 1987 pediatric transplants in relation to month and donor source. ▨, Live donor; ■, cadaver

who have not yet attained their 18th birthday at the time of the index transplant. As a scientific objective, we hope to gain information about current practice and trends in immunosuppressive therapy for children receiving renal transplants in North America. Data submission for the study is organized so as to enable an analysis of patient and/or graft survival, morbidity, and relationships that these endpoints have to such variables as graft source, immunosuppressive treatment, and selected recipient characteristics such as age, sex, primary renal disease, antigen matches, and prior therapy. As we plan to longitudinally follow all patients registered into the program, we anticipate with continued follow-up to be able to analyze growth and its relationship to patient characteristics and therapies. As the study matures, it is our intent to design special studies to focus on questions pertaining to such topics as quality of life, rehabilitation, physical and mental development, or other questions for particular patient subgroups. In this manner, the study will serve as a resource to investigators whose research activities are consistent with the goals and objectives of the program.

The study began in 1987 with organizational efforts and pilot testing of data collection instruments at the Advisory Committee institutions as well as at selected volunteer centers. In October 1987, fullscale data collection was initiated, and participating centers were requested to register all pediatric patients receiving transplants on or after 1 January 1987. This report includes information received at the Data Coordinating Center up to and including 16 February 1989. We are particularly pleased and grateful for the enthusiastic response of the volunteer clinical centers without which this project could not be successful.

A total of 754 patients from 57 centers were registered; this represents 338 patients and 12 more centers than in the initial report. A total of 29 cases were registered without submission of follow-up information; thus follow-up information was available for 725 patients. Transplant forms were submitted for 761 procedures, 725 index transplants and 36 which were the second transplants in the same patient since the start of the study on 1 January 1987. A total of 1,017 monthly status forms were received, while an additional 240 forms which were due by 1 January 1989 had not been received by the time of the closure of the data files. This report summarizes the experience of both patients and transplants. In general, descriptive information focuses on the transplant as the unit of observation. Variables pertinent to the patient (i.e., sex, diagnosis, etc.) use the patient number as the denominator. Formal analysis of failure times – survival, graft, and rejection-free intervals – includes only the first transplant during the study for each patient.

Patient characteristics

Figure 1 shows the distribution of transplants, by month, for the 415 reported transplants from 1987. The transplants were not uniformly distributed throughout the months as an excess of transplants were performed in July and August. We recorded 190, 225, 204, and 137 transplants in each 6-month period starting 1 January 1987; thus we expected to collect about 70 more transplants in 1988. In 1986, the Health Care Financing Administration (HCFA) recorded 518 renal transplants in patients prior to their 18th birthday (P. Eggers, personal communication). The shortfall of patients registered in this study appears to be concentrated in the oldest age groups; the HCFA registry had 39% of its pediatric patients in the 15- to 17-year age group while only 27% of transplants in this study are in the same age range. A significant number of these older children are probably cared for by internists and were thus difficult to enroll in this study.

Recipient history is described in Table 1. A significant excess (60%) of the transplant patients were male. The most common primary renal diagnosis was aplastic/hypoplastic/dysplastic kidneys (18%) followed closely by obstructive uropathy (16%). Among glomerular lesions, focal segmental sclerosis (12%) was the most common reason for transplantation. Systemic diseases such as lupus nephritis and hemolytic uremic syndrome each accounted for less than 5% of the cases. Interestingly no child received a transplant for either diabetic nephropathy, or sickle cell nephropathy.

Eighteen percent of the patients had received a transplant prior to entry into the study, while 4 patients had received three prior transplants. For those with prior transplants, a median of 42 months had elapsed since their first transplant. In 21% of the patients, preemptive transplantation was performed without prior maintenance dialysis. For those with prior maintenance dialysis, the median time of initiation was 14 months (mean 22) prior to the index transplant. Twenty-four percent of patients were not on dialysis, 28% were only on hemodialysis, and 42% were exclusively on peritoneal dialysis immediately prior to the index transplant. Patients who were on dialysis immediate-

Table 1. Recipient characteristics

	n	%
Sex		
Male	437	60.4
Female	286	39.6
Race		
White	508	70.1
Black	95	13.1
Hispanic	77	10.6
Other	45	6.2
Diagnosis		
Aplastic/hypoplastic/dysplastic kidneys	131	18.1
Obstructive uropathy	116	16.0
Focal segmental glomerulosclerosis	87	12.0
Systemic immunologic disease	34	4.7
Reflux nephropathy	30	4.1
Hemolytic uremic syndrome	28	3.9
Congenital nephrotic syndrome	28	3.9
Chronic glomerulonephritis	27	3.7
Syndrome of agenesis of abdominal musculature	26	3.6
Familial nephritis	22	3.0
Pyelonephritis/interstitial nephritis	21	2.9
Medullary cystic disease/ juvenile nephronophthisis	21	2.9
Cystinosis	19	2.6
Renal infarct	16	2.2
Idiopathic crescentic glomerulonephritis	14	1.9
Membranoproliferative glomerulonephritis type I	14	1.9
Polycystic kidney disease	13	1.8
Membranoproliferative glomerulonephritis type II	10	1.4
Oxalosis	7	1.0
Wilms' tumor	5	0.7
Drash syndrome	4	0.6
Membranous nephropathy	3	0.4
Diabetic glomerulonephritis	0	0
Sickle cell nephropathy	0	0
Other	25	3.5
Unknown	24	3.3
Biopsy or nephrectomy confirmation of diagnosis		
No	272	37.6
Yes	358	49.5
Unknown	94	13.0
Number of transplants prior to study		
0	593	81.9
1	107	14.5
2	20	2.8
3	4	0.6
Maintenance dialysis		
Never performed	151	20.8
Performed	574	79.2
Maintenance dialysis immediately prior to index transplant		
No	173	23.9
Yes - hemodialysis	201	27.8
Yes - peritoneal dialysis	307	42.4
Yes - both	43	5.9
Splenectomy - yes	15	2.1
All native renal tissue removed	210	29.0

ly prior to the index transplant were maintained by this therapy for a median of 16 months.

Splenectomy had been performed in only 15 patients while all native renal tissue had been removed in 29% of the patients. Sixty-three percent of the patients with a prior transplant had had their prior grafts removed.

Table 2. Age at transplantation

	n	%
Age at transplantation (years)		
0	14	1.8
1	37	4.9
2	39	5.1
3	37	4.9
4	25	3.3
5	29	3.8
6	31	4.1
7	41	5.4
8	25	3.3
9	38	5.0
10	47	6.2
11	48	6.3
12	44	5.8
13	44	5.8
14	54	7.1
15	64	8.4
16	72	9.5
≥17	72	9.5
Age groupings		
0–1	51	6.7
2–5	130	17.1
6–12	274	36.0
13–18	306	40.2

Table 3. Age at index transplant in relation to patient's sex, race and diagnosis (%)

	Age (years)			
	0–1 (*n* = 47) %	2–5 (*n* = 120) %	6–12 (*n* = 261) %	13–17 (*n* = 297) %
Sex				
Male	70	73	63	52
Female	30	28	37	48
Race				
White	81	73	70	67
Black	11	10	11	17
Hispanic	4	13	12	9
Other	4	4	7	7
Diagnosis				
Aplastic/hypoplastic/ dysplastic kidneys	34	23	22	10
Obstructive uropathy	21	23	16	12
Focal segmental glomerulosclerosis	0	9	15	12
Other	45	45	47	66

Table 2 details the recipient's ages at each transplantation procedure. For this report, we have also grouped ages 0–1, 2–5, 6–12, and 13–17 years. In Table 3, patients' sex and diagnoses are classified by age. The sex distribution was most unbalanced in the youngest age groups, where 70% and 73% of the 0- to 1- and 2- to 5-year-old patients, respectively were male; the sex ratio was nearly even in the oldest age group. The importance of aplastic/hypoplastic/dysplastic kidneys and obstructive uropathy diagnoses also decreased with age. Forty-four percent of male patients fell into these two diagnostic cate-

Table 4. Sex, race and biopsy distributions in relation to primary renal diagnosis

Diagnosis	*n*	Male (%)	White (%)	Not biopsied (%)
Aplastic/hypoplastic/dysplastic kidneys	131	69	76	60
Obstructive uropathy	116	88	78	59
Focal segmental glomerulosclerosis	87	61	61	4
Systemic immunologic disease	34	24	50	12
Reflux nephropathy	30	33	67	60
Hemolytic uremic syndrome	28	57	82	43
Congenital nephrotic syndrome	28	57	71	4
Chronic glomerulonephritis	27	41	44	33
Syndrome of agenesis of abdominal musculature	26	100	65	58
Familial nephritis	22	73	68	5
Pyelonephritis/interstitial nephritis	21	38	67	33
Medullary cystic disease/juvenile nephronophthisis	21	50	81	38
Cystinosis	19	74	89	47
Renal infarct	16	38	81	50
Idiopathic crescentic glomerulonephritis	14	29	71	0
Membranoproliferative glomerulonephritis type I	14	64	71	7
Polycystic kidney disease	13	38	85	54
Membranoproliferative glomerulonephritis type II	10	30	70	10
Oxalosis	7	71	71	14
Wilms' tumor	5	20	80	0
Drash syndrome	4	25	50	0
Membranous nephropathy	3	100	67	0
Other	25	52	68	28
Unknown	24	33	42	58

gories, as opposed to only 19% of the females. The sex disparity disappeared for other diagnoses and only 52% of the patients were male in the remaining diagnostic groups.

Table 4 shows for each primary diagnosis the proportion of patients who were male, the proportion who were white, and the proportion known not to have had the diagnosis confirmed by biopsy or nephrectomy. Sixty percent of patients with aplastic/hypoplastic/dysplastic kidneys were not diagnosed on this basis; similarly 59% of patients with obstructive uropathy and 60% of patients with reflux nephropathy did not have a biopsy or nephrectomy. Comparable rates for focal segmental glomerulosclerosis, hemolytic uremic syndrome, and systemic immunologic disease were 3%, 43%, and 12%, respectively.

With more data, the preemptive transplant rate was observed to be similar across the age groups with rates of 21%, 19%, 25%, and 18% in the 0–1, 2–5, 6–12, and 13–17 age groups, respectively.

Donor history and antigen matches

As shown in Table 5, 58% of the transplants were from a cadaver source, 37% of the allografts came from patients' parents, while the remaining 5% came from other live donors. Twenty-two sibling transplants were performed, and 16 live-donor grafts were from donors under the age of

Table 5. Donor information

Information	*n*	%			
Donor source					
Live parent	281	37.0			
Live sibling	22	2.9			
Live other related	12	1.6			
Live unrelated	4	0.5			
Cadaver	441	58.0			
Donor age (years)	Live donor			Cadaver	
	n	%		*n*	%
0–1	0	0		22	5.1
2–10	0	0		156	36.2
11–20	16	5.0		95	22.0
21–30	80	25.9		62	14.4
31–40	141	44.5		52	12.1
41–50	68	21.5		27	6.3
>50	12	3.8		17	3.9
If cadaver source	*n*	%			
Method of allograft perfusion ($n = 441$)					
Machine	76	17.2			
Iced electrolyte	330	74.8			
Mixed	18	4.1			
Unknown	17	3.9			

Table 6. HLA mismatches (%)

No. of mismatches	Donor source	
	Living related ($n = 315$)	Other[a] ($n = 445$)
HLA-A		
0	18.4	8.5
1	80.0	45.4
2	1.6	46.0
HLA-B		
0	14.6	6.1
1	82.5	38.4
2	2.9	55.5
HLA-DR		
0	14.9	11.0
1	72.7	44.3
2	12.4	44.7
HLA-B HLA-DR		
0	5.7	2.7
1	16.5	6.3
2	61.9	23.8
3	13.0	40.4
4	0.3	27.6

[a] Includes cadaver ($n = 441$) and living unrelated ($n = 4$)

20 years. Three live donors were under 18 years of age. Two of these were identical twins, the younger twins being 13 years old. Twenty-two (5%) cadaveric grafts came from donors either 0 or 1 year old and a total of 41% of cadaver donors were 10 years of age or younger. The oldest cadaver donor was 64 years and the oldest live donor was 57 years. Of the cadaver allografts, 3 out of 4 were maintained with an iced electrolyte perfusion while 17% were maintained by machine perfusion. Fifty-nine percent of the cadaver grafts had cold times of less than 24-h duration with 2 (0.5%) exceeding 48 h. The maximum cold time was 56 h.

Table 7. Medication data – first 30 days

Therapy type	% Treated ($n = 761$)	Median day of initiation	Median initial dose mg/day	Median initial dose mg/kg per day	% Treated day 30 ($n = 691$)	Median day 30 dose mg/day	Median day 30 dose mg/kg per day
Prednisone	92	2	45	1.8	93	20	0.6
Live	92	2	45	1.9	93	20	0.6
Cadaver	91	3	45	1.8	94	20	0.6
Methylprednisolone	69	0	100	3.8	5	26	1.0
Live	64	0	100	3.9	5	25	1.1
Cadaver	73	0	100	3.5	5	28	1.0
Cyclosporine	83	2	260	9.4	81	270	8.6
Live	75	1	240	9.3	75	235	8.6
Cadaver	88	2	280	9.6	86	300	8.7
Azathioprine	81	0	55	2.3	75	50	2.1
Live	81	0	50	2.3	78	50	2.1
Cadaver	81	0	60	2.2	74	50	2.0
ATG/ALG	44	1	419	15.4	–	–	–
Live	37	1	400	18.8			
Cadaver	49	1	433	15.1			
OKT-3	6	6	2.5	0.1	–	–	–
Live	3	9	2.5	0.12			
Cadaver	8	5	2.5	0.12			
Other Immunosuppressive	9						
Live	6						
Cadaver	12						
Concomitant therapy							
Anticonvulsant	11						
Live	7						
Cadaver	14						
Antihypertensive	71						
Live	59						
Cadaver	80						
Antibiotics	59						
Live	57						
Cadaver	60						

ATG/ALG, Antithymocyte globulin/antilymphocyte globulin

There was a strong relationship between preemptive transplantation and donor source, with 31% of live-donor recipients as opposed to 13% of cadaver-donor recipients receiving preemptive transplants. Thus, 64% of the preemptive grafts had live-donor sources, while 38% of transplants in patients with prior dialysis had live donors. Donor-specific transfusions were performed in 32% of the live-donor recipients, although 39% received these transfusions in 1987 versus 25% in 1988. The lifetime total random transfusion distribution differed between donor types as 22% of the live-donor recipients compared with 8% of the cadaver graft recipients had no previous transfusions, while 36% and 57%, respectively, had more than five transfusions.

There were 2 confirmed transplants across blood group compatibility barriers (0 recipient, A donor), while 90% of the donor and recipient blood types were identical. Histocompatibility antigen results are shown in Table 6. We counted an allele as matching only if identical known alleles were reported for both donor and recipient. Among the living-related donors, 87% had at least a single haplotype match, while in 13% only a single HLA-B or HLA-DR match occurred. No matches in either of these loci occurred in 28% of the transplants from other than living-related donors and a single locus match occurred in 40% of these transplants. Only 1.8% of cadaver transplants had matches of all A, B and DR alleles.

Therapy

Because of the multiple drugs used and the changing strategies with time, analysis of therapeutic approaches for graft maintenance are complex. Preoperative immunotherapy was employed in 78% of live-donor transplants and reports of preoperative immunotherapy in cadaver-source transplants are being verified. Table 7 details immunosuppressive medication data for live-donor and cadaver source transplants for the first 30 days post-transplantation. Note that the frequency of various drug usages ranges from 6% of the transplants where OKT-3 was administered, to 92%

Table 8. Followup therapy summary

Therapy type	Treated %	Month 6 ($n = 437$) Median daily dose		Treated %	Month 12 ($n = 268$) Median daily dose		Treated %	Month 18 ($n = 132$) Median daily dose	
		mg	mg/kg		mg	mg/kg		mg	mg/kg
Prednisone	96	10	0.31	94	10	0.22	92	7.5	0.20
Live	95	10	0.31	92	8.8	0.23	90	7.5	0.21
Cadaver	96	10	0.31	96	10.0	0.21	95	7.8	0.18
Cyclosporine	88	220	5.77	87	200	4.96	83	180	4.84
Live	80	200	5.59	80	100	4.08	72	160	3.80
Cadaver	96	220	5.98	93	220	5.62	95	200	5.39
Azathioprine	83	50	1.75	84	50	1.80	84	75	1.74
Live	81	50	1.76	85	50	1.80	86	63	1.69
Cadaver	85	50	1.72	83	75	1.78	82	75	1.74
Other immunosuppressives	4			3			4		
Live	4			3			4		
Cadaver	4			4			3		
Concomitant therapy									
Anticonvulsant	9			7			8		
Live	6			5			4		
Cadaver	12			10			12		
Antihypertensive	69			60			52		
Live	58			53			45		
Cadaver	78			68			63		
Prophylactic antibiotics	42			31			32		
Live	43			32			27		
Cadaver	41			31			37		

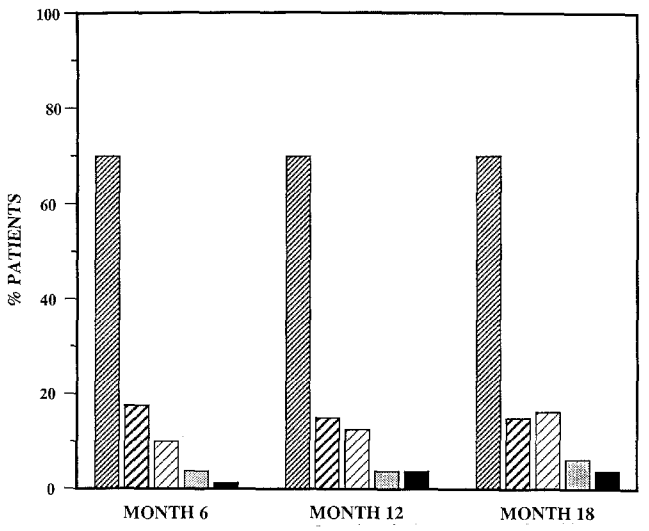

Fig. 2. Maintenance therapy patterns for months 6, 12 and 18. ▨, Triple-drug therapy; ▨, prednisone and cyclosporine; ▨, prednisone and azathioprine; ▨, cyclosporine and azathioprine; ■, single drug only

where prednisone was prescribed. For patients treated with these agents, methyl-prednisolone and azathioprine were typically started by the day of operation, while 31% had begun cyclosporine by this time, 17% on day 1 and 24% after the 1st week. Although graft failures decreased the number of patients still available for immunosuppressive therapy by day 30, little change in the percentages being treated with prednisone, cyclosporine, and azathioprine were seen. Over the month, median doses per transplant decreased from 45 mg/day prednisone to 20 mg/day, while median doses of cyclosporine and azathioprine were nearly constant. The median antithymocyte globulin/antilymphocyte globulin (ATG/ALG) course was 9 days and that for OKT-3 was 10 days. Dose levels for all drugs were quite similar for both allograft sources. Seventy-one percent of the patients were reported to be receiving antihypertensive therapy and over half of the patients received antibiotics (other than perioperative) during the postoperative month (59% live donor, 80% cadaver). Anticonvulsant medication was given to 11% of the patients.

Table 8 details immunosuppressive therapy for living patients with functioning grafts in relation to allograft source, at their 6-month follow-up. Median prednisone doses decreased from 10 to 7.5 mg/day, while the percentage of patients receiving alternate-day prednisone therapy increased from 15% at month 6 to 23% at month 12 to 32% at month 18. Note that there was little change in the proportion of patients receiving prednisone, cyclosporine, and azathioprine at each time point and that the azathioprine dose stayed relatively constant. A small decrease in the median dose of cyclosporine was observed, primarily among live-donor recipients. Among those receiving cyclosporine, the mean and standard deviation of the daily doses were 7.0 ± 4.3, 5.9 ± 3.8, and 5.0 ± 3.1 mg/kg, at months 6, 12, and 18, respectively. Although the proportion of transplant recipients requiring concomitant therapy decreases with time, a large proportion receive antihypertensives and antibiotics throughout the follow-up peri-

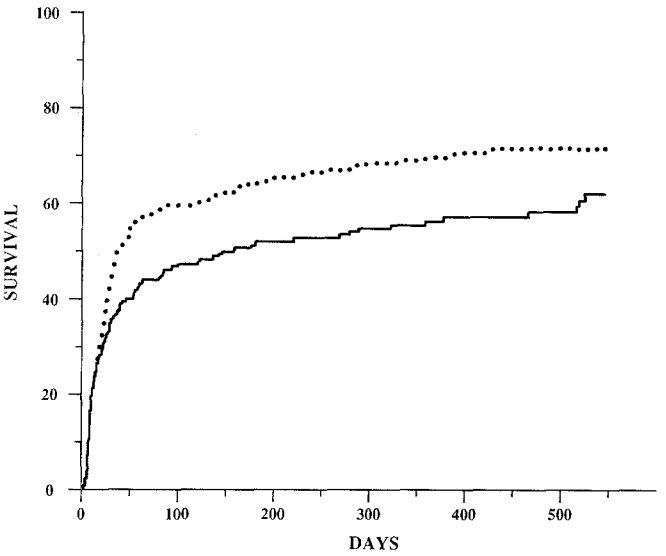

Fig. 3. Time to first rejection episode in relation to allograft source. ———, Live donor; ....., cadaver

od. Figure 2 shows the proportion of patients being treated with various drug combinations at each of the three follow-up time points. Triple-Drug therapy dominated with more than 2 out of 3 of the patients receiving all three drugs in combination. Dosing patterns for patients with functioning grafts were essentially constant at the 6-, 12-, 18-month time points. Cadaveric source recipients were treated with triple-dose therapy in 78%, 75%, and 75% of the cases, at 6, 12, and 18 months respectively, as opposed to 60%, 63%, and 54% of live-donor recipients. Cyclosporine was not used in 4%, 7%, and 6% of the cadaver transplant recipients at 6, 12, and 18 months, respectively, while among live-donor recipients, 19%, 19%, and 28% were not receiving cyclosporine at the same time points.

Each of the three drugs had a positive, but small, correlation with age and weight. For example, at 6 months the rank correlations for prednisone, cyclosporine, and azathioprine with weight were 0.55, 0.36, and 0.46 respectively. These values were also similar at the 12- and 18-month time points. When the daily dose per kilogram was examined, the correlations with weight were all negative at 6 months, i.e., −0.42 for prednisone, −0.41 for cyclosporine, and −0.22 for azathioprine. Thus, lighter patients received more drug per kilogram than heavier counterparts.

Correlations between daily doses of cyclosporine, prednisone, and azathioprine were all positive. Thus, the dosage of one drug was not reduced when another drug was increased. Rank correlation among maintenance immunosuppressives were all small when daily doses per kilogram were examined. For example, the largest at 6 months was the prednisone-azathioprine relationship which had a correlation of 0.13.

Rejection

For the purposes of this study, a rejection episode is reported if the decision is made to initiate specific therapy. A rejection is also considered to have occurred if graft failure

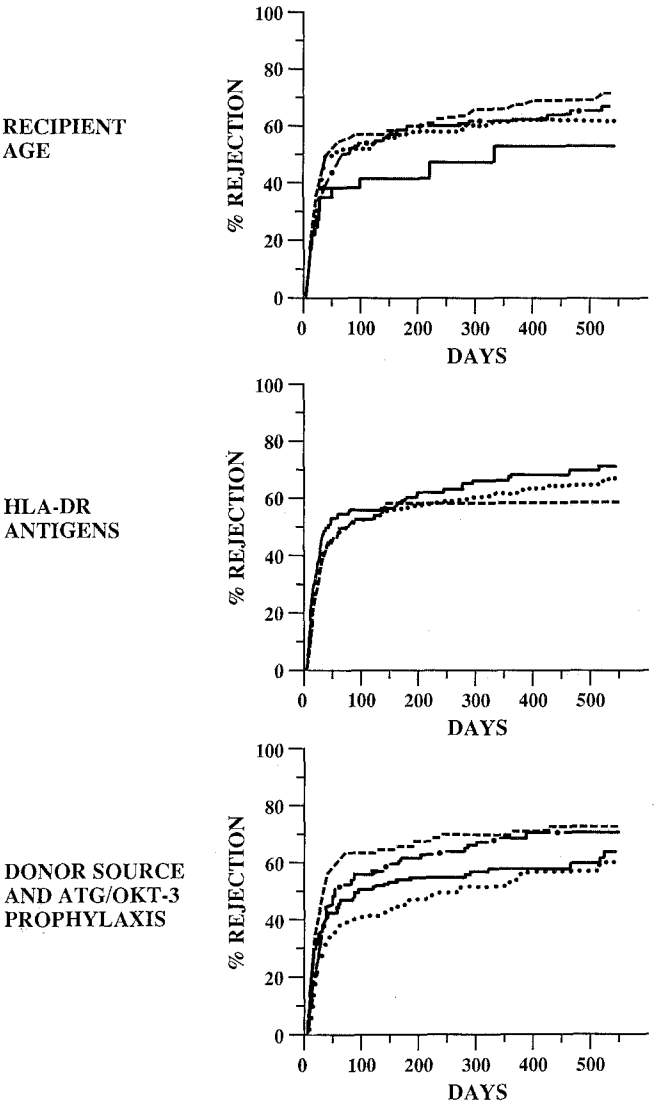

Fig. 4. Time to first rejection episode in relation to: **a** recipient's age; **b** HLA-DR antigens; **c** donor source and antithymocyte globulin *(ATG)/OKT-3* prophylaxis. Recipient's age: ——, 0–1; year; ..., 2–5 years; – –, 6–12 years; ——, 13–18 years. HLA-DR antigens: —, two mismatches; ....., one mismatch; – – –, no mismatches. Donor source and *ATG/OKT-3* prophylaxis; ——, cadaver source without prophylaxis; – – –, cadaver source with prophylaxis; ——, live donor source without prophylaxis; ....., live-donor source with prophylaxis

from rejection occurs. Six-hundred and seventy-five acute rejection forms were filed from 412 transplants. One-hundred and sixty-one reported two or more rejections, with a maximum of seven treated rejections for any treatment. Figure 3 shows the cumulative distribution of times to first rejection in relation to allograft source. In the first weeks, rejection patterns for the two groups were nearly identical, while patients with cadaver source grafts had an increased first rejection risk during the succeeding 2 months. At days 15, 30 and 45, live-donor rejection rates were 0.27, 0.35 and 0.40 versus 0.29, 0.45, and 0.52 for cadaver source transplants. Overall, half of all transplants had a rejection episode by day 58 (median 156 days for live-donor, 36 days for cadaver transplants). Figure 4 shows the cumulative rejection distributions for recipient

Table 9. Rejection reversal in relation to selected characteristics

	$n = 675$	% Complete reversal	% Partial reversal	% Graft failure/ death
Total		57%	35%	9%
Rejection number				
1	412	63	27	10
2	161	53	42	6
3	33	40	53	8
≥4	49	37	57	6
Biopsy				
No	354	65	30	5
Yes - needle	107	38	48	14
Yes - tissue	214	52	35	13
Source				
Live	258	64	31	5
Cadaver	416	52	37	11
DR antigen mismatch				
0	80	59	31	10
1	383	59	36	5
2	211	32	34	15
ATG/ALG/OKT-3 Prophylaxis at transplant				
No	383	55	37	8
Yes	291	59	32	9

ages, HLA-DR antigen mismatches, and prophylactic use of ATG/ALG or OKT-3 at the time of transplantation. Although the rejection distributions for the four age groups did not differ significantly ($P = 0.20$), the youngest age group was not at any disadvantage relative to time to first rejection. HLA-DR antigen mismatches were also not a significant predictor ($P = 0.33$) of rejection times. Use on day 0 or 1 of ATG/ALG or OKT-3 was associated with a significant decrease in times to first rejection, a decrease observed for both cadaver and live-donor source transplants. The large difference in the proportion of rejection-free individuals which was observed at 100 days diminished over the remainder of the 1st year, such that by year's end, the proportion of patients with rejection in either treatment group was nearly identical. Important selection biases in the decision to use this therapy could cause its effect to be either over- or understated; this observation should not be considered a definitive assessment of the role of prophylaxis.

Table 9 details the complete and partial reversal rates for each of the treated rejections. Overall, 57% of the episodes were completely reversed, 35% partially reversed while 9% ended in graft failure or death. Complete reversal rates declined with increasing number of rejections from 63% with the first rejection episode to 37% when four or more episodes had occurred. Non-biopsied rejections also had higher reversal rates, suggesting an association between the severity of the rejection episode and the decision to biopsy. Prophylactic treatment with ATG/ALG or OKT-3 at the time of transplant did not appear to significantly affect the probability of completely reversing later rejections. OKT-3 was used in the treatment of 199 rejection episodes and methylprednisone in 489, while dialysis was used during 15% of the rejection episodes.

Table 10. Causes of graft failure

Cause	Index graft $n = 139$	Second graft failures $n = 13$	Total $n = 152$
Primary non-function	6	0	6 (4)
Vascular thromboses	21	4	25 (16)
Other technical	5	0	5 (3)
Hyperacute rejection <24 h	3	0	3 (2)
Accelerated acute rejection, 2–7 days	15	1	16 (11)
Acute rejection	38	5	43 (28)
Chronic rejection	19	0	19 (13)
Recurrence of original disease	6	1	7 (5)
Death	12	1	13 (9)
Other	14	1	15 (10)

Graft failure

Of 761 transplants in 725 patients, 152 graft failures were reported in 139 patients. Of the failures, 116 (74%) were returned to dialysis, 8 (5%) were retransplanted, 10 had residual native kidney function, 2 had residual prior graft function, 13 (9%) died with functioning grafts, and 3 died with graft failure. Table 10 shows the distribution of graft failure causes. Fifty-three percent of the graft failures were caused by rejection with acute rejection being the leading cause of graft failure (28%). Recurrence of original disease as a cause of graft failure was observed 7 times (focal segmental glomerulosclerosis, 3; hemolytic uremic syndrome, 1; idiopathic crescentic glomerulonephritis, 1;

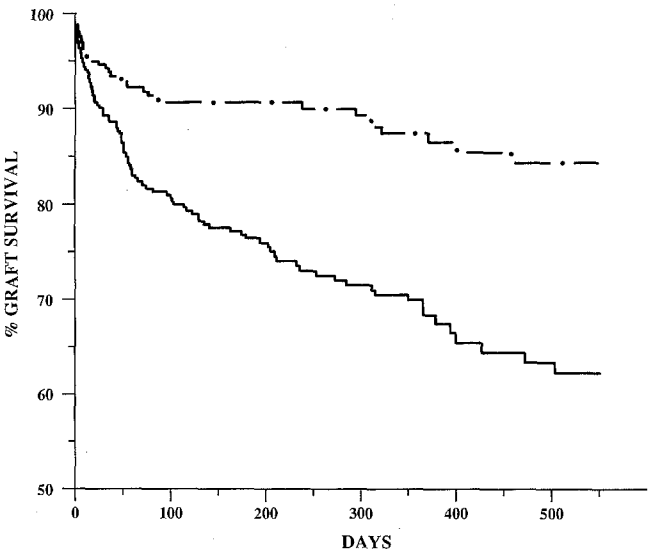

Fig. 5. Graft survival distribution in relation to allograft source. –.–, Live donor; —— cadaver; graft survival range is plotted from 50% to 100%

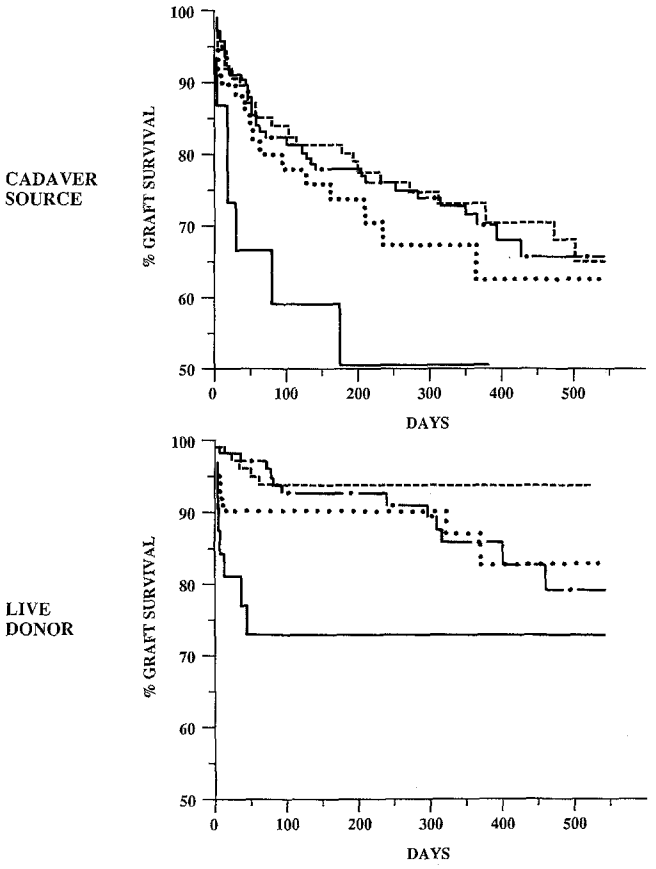

Fig. 6. Graft survival distribution in relation to allograft source and recipient's age: ——, 0–1 year; ....., 2–5 years; – – –, 6–12 years; ———, 13–17 years; graft survival range is plotted from 50% to 100%

membranoproliferative glomerulonephritis type I, 1; oxalosis, 1). Vascular thrombosis was reported to be the cause of graft failure in 16% of the failing cases. Thirty-six graft failures were due to primary non-function, vascular thrombosis, or other technical cases. These data suggest that these technical problems occur in 4.6% (36/761) of transplants. Tissue confirmation of cause was obtained in 108 cases.

Analysis of times to graft failure for the index transplants was performed. A graft is considered to have failed at the time of death in a patient who dies with a functioning graft. Because of the clinical and statistical significance, we present graft failure distributions separately for live-donor and cadaver source transplants. Table II shows graft failure information in relation to transplant source and selected transplant characteristics; the number of grafts in the subgroup, the number of failures, the 1-year graft survival percentage, and its estimated standard error are provided. With the available information, only a few of these variables have proven prognostic significance and we focus on recipient age, which is a significant factor after adjustment for allograft source and for cadaver grafts, on donor age.

Figure 5 shows the survival distribution estimates at times of graft failure for live-donor and cadaver source transplants. A significant difference in failure pattern was observed with a 1-year graft survival estimate of 0.88 for

Table 11. Graft failure summary in relation to allograft source and transplant chracteristics

	Live donor			Cadaver		
	No. of failures/n	Probability of 1-year function	SE	No. of failures/n	Probability of 1-year function	SE
Total	36/317	0.88	0.02	103/408	0.71	0.03
Sex						
Male	27/199	0.85	0.03	57/238	0.73	0.03
Female	9/118	0.92	0.03	46/168	0.68	0.04
Race						
White	30/250	0.87	0.02	61/258	0.72	0.03
Black	4/28	0.81	0.09	22/67	0.64	0.07
Hispanic	2/28	0.96	0.04	12/49	0.73	0.07
Other	0/11	–	–	8/34	0.75	0.08
Prior transplant						
No	32/287	0.88	0.02	72/306	0.72	0.03
Yes	4/30	0.89	0.06	31/101	0.67	0.05
Prior dialysis						
No	12/97	0.88	0.04	7/54	0.85	0.06
Yes	24/220	0.87	0.03	96/354	0.69	0.03
Recipient age (years)						
0–1	8/32	0.73	0.08	8/15	0.51	0.14
2–6	8/62	0.87	0.05	17/58	0.67	0.07
7–12	7/114	0.94	0.02	34/147	0.73	0.04
13–17	13/109	0.86	0.04	44/188	0.72	0.04
Donor age						
0–5	NA			40/113	0.55	0.06
6–10	NA			19/60	0.67	0.07
>10	NA			44/235	0.79	0.03
Cold time (h)						
≤24	NA			49/225	0.74	0.04
>24	NA			34/169	0.65	0.04
Preservation						
Machine only	NA			18/70	0.70	0.06
Iced electrolyte	NA			78/306	0.72	0.03
Other	NA			7/30		
HLA-A mismatch						
0	9/59	0.81	0.06	14/36	0.57	0.10
1	26/251	0.89	0.02	47/184	0.71	0.04
2	1/7	–	–	42/188	0.74	0.04
HLA-B mismatch						
0	5/45	0.85	0.06	7/24	0.65	0.13
1	29/262	0.88	0.02	36/158	0.75	0.04
2	2/10	–	–	60/226	0.69	0.04
HLA-DR mismatch						
0	5/47	0.86	0.06	9/45	0.73	0.08
1	28/231	0.87	0.03	45/188	0.73	0.04
2	3/39	0.91	0.05	49/175	0.68	0.04
Preoperative immunotherapy						
No	9/71	0.85	0.05	NA		
Yes	27/246	0.88	0.02	NA		
Native nephrectomy						
No	28/211	0.85	0.03	81/304	0.69	0.03
Yes	8/106	0.93	0.03	22/104	0.75	0.05
Lifetime transfusion						
0	8/68	0.88	0.04	5/33	0.83	0.07
1–5	13/131	0.89	0.03	27/144	0.75	0.05
>5	14/109	0.85	0.04	66/219	0.68	0.04
ATG/ALG or OKT-3 Prophylaxis						
No	23/199	0.88	0.03	58/201	0.70	0.04
Yes	13/118	0.87	0.04	45/207	0.72	0.04

NA, Not applicable

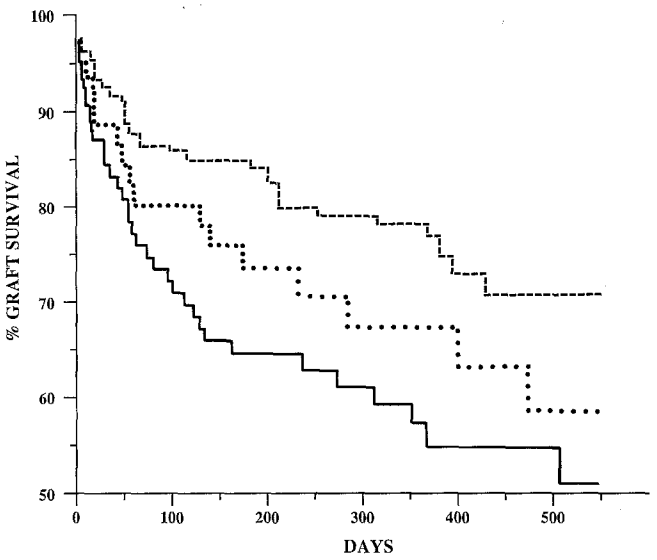

Fig. 7. Graft survival distribution for cadaver source transplants in relation to age: ——, 0–5 years; ....., 6–10 years; – – –, >10 years; graft survival is plotted from 50% to 100%

live-donor and 0.71 for cadaver grafts. Figure 6 shows graft survival distribution for 0- to 1-, 2- to 5-, 6- to 12-, and 13- to 17-year-old recipients by donor type. Adjusting for graft source, recipient age was a significant prognostic factor with the youngest recipients having the lowest 1-year graft survival rates. In Fig. 7, a clear trend in graft survival is seen in cadaver source transplants as donor age increases from 0–5 to 6–10 to greater than 10 years. Further follow-up is required to better identify the relative and long-term impact of these and other variables on the probabilities of graft survival.

Morbidity, malignancy, and mortality

Morbidity

The median duration of hospitalization at the time of transplant was 18 days. The longest hospitalization following transplant was 109 days with lower and upper quartiles of 13 and 26 days. Because of rehospitalization, the median time of hospitalization was 20 days during the month of transplantation.

Table 12. Hospitalization results for patients with functioning grafts in specified followup periods

	Months 1–5 ($n = 437$)	Months 6–11 ($n = 268$)	Months 12–17 ($n = 132$)
Days hospitalized (all patients)			
median	5.0	0	0
mean	10.0	3.5	3.0
Days hospitalized (hospitalized patients only)			
median	12.0	9.0	7.0
mean	16.7	12.6	10.6
% Hospitalized for:			
bacterial infection	12.9	5.9	6.8
fungal infection	1.7	0.4	0
viral infection	13.9	7.0	6.8
rejection	29.4	9.6	10.6
hypertension	8.7	4.0	2.3
any reason	62.0	30.0	28.0

Table 12 details the length of hospital stays and reasons for hospitalization for the surviving patients with functioning grafts. During months 1–5, 62% of the patients were rehospitalized. The most common reason for hospitalization was treatment of rejection which occurred in 29% of the patients. Viral (14%) and bacterial (13%) infections and treatment of hypertension (9%) were other major causes of hospitalization. All patients were hospitalized for a median of 5 days during this 5-month period with a mean duration of 10 days. If we consider only hospitalized patients, the median duration of the stay was 12 days. Hospital stays, in both frequency and length, decreased in months 6–17, while treatment of rejection episodes remained the primary reason for hospitalization. Mean (median) hospitalized patient stays were less than 13 (9) days in each of the later 6-month periods.

Malignancy

Table 13 summarizes information on the 9 malignancies reported to date. Of these, 5 were lymphoproliferative disorders, 3 sarcomas and 1 a thyroid carcinoma. In 5 of the

Table 13. Summary of reported malignancies

Transplant date	First transplant	Age	Diagnosis months posttransplant	Status	Survival months posttransplant	Diagnosis
15 Jan. 1987[a]	Oct. 1985	14	0	Died	10	Leiomyosarcoma
2 Feb. 1987[a]	May 1980	14	17	Alive	18	Papillary thyroid carcinoma
4 March 1987[a]	–	17	11	Alive	18	Large cell CNS lymphoma
19 April 1987	March 1987	<1	3	Died	3	EBV Lymphoproliferative disease
22 June 1987	Oct. 1985	13	5	Alive	5	Abdominal lymphoma surrounding kidney
7 Jan. 1988	–	13	3	Died	3	Lymphoma found on autopsy
12 Jan. 1988	–	9	2	Died	2	Lymphoproliferative disorder
28 May 1988	–	17	4	Died	4	Immunoblastic sarcoma
17 July 1988	–	6	3	Died	3	Immunoblastic sarcoma

EBV, Epstein-Barr virus

[a] Graft functioning at last observation

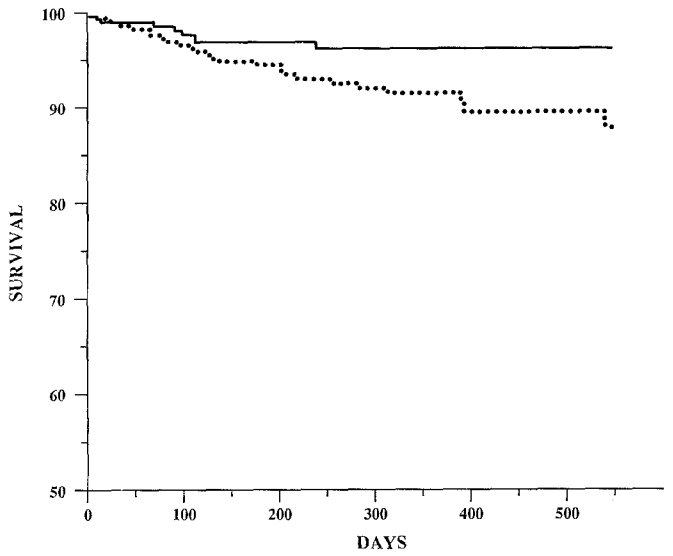

Fig. 8. Patient survival distribution estimates in relation to allograft source: —, Live donor; ....., cadaver

cases, the malignancy was observed after the patients' first renal allograft. Six of the patients died and 5 of these deaths were in the month of diagnosis. One malignancy was observed at autopsy and one of the patients had a functioning graft at the time of death. Two additional patients not included in this list have lymphoproliferative disorders that may be due to malignancy, but no diagnoses have been established.

Mortality

Thirty-five deaths were reported. Of these, 16 were attributed to infection and 19 to other causes. Five of these latter cases were hemorrhages and 4 were caused by cancer. In 13 patients, the graft was reported to be functioning at the time of the patient's death. Eight deaths occurred within the month of transplant, 2 of which were in the postoperative week. The survival distribution estimates by donor source are provided in Fig. 8; the overall 1-year survival rate was 0.94 with a 0.96 1-year survival for index live-donor and 0.92 for index cadaver source transplants. Standard errors for 1-year survival estimates ranged from 0.011 to 0.017. Twenty-one of the expired subjects were male, 24 were 6 years of age or older, and 26 had received cadaver grafts.

List of participating centers and the names of the investigators

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St. Louis Children's Hospital	St. Louis	Barbara R. Cole, MD
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