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Factors Related to Graft Outcome in Pediatric Renal Transplantation: a Single Center Study

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1. Introduction

Over the last decades, renal transplantation has evolved from an experimental procedure into the treatment of choice for children with end-stage renal disease. Differences in size and weight of the recipient, cause of renal failure, immune responsiveness, susceptibility to infection, pharmacokinetics of immunosuppressive drugs, and psychological aspects distinguish renal transplantation in children from adults. The longevity of an allograft is particularly important for the pediatric transplant recipient, because renal replacement therapy is necessarily a lifelong undertaking. The aim of the present study is to determine by means of a multivariable analysis the factors that significantly affect graft outcome in the paediatric transplant population. Knowledge of predictors of graft survival can be beneficial in planning the renal replacement therapy in children and improving transplantation results.

Registry studies, essentially from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) (Benfield et al., 1999; NAPRTCS, 2010) and from the United Network for Organ Sharing (UNOS) (Hwang et al., 2005), have been performed to analyse factors related to graft outcome in children. Registry studies have the advantage of being able to include large number of patients. However these studies usually involve heterogeneous populations with different pre-transplant selections, transplant procedures and post-transplant management. Therefore single center studies using a more homogeneous patient group and more uniform management protocols may be valuable in the analysis of transplant outcome. Nevertheless such single center studies using multivariable techniques to analyse transplant outcome are very scarce in paediatric renal transplantation (Vats et al., 2002).

We analysed all renal transplantations performed in children at our institution between 1980 and 2010 and included in our analysis various factors concerning recipient characteristics, donor characteristics, perioperative characteristics and post-transplant events.

2. Patients, materials and methods

2.1 Patients

The study population consisted of 151 kidney transplants performed between June 1980 and October 2010 in 135 children (81 boys and 54 girls) with mean age 10.7 years (± 4.9) at

transplantation. There were 132 first grafts, 15 second grafts, 3 third grafts and 1 fourth graft.

The original disease was congenital or hereditary in 74% and acquired in 26%. Thirteen children were transplanted preemptively. Kidney came from living related donors (LRD) in 33 cases (22%) and from deceased donors (DD) in 118 cases (78%). Four children underwent combined liver-kidney transplantation.

Immunosuppression consisted of an induction with antilymphocyte antibodies and a maintenance regimen with cyclosporine A (CsA) (since December 1984), azathioprine and prednisolone. Newer immunosuppressive agents were introduced more recently: tacrolimus in 1998, mycophenolate mofetyl in 1998, basiliximab and daclizumab in 1999.

2.2 Data source

Data were retrieved from the patients' medical files and from the archives and database of Eurotransplant. The follow-up period ended in February 2011.

2.3 Analytic variables and statistical analysis

The following variables were studied as potential factors affecting graft outcome:

- *Recipient characteristics*: age (years), gender, height (cm), weight (kg), body surface area (BSA, m²), body mass index (BMI, kg/m²), prior transplant, primary kidney disease, peak and current panel-reactive antibody percentage (PRA), ABO blood group, CMV serological status, number of prior blood transfusions (0-5 vs. >5), native nephrectomy, dialysis modality before transplantation, dialysis duration (years), time on the waiting list (years), hypertension (defined as the use of antihypertensive medications), year of transplantation.
- *Donor characteristics*: age, gender, height, weight, BSA, BMI, ABO group, CMV status, donor type (LRD vs. DD), cause of death for the deceased donors, serum creatinine level (mg/dl) at organ retrieval, diuresis (ml) during the last 24 hours and the last hour before organ retrieval.
- *Donor recipient relationships*: donor/recipient age ratio, height ratio, weight ratio, BSA ratio, BMI ratio, gender mismatch, human leukocyte antigen (HLA) mismatch, ABO mismatch (all grafts were ABO compatible but one), CMV mismatch (D+/R-, D-/R+, D+/R+, D-/R-).
- *Organ preservation and perioperative characteristics*: donor kidney preservation solution (Eurocollins (EC) vs. University of Wisconsin (UW) vs. histidine-tryptophan-ketoglutarate (HTK)), cold ischemia time (hours), warm ischemia time (minutes).
- *Immunosuppression*: induction therapy (polyclonal vs. monoclonal vs. none) and maintenance immunosuppression at time of discharge from the initial hospitalization including use of calcineurin inhibitors and type (CsA vs. tacrolimus), use of antimetabolites and type (azathioprine vs. mycophenolate mofetyl).
- *Post-transplant characteristics*: duration of initial transplant hospitalization (days), occurrence of delayed graft function (DGF) defined as the need for dialysis in the first week post-transplant, occurrence of acute rejection episodes, creatinine clearance (ml/min/1.73 m²) at 1 year post-transplant (calculated using the Schwartz formula: creatinine clearance = 0.55*height (cm)/plasma creatinine (mg/dl)), hypertension (defined as the use of antihypertensive medications) and its severity as reflected by the

number of antihypertensive medications at 1 year post-transplant, proteinuria (>1 g/24 h) at 1 year post-transplant, hemoglobin (g/dl) at 1 year post-transplant. Acute Rejection was defined as any rejection treatment. Acute rejection was suspected when the serum creatinine level increased to 20% above the baseline level and was biopsy proven in most cases.

Univariable analysis was performed on each of these variables using the Cox proportional hazards regression model. Variables with a p-value <0.10 in the univariable analysis were then entered into the multivariable analysis. Cox regression was applied with forward stepwise selection using likelihood-ratio tests. Variables were retained in the model at $p < 0.05$. Acute rejection was considered as a time dependent covariate.

The hazard ratios (HR) for graft failure and corresponding 95% confidence intervals were estimated. Graft failure was defined as return to dialysis, re-transplantation or death with a functioning graft. Graft survival time was defined as the time between the date of transplantation and graft failure or the end of the study period.

Two models were constructed: one starting at the time of transplantation thus including all transplants (n=151) and one starting after the end of the first year post-transplant including transplants that functioned beyond the first year (n=140). Hypertension at 1 year, creatinine clearance at 1 year, proteinuria at 1 year (>1 g/24 h), hemoglobin at 1 year were included in the second model as additional potential predictors for graft survival after 1 year.

Patient and graft survivals were calculated with the Kaplan–Meier method.

Statistical analyses were performed using Statistica 8.1 (StatSoft Inc., Tulsa, OK., USA) and SPSS 18.0 (SPSS Inc., Chicago, IL., USA). Statistical significance was defined as $p < 0.05$.

3. Results

3.1 Patient and graft survival

The actuarial patient survival was 97% at 1 year, 96% at 3 years, 94% at 5 years and 92% at 10 years (Figure 1). Nine patients died, three of them with a functioning graft. The cause of death was bacterial infection in four children, *Pneumocystis carinii* infection in one, malignant lymphoproliferative disorder in one, and a cardiovascular complication in three (two of whom died following cerebral haemorrhage and one following a myocardial infarction).

The overall actuarial graft survival was 94% at 1 year, 86% at 3 years, 80% at 5 years and 64% at 10 years (Figure 1). Mean follow-up time was 9.3 ± 6.5 years.

The actuarial graft survival at 1, 3, 5, 10 years was 94%, 90%, 83% and 68% respectively for recipients of living-related donor and 94%, 83%, 79% and 63% respectively for recipients of deceased donor (Log-Rank Test $p = 0.95$). In children younger than 5 years the graft survival was 92% at 1 and 3 years, and 83% at 5 and 10 years; in this group the prevalence of LRD was rather high (11/24; 46%).

In total 68 grafts were lost during the study period, 9 of them during the first year post-transplant. The causes of graft loss are given in Table 1; chronic rejection being the leading cause. Non compliance was documented in 19% of the failure due to chronic rejection (9 cases). Recurrence of the initial disease was the second most frequent cause of graft failure.

The main characteristics of the study population are detailed in Table 2.

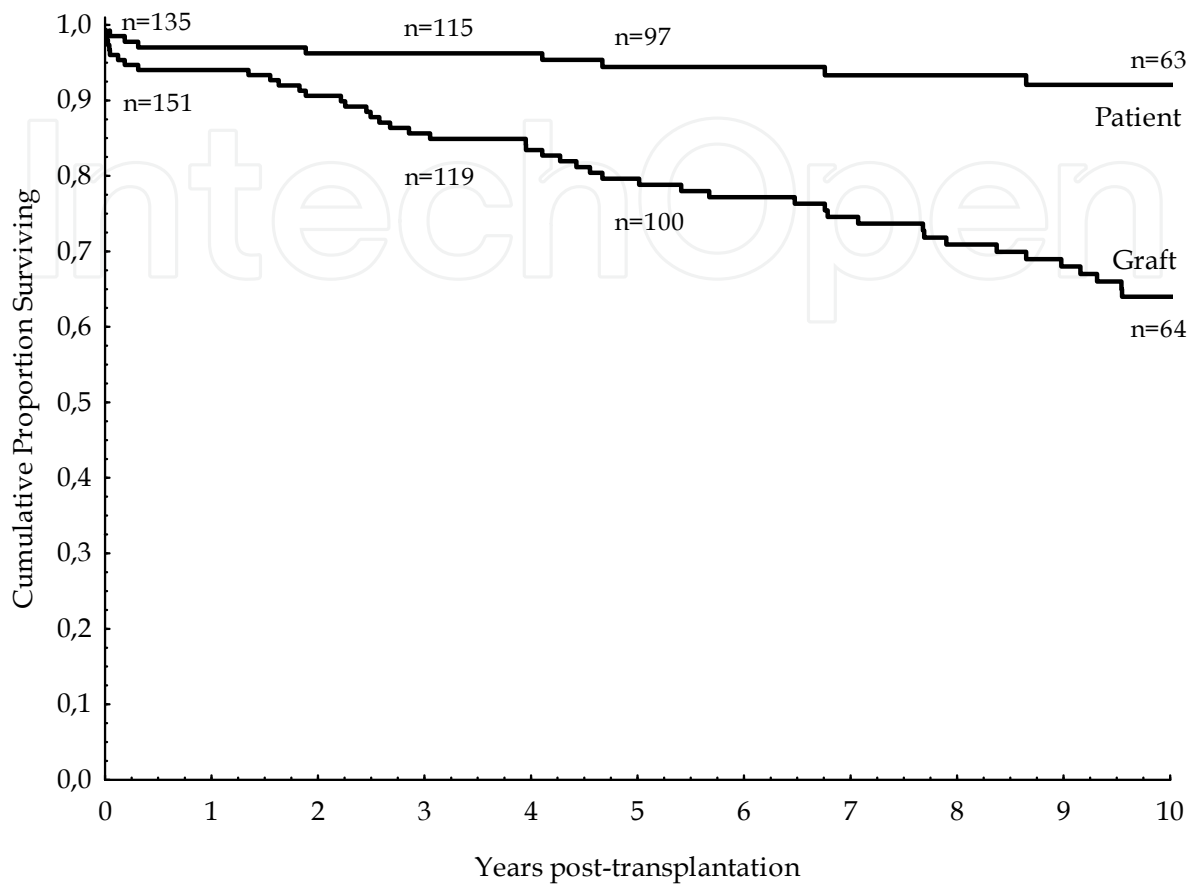


Fig. 1. Kaplan Meier plot of patient and graft survivals (n indicates the number of subjects at risk at 0, 3, 5 and 10 years).

	n	%
Chronic rejection	47	69.1
Recurrence of primary disease	8	11.8
Death with functioning graft	3	4.4
Malignancy	2	2.9
Infection	2	2.9
Technical failure	2	2.9
Primary non-function	2	2.9
Polyoma nephropathy	1	1.5
Thrombosis renal artery	1	1.5

Table 1. Causes of graft failure

	N*	Mean \pm SD or n	Range or %
Recipient characteristics			
Age (year)		10.7 \pm 4.7	1.3-21.9
0-4		24	15.9%
5-9		38	25.2%
\geq 10		56	59.0%
Gender M/F		91/60	59.6/40.4%
Weight (kg)		20.5 \pm 14.5	8.4-76.4
Primary Tx/ReTx		132/19	87.4/12.6%
Primary kidney disease			
Congenital uro-nephropathy		72	47.7%
Hereditary nephropathy		40	26.5%
Acquired nephropathy		39	25.8%
Renal replacement therapy at Tx			
Hemodialysis		125	76.1%
Peritoneal dialysis		22	14.6%
Transplantation		1	0.7%
None		13	8.6%
Years of pre-transplant dialysis		1.93 \pm 1.73	0-8.18
Years on waiting list	106	1.26 \pm 1.12	0.04-6.25
>5 pre-transplant transfusions		62	41.1%
Current PRA>50%/Peak PRA>50%		16/33	10.6/21.9%
CMV serology: neg/pos/unknown		114/36/1	75.5/23.8/0.7%
On Antihypertensiva at time of Tx	149	81	54.4%
Donor characteristics			
Age (year)		23.8 \pm 14.8	0.5-54.5
0-4		18	11.9%
5-19		48	31.8%
20-39		54	35.8%
40-55		31	20.5%
Gender M/F	150	86/64	57.3/43.7%
Weight (kg)	127	55.5 \pm 23.5	7-101
Donor type			
DD/LRD		118/33	78.1/21.9%
Cause of donor death			
Trauma/CVA/others	117	71/24/22	60.7/20.5/18.8%
Donor/Recipient relationships			
Donor/Recipient Weight ratio	127	2.35 \pm 1.78	0.29-8.47
Donor/Recipient BSA ratio	125	1.70 \pm 0.88	0.21-4.51
Donor/Recipient BMI ratio	125	1.28 \pm 0.28	0.53-2.15
CMV serology			
D-/R-		68	
D-/R+		23	
D+/R-		33	
D+/R+		10	

Table 2. Characteristics of the study population

	N*	Mean ± SD or n	Range or %
HLA Mismatch	150		
HLA-A		0.83 ± 0.60	
0/1/2		42/91/17	28.0/60.7/11.3%
HLA-B		1.03 ± 0.51	
0/1/2		17/111/22	11.3/74.0/14.7%
HLA-DR		0.77 ± 0.55	
0/1/2		44/97/9	29.3/64.7/6.0%
HLA-ABDR		2.62 ± 1.06	
0		7	4.7%
1		9	6.0%
2		46	30.7%
3		67	44.7%
4		15	10.0%
5		5	3.3%
6		1	0.7%
Perioperative characteristics			
Organ preservation solution	149		
Eurocollins/UW/HTK		48/64/37	32.2/43.0/24.8%
Cold ischemia time (hours) for DD	117	20.34 ± 7.70	8.40-50.47
>30 hr		10	9.3%
Warm ischemia time (min)	148	38.1 ± 11.8	15.0-95.0
>40 min		53	35.8%
Immunosuppression (IS)			
Induction	150		
Polyclonal (ALS/ ATG)		92 (43/49)	61.3%
Monoclonal (anti-IL2r/OKT3)		52 (51/1)	34.7%
None		6	4%
Maintenance IS at discharge			
Cyclosporine A/Tacrolimus/No		104/31/16	68.9/20.5/10.6%
Azathioprine/MMF/No		104/45/2	68.9/29.8/1.3%
Post-transplant characteristics			
Tx hospitalization (days)		19.3 ± 12.9	7-113
Delayed graft function(DGF)		25	16.6%
Acute rejection			
Yes vs. No		69/82	45.7/54.3 %
Within the first year post Tx		58	38.4 %
Beyond the first year post Tx		23	15.7 %
Time first rejection episode (days)		46 (10-174)§	1-5474
Hemoglobin level at 1 yr (g/dl)	139	11.5 ± 1.4	6.4-14.0
Proteinuria (>1 g/24 h) at 1 yr	140	10	7.1%
Creatinine Clearance at 1 yr (ml/min/1.73 m ²)	140	72.1 ± 22.0	14.7-156.5

*N=number of transplants for whom data are available; if not specified n=151. §data given as median (interquartile range). CVA: cardiovascular accident; DD: deceased donor; DGF: delayed graft function ; LRD: Living related donor.

Table 2. Cont.

3.2 Univariable analysis of factors influencing graft outcome

Table 3 summarizes the predictors of graft outcome in univariable analysis ($p < 0.10$).

Duration of pre-transplant dialysis, multiple blood transfusions pre-transplant (>5), warm ischemia time (superior to 40 min), cold ischemia time, delayed graft function (DGF) and acute rejection were found to significantly affect outcome adversely. Transplants that did not benefit from calcineurin inhibitors had a fourfold increased risk of graft failure ($p < 0.0001$). In addition, over the time of our transplant program, there was a significant lower risk for graft failure with each subsequent year ($p = 0.008$). As far as HLA matching is concerned, two mismatches on HLA-A tended to be detrimental ($p = 0.064$).

Kidney function (creatinine clearance) at 1 year, proteinuria (>1 g/24 h) at 1 year and the level of hemoglobin at 1 year were found to be significant predictors of graft outcome for the transplants that functioned beyond the first year. Risk of graft loss increased with the presence of proteinuria and decreased with an increase in hemoglobin level and an increase in creatinine clearance.

Variables that were not retained as predictors ($p > 0.10$) of graft outcome included among others: primary kidney disease, recipient and donor gender and age, recipient and donor anthropometric parameters (weight, height, BSA, BMI), age ratio and anthropometric parameters ratio between the donor and the recipient, peak and current PRA levels, recipient and donor blood group, donor type, organ preservation solution type, CMV matching status, repeat transplant, and hypertension at transplantation and at 1 year post-transplant.

	df	HR	95% CI	p Value
Time on dialysis (years)	1	1.17	1.02-1.34	0.030
>5 Transfusions pre-Tx	1	1.82	1.12-2.97	0.016
HLA-A mismatch (2 vs. 0-1)	1	1.96	0.96-3.98	0.064
Cold ischemia time (h) (DD)				
continue variable	1	1.03	1.002-1.065	0.034
>30 h vs. \leq 30 h	1	2.63	1.31-5.26	0.006
Warm ischemia time (min)				
as continue variable	1	1.016	0.996-1.037	0.11
>40 min vs. \leq 40 min	1	1.66	1.02-2.71	0.042
Year of transplantation	1	0.95	0.91-0.99	0.008
Absence of calcineurin inhibitors	1	4.31	2.44-7.63	<0.0001
Dialysis in the first week post-Tx (DGF)	2			0.001
Risk graft failure within first 3 months	1	16.89	3.41-83.80	0.001
Risk graft failure after first 3 months	1	1.05	0.54-2.04	0.88
Acute rejection	1	2.61	1.55-4.40	0.0003
Proteinuria (>1 g/24 h) at 1 year	1	4.13	2.01-8.48	0.0001
Hemoglobin at 1 year (g/dl)	1	0.67	0.54-0.82	0.0002
Creatinine clearance at 1 year (ml/min/1.73 m ²)	1	0.97	0.95-0.98	<0.0001

df: degrees of freedom; HR: hazard ratio; CI: confidence interval

Table 3. Predictors of graft outcome in univariable analysis ($p < 0.10$)

3.3 Multivariable analysis of factors influencing graft outcome

3.3.1 Considering all transplants - graft survival from the time of transplantation

Multivariable Cox regression analysis showed that the significant factors contributing to graft failure were: absence of calcineurin inhibitors, two mismatches on HLA-A, occurrence of acute rejection and occurrence of DGF. The need for dialysis in the first week post-transplant was linked with a very high risk for graft failure within the first three months post-transplant; beyond this period it had no significant impact on graft outcome. The hazard ratios for graft failure and their confidence intervals are given in Table 4. The other factors that were found significant in univariable analysis (multiple pre-transplant transfusions, cold and warm ischemia times, year of transplantation, duration of pre-transplant dialysis) did not significantly affect outcome when subjected to a multivariable analysis.

	df	HR	95% CI	p Value
Absence of calcineurin inhibitors	1	3.98	2.15-7.36	<0.0001
2 HLA-A mismatches	1	2.77	1.31-5.84	0.008
DGF	2			0.002
Risk graft failure within first 3 months	1	3.21	2.62-66.50	0.002
Risk graft failure after first 3 months	1	1.31	0.66- 2.61	0.44
Acute rejection	1	2.10	1.25-3.52	0.005

Likelihood ratio Chi-square 46.208, df 5, $p < 0.0001$ (n=150)

Table 4. Multivariable Cox regression analysis of graft survival from the time of transplantation: analysis of all grafts.

3.3.2 Considering transplants with ≥ 1 year survival - graft survival after 1 year

This analysis was done on the subset of transplants that were still functioning at 1 year. Nine grafts were lost in the first year. Multivariable Cox regression analysis showed that significant risk factors contributing to graft failure after 1 year were: absence of calcineurin inhibitors, two HLA-A mismatches, kidney function (creatinine clearance) at 1 year, proteinuria at 1 year (superior to 1 g/24 h) and hemoglobin level at 1 year. The hazard ratios for graft failure and their confidence intervals are given in Table 5.

	df	HR	95% CI	p Value
Absence of calcineurin inhibitors	1	6.73	3.19-14.21	<0.0001
2 HLA-A mismatches	1	3.25	1.45-7.27	0.004
Creatinine clearance at 1 yr (ml/min/1.73 m ²)	1	0.97	0.96-0.99	0.002
Proteinuria (>1 g/24 h) at 1 yr	1	3.13	1.44-6.81	0.004
Hemoglobin level at 1 yr (g/dl)	1	0.76	0.61-0.94	0.011

Likelihood ratio Chi-square 52.383, df 5, $p < 0.0001$ (n=139)

Table 5. Multivariable Cox regression analysis of graft survival after 1 year post-transplantation: analysis of grafts that survived beyond the first year.

4. Discussion

This single center study investigated factors that affect renal transplant outcome in children. Numerous factors concerning recipient characteristics, donor characteristics, perioperative characteristics and post-transplant events were included in the analysis.

Univariable analysis identified a number of factors associated with outcome. Multiple blood transfusions pre-transplant, duration of dialysis pre-transplant, prolonged cold and warm ischemia times, absence of calcineurin inhibitors, occurrence of acute rejection, occurrence of delayed graft function, absence of HLA-A matching, presence of marked proteinuria at 1 year post-transplant were associated with poor outcome. Risk of graft failure decreased with higher creatinine clearance at 1 year, higher level of hemoglobin at 1 year and later year of entry in the transplant program. Certainly in term of single variable determinants, these specific factors appear familiar to professionals in renal transplantation.

The following factors remained of significance after multivariable analysis: use of calcineurin inhibitors, absence of HLA-A matching, delayed graft function defined as the need for dialysis in the first week post-transplant, occurrence of acute rejection, proteinuria superior to 1 g/24 h at 1 year, hemoglobin level at 1 year and kidney function at 1 year.

Transplants that did not benefit from **calcineurin inhibitors** had a fourfold increased risk of graft failure. Most of these transplants (14 of 16) were performed in the period 1980-1984 before CsA was introduced. As the period 1980-1984 represents also the first years of our pediatric transplant program, the lack of center experience, the so called learning curve, may be partly a confounding factor. We found CsA to impact significantly and independently both on early and long term graft survival. This is similar to the findings of two single center pediatric studies (Chavers et al., 1994; Offner et al., 1999) reporting a beneficial effect of CsA up to 5 and 8 years post-transplant. The introduction of CsA in the mid-1980s for the prevention of acute rejection has been a major breakthrough in the transplantation field. However it has been reported to impact mostly on early graft survival by lowering acute rejection rates; its effect on long term outcome being much more controversial (Chapman & Nankivell, 2006; Pascual et al., 2002; Schurman & McEnery, 1997). One of the major concerns for long term outcome is the calcineurin inhibitor-induced chronic nephrotoxicity leading to progressive nephron loss and declining renal transplant function (Chapman & Nankivell, 2006; Nankivell et al., 2004). Hence with the broadening of the immunosuppressive drugs arsenal, calcineurin inhibitor minimization, calcineurin inhibitor withdrawal or avoidance strategies have been developed. Calcineurin inhibitor withdrawal and avoidance protocols have been associated with an amelioration of the renal function, however at the cost of a higher rejection rates (Guerra et al., 2007; Höcker & Tönshoff, 2011). The long-term safety and efficacy of calcineurin inhibitor withdrawal and avoidance strategies need to be further validated in controlled clinical trials. At present the safest therapeutic strategy for pediatric renal allograft with chronic calcineurin inhibitor induced nephrotoxicity appears to be a mycophenolate based regimen with low dose calcineurin inhibitor and corticosteroids (Höcker & Tönshoff, 2011).

Two **HLA-A** mismatches was in our population a strong predictive risk factor for graft failure. Matching for HLA-DR and HLA-B has generally received priority over matching for HLA-A in children as well as in adults. Multivariable analysis of the data from the large NAPRTCS registry showed that the absence of HLA-B match and the absence of HLA-DR match were significant risk factors for graft failure (NAPRTCS, 2010). Roberts and colleagues reported that matching at the HLA-DR locus has significant effect on the survival

of renal grafts from DD whereas matching at the HLA-A and B loci has only small effect (Roberts et al., 2004). However, Zantvoort and colleagues from Eurotransplant (Zantvoort et al., 1996) found an independent HLA-A matching effect on long term survival of DD kidney grafts with an increasing effect over time (up to 6 years post-transplant). This was in contrast to the strong, short-lived, effects of HLA-DR and -B matching, which could only be detected up to 6 months and 2 years after transplantation, respectively. A clear additive beneficial effect of HLA-A matching was shown in the group without B and DR mismatches. They concluded that prospective matching for the HLA-A antigens remains important for renal allograft survival and our data are in agreement with this. Data from the Collaborative Transplant Study indicated that class II HLA-DR locus has a stronger impact than the class I HLA-A and HLA-B loci during the first post-transplant year but that during subsequent years the three loci have an equivalent and additive influence on graft survival: to obtain optimal long term survival all three loci must be considered in the donor-recipient matching procedure (Opelz et al., 1999). This has been our policy through the years of our program as reflected by the very low percentage of transplants with more than 3 HLA-A,-B,-DR mismatches (14%). Obtaining the best possible HLA match for children is also an important part of the Eurotransplant allocation process. In contrast, in the United States, matching for HLA-A and -B has been abandoned and only HLA-DR is considered during the kidney allocation process. Based on an retrospective analysis of the UNOS registry data from 1585 pediatric recipients of DD kidney between 1996-2004 showing no advantage for HLA-DR matching, it has been recommended that, in the modern era of immunosuppression, the HLA match should be entirely disregarded when allocating donor kidneys to pediatric recipients (Gritsch et al., 2008). This will allow shortening the waiting time on dialysis for children. This view has been challenged in a recent report by Opelz and Döhler who examined the outcomes of 9209 pediatric recipients of DD kidneys from the CTS registry (Opelz & Döhler, 2010). Comparing two decades (1988-1997 and 1998-2007), they showed that, although overall graft survival improved over time, HLA matching remained highly significant and similarly strong despite the introduction of newer and more potent immunosuppression. A hierarchical relationship was observed for the effect of increasing number of mismatches on graft survival in both periods. Interestingly, they found a strong association between two HLA-DR mismatches and non Hodgkin lymphoma, and recommended therefore to avoid transplants with 2 HLA-DR mismatches.

In our view, a well matched first kidney is especially important in children as they have a high likelihood of needing more than one transplant during their lifetime. A poor matched kidney is more likely to result in HLA allosensitization, resulting therefore in long waiting time for a second transplant when the first graft fails and compromising the chance of a successful retransplantation (Meier-Kriesche et al., 2009).

The need for dialysis in the first week after transplantation carried in our transplant population a very high risk of graft failure within the first months post-transplant but did not impact significantly on the long term outcome. Similar findings emerged out of the analysis of the NAPRTCS registry (Tejani et al., 1999). DGF was found to be a significant independent predictor of graft failure. However, when patients whose grafts had failed during the first year were censored, no differences in graft survival were noted between patients with and without DGF for either LRD or DD recipients. Similarly DGF was not an independent predictor of long term graft survival in a large single center analysis of pediatric renal recipients (Vats et al., 2002). Good long term graft survival has also been

obtained with non-heart-beating donors despite a higher incidence of DGF (Koffman & Gambaro, 2003; Sanchez-Fructuoso et al., 2004; Summers et al., 2010). Others have reported a negative influence of DGF on long term graft outcome (Gjertson, 2000; Moreira et al., 2011). It remains however difficult to determine whether this negative impact of DGF is independent of two associated known risk factors for long-term outcome: acute rejection (AR) and degree of kidney function (Geddes et al., 2002; Troppmann et al., 1996). The combination of DGF and AR seems to be the most detrimental for graft survival (Matas et al., 2000; McLaren et al., 1999).

The **occurrence of acute rejection** was an independent predictor of graft survival when all transplants were included in the analysis. When only the grafts that functioned beyond the first year were considered, acute rejection disappeared from the significant factors in the multivariable analysis. The lack of significance can be due to the reduced power as acute rejection was introduced as a time dependent covariate and most of the events (acute rejection) occurred within the first year.

Acute rejection is an important predictor of chronic rejection which is the most common cause of graft loss. Single and multicenter studies in adult and children have shown an association between acute rejection and subsequent development of chronic rejection (Dart et al., 2010; Matas, 2000; Tejani & Sullivan, 2000). It is therefore expected that a reduction in the incidence of acute rejection - in our program the incidence of acute rejection in the period 2000-2010 has dropped to 7% - should result in the reduction of chronic rejection and thus in better long term graft survival. This is supported by a NAPRTCS study (Tejani et al., 2002). Moreover some studies clearly indicate that a rejection free milieu can truly provide improved long term survival. Vats et al. in one of the largest single center study to date on long term graft outcome in pediatric renal transplant patients found freedom from acute rejection in the first year post-transplant to be the strongest independent predictor of improved graft survival (Vats et al., 2002). In an analysis of the UNOS data on 93934 adult patients, Hariharan et al. reported an increase in graft half-life from 11.9 years for patients with an episode of clinical acute rejection during the first year post-transplant to 27.1 years for those who did not have such an episode (Hariharan et al., 2000). Meier-Kriesche group, on the contrary, reported that the significant reduction in the acute rejection rates observed in the modern era has resulted in a marked improvement of the short term graft survival but in negligible progress in longer term survival as the attrition rate beyond the first year show little improvements (Lamb et al., 2011; Meier-Kriesche et al., 2004).

We found **kidney function at 1 year** to be an independent predictor of long term graft survival indicating that preservation of renal function during the first year is important and that events occurring within the first year impacting on this function are of critical importance for long term survival. Several authors have reported that renal function after transplantation has a strong impact on long term graft survival. Hariharan et al. analysing factors influencing graft survival for 105742 adult renal transplants between 1988 and 1998 reported one year creatinine and delta creatinine 6 months-1 year values to be the best predictors of long term survival and that the recent improvement in graft half-lives are related to conservation of renal function within the first year post-transplant (Hariharan et al., 2002). As it is the case in our study, when renal function within the first year and clinical acute rejection were included in their model for long term graft failure it was the creatinine at 1 year that was significant and not clinical acute rejection. Thus in the setting of acute rejection it is the preservation of renal function that is more important for graft survival. Data from a multicenter study pointed the 1 year estimated glomerular filtration rate to be

the most relevant predictor of long term graft function. The impact of DGF and acute rejection on the long term graft function appeared to be fully mediated by their influence on the 1 year GFR (Salvadori et al., 2006). Similar to us, three studies found allograft function at 1 year to be a significant and independent predictor of graft outcome in children (Filler et al., 2002; Mitsnefes et al., 2003; Muscheites et al., 2009). Kidney function at one year might be thus a useful surrogate end point for renal transplant clinical trials in children.

Anemia is a significant complication of renal failure being associated with numerous adverse outcomes, including compromised renal and cardiac function, cardiovascular disease, decreased exercise tolerance, cognitive impairment, poorer quality of life, increased risk for hospitalization and mortality (Koshy & Geary, 2008; Warady & Ho, 2003). Anemia is expected to resolve after transplantation. More and more data indicate on the contrary that anemia is a common phenomenon in pediatric kidney recipients with reported prevalence rates ranging from 25% to 80% depending on the definition of anemia used and the time post-transplantation (Al-Khoury et al., 2006; Mitsnefes et al., 2005; Yorgin et al., 2002). The prevalence of anemia at 1 year (defined as hemoglobin level <11 g/dl (Al-Khoury et al., 2006; Mitsnefes et al., 2005)) was 30% among our transplanted children. The pathogenesis of post-transplant anemia is multifactorial and include iron deficiency, bone marrow suppression effects of immunosuppressive medications and other therapeutic agents, chronic inflammatory conditions caused by infections, frequent blood draws, and deteriorating renal function (Al-Uzri et al., 2003). In our multivariable analysis, hemoglobin level at 1 year post-transplant was a significant predictor of long term graft outcome, a higher level of hemoglobin being associated with a lower risk of graft failure. When hemoglobin was dichotomized at 11 g/dl, the HR for anemia in the multivariable model was 1.93 (p=0.024; 95% CI 1.09-3.42) while the HRs of the other covariates (table 5) remained in the same order of magnitude (data not shown). It was significant in the presence of “kidney function” indicating that anemia is just not merely a surrogate marker of a declining function of the allograft. Anemia is an independent risk factor for progression of renal failure in pre-dialysis adults (Kovesdy et al., 2006) and treating anemia slows down the decline of kidney function in these patients (Gouva et al., 2004). Our findings are in line with several studies in the adult population showing post-transplant anemia to be associated with increased risk for subsequent graft loss (Chhabra et al., 2008; Imoagene-Oyediji et al., 2006; Kamar & Rostaing, 2008; Molnar et al., 2007). In these studies, anemia was also associated with impaired patient survival and with a higher proportion of cardiovascular deaths. Whether this is also the case in children remains to be determined but a cross sectional study of pediatric kidney recipients pointing anemia to be predictive of left ventricular hypertrophy - an independent predictor of cardiovascular morbidity and mortality in adults - raises concern. Post-transplant anemia has also been reported to impact on the quality of life; anemic children presenting more physical discomfort (Riano-Galan et al., 2009). For all these reasons including our findings that anemia predicts poorer graft survival, anemia deserves to be recognized early after transplantation, properly investigated and corrected.

The presence of marked **proteinuria** at 1 year was in our study population a strong and independent predictor of impaired graft outcome. This is in good agreement with several studies in adults showing increasing levels of proteinuria at 1 year post-transplant to be associated with increasing risk of graft failure (Amer et al., 2007; Fernandez-Fresnedo et al., 2004; Roodnat et al., 2001). Persistent proteinuria is also associated in these studies with increased mortality. In our population, persistent proteinuria was attributed to biopsy

proven chronic allograft nephropathy, recurrence of primary kidney disease (FSGS and dense deposit disease) and de novo glomerulonephritis; this is in line with reports in adult kidney recipients (Barama, 2008). The underlying cause of proteinuria and not the proteinuria per se could thus be the factor contributing to transplant dysfunction and failure. However it is now recognized that proteinuria is not only a sensitive marker of renal disease but is directly damaging to the kidney by various mechanisms including direct mesangial toxicity, tubular overload, induction of a proinflammatory state and release of substances associated with the development of fibrogenesis and glomerulosclerosis (Baines & Brunskill, 2008). Recent reports indicate that even early (1-3 months post-transplant) very low (<0.5 g/24 h) and low grade (<1 g/24 h) proteinuria - often referred as 'subclinical' or 'negligible' - is a potent predictor of graft loss in adult kidney recipients and that short term reduction in proteinuria is associated with improved long term graft survival (Halimi et al., 2005; Sancho Calabuig et al., 2009).

While ACE inhibitors have been shown to be effective and safe in proteinuric adult kidney recipients (Barama, 2008; Hiremath et al., 2007), there is a paucity of data in the pediatric transplant population. In one retrospective study, children treated with ACEI had slightly lower proteinuria than those who did not receive such treatment (Arbeiter et al., 2004). A recent uncontrolled small prospective study showed a reduction of proteinuria in nearly all children treated with ACEI (Seeman et al., 2010).

Several factors such as donor source, donor age, recipient age and hypertension were in contrast with the literature not found significant in our study.

Large registry and single centers studies show better graft survival for recipients of LRD as compared to recipient of DD kidney (Gjertson & Cecka, 2001; Magee et al., 2008; NAPRTCS, 2010). Data from the NAPRTCS indicate that the 1 year graft survival obtained with deceased donors has reached that of the living donors. In our population, graft survival is also equivalent with both donor sources at 1 year and thereafter superior for LRD. However, this difference is not statistically significant, possibly because of the small number of LRD recipients. Another explanation is that we achieved good survival rates with the DD recipients, due to our strict policy of donor selection, good HLA matching and short ischemia times.

There are a number of reports indicating poorer results with kidney from **young donors**, essentially due to an increase incidence of vascular thrombosis, primary non function and other technical causes (Cransberg et al., 2000; Postlethwaite et al., 2002; Seikaly et al., 2001). Earlier NAPRTCS reports of poor graft survival with young donors have led to a constant decrease of the use of these donors in pediatric recipients: donor younger than 10 years represented 38% of the DD for pediatric recipients in the 1988 cohort, 13% in the 2000 cohort, 8% in the 2005 cohort and less than 5% in the 2009 cohort (NAPRTCS, 2010). We have obtained good results with young deceased donors with short and long term survival comparable to older donor (Van Damme-Lombaerts et al., 2001). Data indicate also that pediatric donor organs perform better than adult donor organs in pediatric patients (Nashan, 2004; Pape et al., 2004) and it seems thus justify that pediatric donors should preferentially be allocated to pediatric recipients. This might be stimulated by a very recent analysis of the NAPRTCS registry showing comparable 3-year graft survival and comparable kidney function in recipient of young donors (Moudgil et al., 2011).

Young recipient age (<5 yr) has been traditionally associated with poorer short term graft survival due to a high incidence of vascular thrombosis, technical complications and acute rejection (Cransberg et al., 2000; Gagnadoux et al., 1993; Kari et al., 1999; Postlethwaite et al.,

2002). However, there are a few single center reports, including ours, indicating that excellent renal transplantation results can be obtained in this high risk group of patients with careful and meticulous surgical techniques, vigilant management of fluids administration, use of low molecular weight heparin in the early postoperative period and close monitoring of immunosuppression with early diagnosis and treatment of rejection (Gagnadoux et al., 1993; Ojogho et al., 2002; Vats et al., 2002). Furthermore, past the first post-transplant year, graft survival in these youngest children has been reported to be excellent: as good or even superior to older children and adults (Gjertson & Cecka, 2001; Ojogho et al., 2002; Vats et al., 2002).

In our study **hypertension** was not a significant predictor of graft failure. This may be due to the fact that we relied on the use of antihypertensive medications and their numbers as surrogates for defining hypertension and its severity. Studies using actual blood pressure measurements found early post-transplant hypertension to be a significant and independent predictor of early allograft function and long term graft outcome in pediatric renal transplant recipients (Mitsnefes et al., 2003; Mitsnefes et al., 2001).

5. Conclusion

Despite its limitation due to the small number of patients, our study shows that several factors influence the outcome of renal allograft in our pediatric population. The introduction of CsA had a very significant impact in improving graft survival. A good HLA match remains important and matching for HLA-A locus in children should not be neglected. Early recognition, investigation and treatment of post-transplant anemia and proteinuria may play an important role in ultimately improving outcomes.

Prevention and adequate management of DGF, prevention and effective treatment of acute rejection episodes, therapeutic monitoring of calcineurin inhibitors to limit their nephrotoxicity, prevention of other injuries to the allograft by factors such as severe infection, hypertension, obstruction should contribute to the preservation of the renal function during the first year and lead to improved long term outcome.

6. Acknowledgment

We are very grateful to Dr. Steffen Fieuws from the Department of Biostatistics for his help with statistical analysis.

7. References

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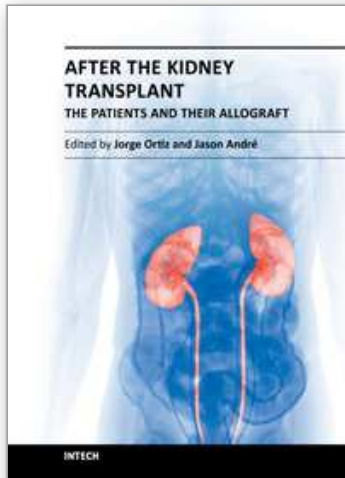
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After the Kidney Transplant - The Patients and Their Allograft

Edited by Prof. Jorge Ortiz

ISBN 978-953-307-807-6

Hard cover, 386 pages

Publisher InTech

Published online 17, August, 2011

Published in print edition August, 2011

There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipient's tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Jean Herman and Rita Van Damme-Lombaerts (2011). Factors Related to Graft Outcome in Pediatric Renal Transplantation: a Single Center Study, *After the Kidney Transplant - The Patients and Their Allograft*, Prof. Jorge Ortiz (Ed.), ISBN: 978-953-307-807-6, InTech, Available from: <http://www.intechopen.com/books/after-the-kidney-transplant-the-patients-and-their-allograft/factors-related-to-graft-outcome-in-pediatric-renal-transplantation-a-single-center-study>

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