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Curent state of pediatric renal transplantation

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1. ABSTRACT

Renal transplantation is the goal for the pediatric patient with end stage renal disease. Recent advances in technology and immunosuppression have greatly enhanced patient and graft survival. However, the chronic immunosuppression exposes children to multiple complications and side effects. The current objective of pediatric renal transplantation is to develop management strategies which minimize or eliminate immunosuppression morbidities in order to maximize the growth and development of this unique population.

2. INTRODUCTION

Renal transplantation has long been recognized as the treatment of choice for children with end stage renal disease. Advances of the past decade have seen steady improvements in both graft and patient survival. With the marked decrease in acute rejection rates, the focus is now on the development of immunosuppressive strategies which minimize long-term toxicity. This review summarizes the current state of pediatric renal transplantation using data from North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS) transplant registry. This cooperative group has collected clinical information on children undergoing a renal transplantation since 1987 and now includes over 150 participating medical centers in the United States, Canada, Mexico, and Costa Rica. Currently, the NAPRTCS transplant registry includes information on 9837 renal transplants in 8990 patients. Since the first data analysis in 1989, NAPRTCS reports have documented marked improvements in outcome after renal transplantation in addition to identifying factors associated with both favorable and poor outcomes. The registry has served to document and influence practice patterns, clinical outcomes, and changing trends in renal transplantation.

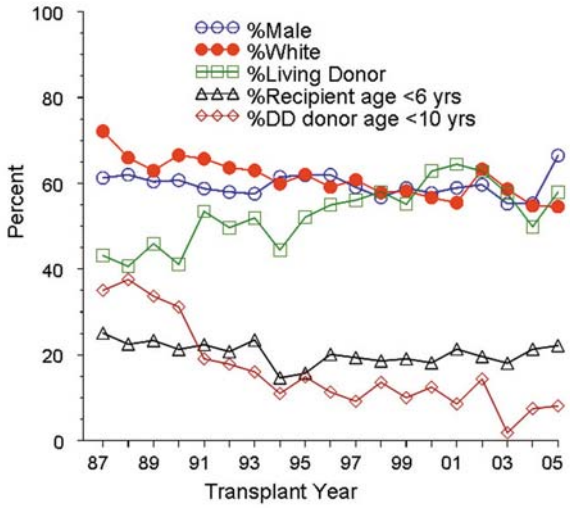

Figure 1. Recipient characteristics (NAPRTCS transplant registry).

3. PATIENT DEMOGRAPHICS

This gender distribution of patients with renal transplants has remained relatively stable over the past 15 years (Figure 1). Based on data from the NAPRTCS transplant registry, the current percentage of Caucasian recipients is currently 61%, which has decreased from a high of 72% in 1987. Seventeen percent of pediatric renal transplant recipients are African American and 16% are Hispanic. The etiology of end stage renal disease (ESRD) is summarized in Table 1. There has been no significant change in the etiology of ESRD in the pediatric population.

4. DONOR CHARACTERISTICS

Characteristics of the donors to pediatric recipients are summarized in Table 2. There has been a steady increase in living donor recipients from 43% in 1987 to 60% in 2000 and beyond, with parents representing 81% of living donors. There have been 348 transplants between siblings with 170 from those less than 21 years. The number of unrelated living donors has increased from an average of 3 per year in 1987-1995 to 17 per year since then. There has been a corresponding decrease in the number of deceased donors from 57% in 1987 to 40% since 2002.

Most of the transplants in the infant group (age 0-1 yrs) are from living donors (76%). In the other age groups, the percent of living donor (LD) and deceased donor (DD) are relatively equal at 57%, 52% and 48% LD in the 2-5, 6-12 and >12 year old groups, respectively.

The rate of pre-emptive transplant in the NAPRTCS registry is 25%. The donor source is more likely to be LD as 76% of pre-emptive transplants are from LD. Children aged 6-12 years have the highest rate of pre-emptive transplant (28%). The rate of pre-emptive transplant is highest among Caucasians, 30% compared to 14% in African American and 16% in Hispanic recipients.

5. IMMUNOSUPPRESSION

Figure 2 demonstrates that induction medication use has changed significantly from 1996 to 2005. In general, the percent of patients receiving no induction has decreased from 50.1% in 1996 to 33.1% in 2005. There have been significant decreases in the use of OKT3 (22.0% to 0%) and anti-thymocyte globulin/anti-lymphocyte globulin (ATG/ALG) (28.1% to 11.6%) with corresponding increases in the use of IL-2 (interleukin) receptor antagonists, basiliximab (32.6%) and daclizumab (22.7%). Table 3 shows the dramatic changes in the immunosuppression used at day 30 post-transplant, an indication of early maintenance immunosuppression choices. There has been a significant decrease in the use of cyclosporine from 77.7% in 1997 to 11.5% in 2005 with a corresponding increase in tacrolimus use from 14.5% in 1997 to 63.2% in 2005. Mycophenolate mofetil use has increased from 44.0% in 1997 to 64.9% in 2005. Azathioprine use has decreased from 33.9% in 1997 to 1.7% in 2005. Since its introduction in 1998, sirolimus use has increased slowly to 7.5% in 2005.

6. REJECTION

Table 4 summarizes the 12-month probability of first rejection by transplant year. There have been significant deceases in the rates of acute rejection. Donor source specific analyses were performed to assess the influence of specific patient and transplant characteristics on the occurrence of first rejection episodes in patients transplanted from 1996 to 2005 and in the earlier era. African American race, multiple HLA-DR mismatches and lack of use of induction antibody were associated with increased rejection risks (each $p< 0.001$) in both LD and DD transplants in the earlier era with relative hazard ratios ranging from 1.23 to 1.45.

Rejection reversal is defined as a return to the patient's baseline serum creatinine. Among living donor recipients, 53% had a complete rejection reversal, 43% had a partial reversal, and 4% had graft failure or the patient died. Among deceased donor recipients, 47% had a complete rejection reversal, 47% had a partial reversal, and 6% had graft failure or the patient died. Over the time of the registry, the proportion of complete versus partial rejection reversals has been nearly constant.

7. GRAFT SURVIVAL

Historically, acute rejection was the leading cause of graft loss. However, recent improvements in immunosuppression and post-transplant management have had a significant impact on reducing rates of acute rejection. Table 5 demonstrates the causes of graft failure among both index and subsequent transplants. Looking at transplants since January 1, 2000, chronic rejection is the leading cause of graft loss (41.3%) followed by vascular thrombosis (8.1%), recurrent disease (7.9%), acute rejection (6.3%), and medication discontinuation (6.3%). The emergence of thrombosis as a leading cause of graft loss in the past decade has prompted further investigation

Table 1. Etiology of end stage renal disease (NAPRTCS transplant registry)

Diagnosis	N (%)	% Male	% White	% Not Biopsied
Total	8990	59	65	44
Diagnosis				
Aplasia/hypoplasia/dysplasia	1432 (16)	62	69	71
Obstructive uropathy	1424 (16)	85	68	69
Focal segmental glomerulosclerosis	1049 (12)	58	50	6
Reflux nephropathy	466 (5)	44	79	65
Chronic glomerulonephritis	307 (3)	42	51	26
Polycystic disease	262 (3)	51	78	49
Medullary cystic disease	249 (3)	49	88	35
Hemolytic uremic syndrome	244 (3)	57	84	48
Prune Belly	239 (3)	98	63	62
Congenital nephrotic syndrome	230 (3)	53	70	13
Familial nephritis	200 (2)	81	63	26
Cystinosis	185 (2)	52	90	54
Idiopathic crescentic glomerulonephritis	166 (2)	34	57	5
Pyelo/interstitial nephritis	164 (2)	48	79	24
Membranoproliferative glomerulonephritis - Type I	162 (2)	45	61	3
SLE nephritis	141 (2)	18	28	5
Renal infarct	127 (1)	48	82	63
Berger's (IgA) nephritis	116 (1)	56	73	6
Henoch-Schonlein nephritis	107 (1)	40	75	15
Membranoproliferative glomerulonephritis - Type II	79 (1)	52	80	4
Drash syndrome	49 (1)	57	71	8
Wegener's granulomatosis	48 (1)	44	80	6
Wilms tumor	47 (1)	53	81	9
Oxalosis	45 (1)	58	90	24
Membranous nephropathy	41 (1)	59	55	7
Other systemic immunologic disease	32 (1)	13	62	6
Sickle cell nephropathy	15 (1)	53	0	27
Diabetic glomerulonephritis	10 (1)	30	30	40
Other	806 (9)	52	66	36
Unknown	548 (6)	52	34	69

N: 8990

Table 2. Donor characteristics (NAPRTCS transplant registry)

			N (9837)			% (100.0)
Donor Source						
Live donor/parent			4129			42.1
Live donor/sibling			348			3.5
Live donor/other related			449			4.6
Live donor/unrelated			196			2.0
Deceased donor			4697			47.8
Donor Age	**Living**			**Deceased**		
0-1	—	—		69	1.6	
2-5	—	—		425	9.6	
6-12	—	—		595	13.5	
13-17	13	0.3		650	14.7	
18-20	157	3.2		475	10.8	
21-30	1076	21.9		735	16.6	
31-40	2237	45.4		659	14.9	
41-50	1252	25.4		538	12.2	
> 50	188	3.8		270	6.1	
Deceased Donor Source Transplants						
Cold Ischemia Time						
< 24 hours			2983			70.1
> 24 hours			1275			29.9

N: 9837

Table 3. Percent drug utilization day 30 post-transplant (NAPRTCS transplant registry)

	1997 (N=593)	1998 (N=542)	1999 (N=553)	2000 (N=451)	2001 (N=491)	2002 (N=445)	2003 (N=378)	2004 (N=345)	2005 (N=174)
Cyclosporine	77.7	71.2	66.9	56.3	46.8	27.0	15.3	8.7	11.5
Tacrolimus	14.5	22.0	23.3	33.5	40.9	57.3	59.8	71.0	63.2
Mycophenolate	44.0	65.7	66.0	63.0	53.2	57.3	55.8	64.1	64.9
Azathioprine	33.9	19.7	15.2	13.3	12.8	1.8	4.2	3.5	1.7
Sirolimus	—	0.2	0.4	5.8	15.5	20.5	18.5	11.0	7.5

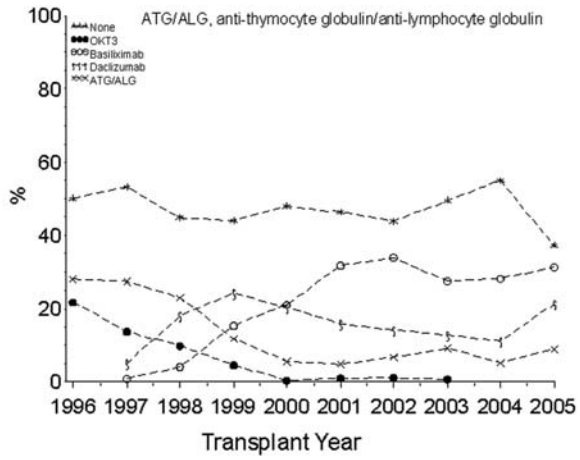

Figure 2. Induction antibody use by year (NAPRTCS transplant registry).

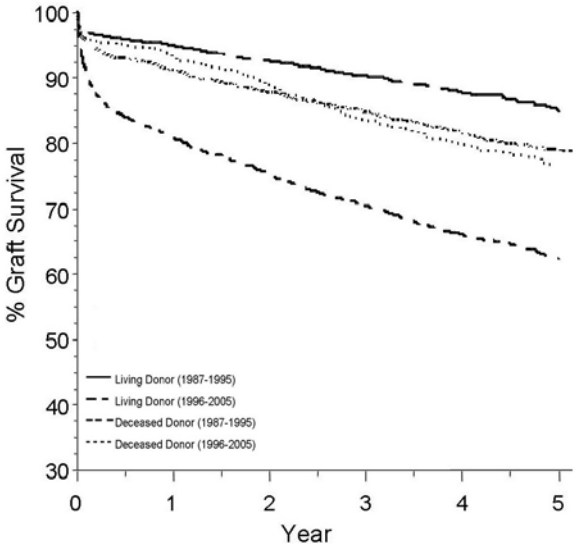

Figure 3. Percent graft survival by era and primary allograft source (NAPRTCS transplant registry).

Several risk factors have been identified including deceased donor source, cold ischemia time > 24 hours, history of prior transplant, pre-transplant peritoneal dialysis, and history of > 5 pre-transplant blood transfusions (1). Most recently, a NAPRTCS analysis showed a decreased risk of renal allograft thrombosis with the use of IL–2 receptor antagonists (2).

Graft survival by allograft source and transplant era is shown in Figure 3. Since 1987, estimated graft survival probabilities are 92.2% + 0.39%, 85.8% + 0.54%, and 79.7% + 0.68% at years 1,3, and 5 years among LD recipients. Corresponding estimates for DD recipients are 83.6% + 0.58%, 73.1% + 0.74%, and 65.1% + 0.87%. For the last decade, graft retention has improved with 5 year estimated graft survival of 85.1% + 1.03 for LD and 76.9% + 1.53 for DD transplants.

Numerous studies have evaluated patient and recipient factors that influence outcome. Recipient age has been identified as an important determinant of outcome. Among living donor recipients, adolescents have the worst 5-year graft survival rates (3). Among deceased donor recipients, excluding the immediate post-op period where infants had an increased incidence of graft loss secondary to technical complications, adolescents have the worst long-term graft survival. Adolescents have the highest rates of late initial rejection. Once diagnosed with rejection, adolescents do not respond as well to treatment with significantly fewer complete rejection reversals and more partial reversals. The reasons for the poor long term outcome for the adolescent group are unknown. It is hypothesized that medication non-adherence plays an important role in this age group. Other potential explanations identified by NAPRTCS analyses include an unexplained high frequency of graft thrombosis (1) and the high incidence of recurrence of FSGS (4), the most common acquired cause of ESRD in this age group. Studies have consistently demonstrated inferior allograft survival in African Americans of all age groups compared to all other ethnic groups (5-9). Multiple factors contribute to the inferior outcomes observed among African Americans including higher incidence of FSGS as primary diagnosis, higher rate of deceased donor source, higher risk of delayed graft function, and higher incidence of acute rejection and late rejection. Table 6 shows the results of a multivariate model of risk factors for graft loss at any time during the follow-up period. For LD recipients, the significant risk factors for graft loss include African American race, history of prior transplant, greater than 5 lifetime blood transfusions, HLA mismatch, no induction therapy, and female gender. For DD recipients, additional risk factors include recipient age < 1 yr, prior dialysis, and cold ischemia time >24 hours. Later transplant years are at lower risk for graft failure in both donor groups.

8. PATIENT SURVIVAL

Among LD recipients, patient survival rates were 98.2% + 0.20, 97.4% +0.24, and 95.6% + 0.35 at years 1, 3, and 5 years post-transplant. Among DD recipients, patient survival rates were 97.1% +0.28, 96.0% +0.33, and 92.6% + 0.51 at years 1, 3, and 5 years post-transplant, which is significantly poorer than for LD recipients ($p<0.001$). Patient survival has significantly improved for DD recipients with a 5 year patient survival of 90.8% + 0.66 in the early era to 95.8% + 0.80 in the more recent era.

Although infants' post-transplant survival is lower compared to other age groups, there has been a significant improvement in their outcomes over the time of the registry. The three year patient survival of infants receiving DD allograft has increased from 78.5% between 1987-1995 to 92.8% from 1996 and beyond. Similarly, among infants receiving LD allografts, the 3-year patient survival has improved from 89.8% in the early era to 94.8% in the later era.

Crude mortality rates among LD and DD recipients are 4.7% and 7.0%, respectively. The causes of death are summarized in Table 7 with infection accounting for 28.9% of deaths, cardiopulmonary 15.7%, and malignancy 11.0%.

Table 4. Twelve month probability (%) of first rejection by transplant year (NAPRTCS transplant registry)

Transplant Year	Living donor		Deceased donor	
	%	SE	%	SE
1987-1990	54.2	1.7	69.1	1.5
1991-1994	44.8	1.5	60.6	1.6
1995-1998	33.4	1.4	40.8	1.7
1999-2002	22.6	1.3	26.8	1.9
2003-2005	13.2	1.9	15.8	2.3

Table 5. Causes of graft failure (NAPRTCS transplant registry)

	Index graft failures		Subsequent graft failures		All graft failures	
	N	%	N	%	N	%
Total	2251	100	305	100	2556	100
Death with functioning graft	211	9.4	23	7.5	234	9.2
Primary non-function	58	2.6	2	0.7	60	2.3
Vascular thrombosis	231	10.3	38	12.5	269	10.5
Other technical	28	1.2	4	1.3	32	1.3
Hyper-acute rejection	13	0.6	4	1.4	17	0.7
Accelerated acute rejection	33	1.5	8	2.6	41	1.6
Acute rejection	291	12.9	40	13.1	331	12.9
Chronic rejection	776	34.5	111	36.4	887	34.7
Recurrence of original kidney disease	145	6.4	29	9.5	174	6.8
Renal artery stenosis	15	0.7	.	.	15	0.6
Bacterial/viral infection	44	2.0	4	1.3	47	1.8
Cyclosporine/tacrolimus toxicity	11	0.5	.	.	11	0.4
De novo kidney disease	7	0.3	2	0.7	9	0.4
Patient discontinued medication	104	4.6	8	2.6	112	4.4
Malignancy	30	1.3	2	0.7	32	1.3
Other/unknown	254	11.3	30	9.8	284	11.1

Table 6. Relative hazard of graft loss in a multivariate proportional hazards models (NAPRTCS transplant registry)

	Living donor		Deceased donor	
	RH	(P-value)	RH	(P-Value)
Recipient age (>2 vs. 0-1 years)	1.13	(24)	0.59	(<0.001)
Prior transplant	1.35	(0.006)	1.43	(<0.001)
No induction antibody administration	1.15	(0.035)	1.09	(24)
>5 lifetime transfusions	1.31	(0.003)	1.28	(<0.001)
No HLA-B matches	1.40	(0.008)	1.16	(0.014)
No HLA-DR matches	0.87	(24)	1.14	(0.024)
African American race	1.95	(<0.001)	1.56	(<0.001)
Prior dialysis[1]	1.16	(0.052)	1.23	(0.040)
Cold storage time >24 Hours	—	—	1.14	(0.034)
Transplant year (per year)	0.95	(<0.001)	0.94	(<0.001)
No native nephrectomy	0.87	(0.051)	0.96	(24)
Male gender	0.87	(0.036)	0.85	(0.005)

[1]Reported as having ever had dialysis. RH, relative hazard; NS, not significant; HLA, human leukocyte antigen

Table 7. Causes of death following index renal transplantation (NAPRTCS transplant registry 1987-2007)

	Total			Living Donor			Deceased Donor		
	N	%	Number of functioning grafts	N	%	Number of functioning grafts	N	%	Number of Functioning Grafts
All deceased patients	510	100.0	237	227	100.0	113	283	100.0	124
Cause of death									
Viral infection	43	8.4	22	23	10.1	12	20	7.1	10
Bacterial infection	64	12.5	31	31	13.7	14	33	11.7	17
Other infection	41	8.0	12	21	9.3	6	20	7.1	6
Cancer/malignancy	56	11.0	39	31	13.7	23	25	8.8	16
Cardiopulmonary	80	15.7	37	29	12.8	15	51	18.0	22
Hemorrhage	33	6.5	12	9	4.0	2	24	8.5	10
Disease recurrence	8	1.6	1	2	0.9	1	6	2.1	--
Dialysis-related complication	14	2.7	--	7	3.1	--	7	2.5	--
Other	123	24.1	59	56	24.7	31	67	23.7	28
Unknown	47	9.2	24	17	7.5	9	30	10.6	15

9. INFECTIONS POST-TRANSPLANT

The risk of infection is a serious threat in the immunosuppressed renal transplant patient. The more potent immunosuppressive therapy that has successfully reduced the incidence of acute rejection has also resulted in a higher incidence of viral infection Post-transplant infections have now replaced rejection as the leading cause for hospitalization in pediatric renal transplant recipients (10). In addition, infection is the major cause of death of transplanted children, particularly in the first post-transplant years (7). Post-transplant lymphoproliferative

disease (PTLD) associated with uncontrolled Epstein-Barr Virus (EBV) replication has emerged as a significant cause of morbidity and mortality in the pediatric transplant population (11). NAPRTCS data demonstrate an increasing incidence of PTLD over the past decade most likely as a result of the use of more potent immunosuppressive agents in the most recent transplant era (11-13).

10. GROWTH

Optimizing growth and development are a main focus in the care of the pediatric transplant recipient. Studies demonstrate that a functioning renal transplant enables children to develop normally, grow reasonably well, and normalize their school performance levels (14-17). In general, there has been improvement in the height deficit seen at the time of transplant. In 1987, patients receiving their initial transplant were an average of 2.4 standard deviations below average compared to 1.5 standard deviations below average in the 2003 cohort. However, catch-up growth in renal transplant recipients has been seen in only 47% of children between the ages of two and five years. Unfortunately, for children over the age of five years, little catch-up growth has been noted (18, 19). Alternate day steroid dosing has been shown to improve growth without adversely affecting graft survival or long-term graft function (20). A subsequent report by Fine described the impact of recombinant growth hormone treatment in renal transplant recipients who had chronic renal insufficiency, as well as long-term use of recombinant human growth hormone in pediatric allograft recipients (21, 22). Recently, evidence from steroid avoidance protocols has demonstrated excellent growth (23).

11. PERSPECTIVE

Renal transplantation remains the goal for the pediatric patient with ESRD. Recent advances in technology and immunosuppression have greatly enhanced patient and graft survival. However, the chronic immunosuppression exposes children to multiple complications and side effects. The current goal of pediatric renal transplantation is to develop management strategies which minimize or eliminate immunosuppression morbidities in order to maximize the growth and development of this unique population.

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