American Journal of Transplantation 2008; 8: 2056–2061
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02320.x

Should Pediatric Patients Wait for HLA-DR-Matched Renal Transplants?

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Graft survival rates from deceased donors aged 35 years or less among all primary pediatric kidney transplant recipients in the United States between 1996 and 2004 were retrospectively examined to determine the effect of HLA-DR mismatches on graft survival. Zero HLA-DR-mismatched kidneys had statistically comparable 5-year graft survival (71%), to 1-DR-mismatched kidneys (69%) and 2-DR-mismatched kidneys (71%). When compared to donors less than 35 years of age, the relative rate of allograft failure was 1.32 ($p = 0.0326$) for donor age greater than or equal to age 35. There was no statistical increase in the odds of developing a panel-reactive antibody **(PRA) greater than 30% at the time of second waitlisting, based upon the degree of HLA-A, -B or -DR mismatch of the first transplant, nor was there a 'dose effect' when more HLA antigens were mismatched between the donor and recipient. Therefore, pediatric transplant programs should utilize the recently implemented Organ Procurement and Transplantation Network's (OPTN) allocation policy, which prioritizes pediatric recipients to receive kidneys from deceased donors less than 35 years of age, and should not turn down such kidney offers to wait for a better HLA-DR-matched kidney.**

Key words: Deceased donor, histocompatibility matching, kidney, organ allocation, pediatric, transplant

Received 26 February 2008, revised 28 April 2008 and accepted for publication 16 May 2008

Introduction

Renal transplantation is the optimal treatment for nearly every child with end-stage renal disease. Between 1996 and 2005, children accounted for only 1.5% or less of renal transplant candidates placed yearly on the Organ Procurement and Transplantation Network's (OPTN) waiting list (1). The OPTN's kidney allocation policies have evolved over many years. The initial goal was to improve renal allograft survival by promoting histocompatibility matching between the donor and recipient. However, growing demand for deceased donor organs caused increases in waiting time that adversely effected growth, physical and psychological development and education in children. In November 1998, the OPTN kidney allocation algorithm was modified to provide children with new allocation priority (4 points for those under age 11, and 3 for those aged 11–17, and then local allocation priority to children aged 0–5, 6–10 and 11–17 years who were not transplanted within 6, 12 or 18 months, respectively). Despite these policies intended to preferentially distribute deceased donor kidneys to children, the median waiting time to transplantation for pediatric candidates aged 11–17 years increased between 1995 and 2004 from 276 to 450 days (2). This observation stimulated a critical review of national deceased donor organ allocation policies by the OPTN's Pediatric, Minority Affairs, and Kidney and Pancreas Transplant Committees, and led to the implementation of a new OPTN policy in November 2005, Policy 3.5.11.5.1. This new policy requires that mismatched kidneys from deceased donors less than 35 years of age, and allocated within the recovering donor service area for kidney-alone transplantation, be offered first to kidney transplant candidates who are less than 18 years of age. This local allocation priority occurs irrespective of the number of points assigned to the pediatric candidate relative to other waitlisted candidates who are 18 years of age or older.

The current policy is complex and attempts to balance both opportunity for transplantation (equity) and

to optimize renal allograft survival (utility) (3). Deceased donor kidneys with a blood type compatible zero HLA antigen-mismatch are still allocated first to pediatric recipients by local, and then by regional, and finally national priority. Donor and recipient matching at the HLA-A and HLA-B locus was excluded nationally for both adults and children from the kidney allocation algorithm, since the survival benefit from such similarity was found to be small and to contribute significantly to inequalities in waiting time by race/ethnicity (4).

The intention of this policy is for pediatric candidates to undergo kidney transplantation soon after being placed on the waiting list, avoiding those complications of end-stage renal disease that are unique to the pediatric population. These include, but are not limited to, impaired growth and development and disruption in education (2).

However, critics of this new policy have reasoned that children who undergo kidney transplantation soon after being listed will be less likely to receive kidneys that are well-matched for HLA. In adults, HLA-DR matching provides a statistically significant but small clinical benefit in allograft survival (4). Opponents argue that as a consequence of this change in allocation policy, pediatric patients will receive more grafts from poorly HLA-DR-matched donors, worsening the risks of rejection and allograft failure. Additionally, pediatric patients who experience graft loss because of rejection would subsequently be at risk of developing anti-HLA antibodies, potentially reducing their access to repeat transplantation.

There are currently no comprehensive studies to address these concerns in children. Yet, such a study is necessary to more completely evaluate the benefits and potential downsides to the expanded access policy in pediatric transplantation. In an attempt to study these questions, we performed the following analyses of data from the OPTN and Scientific Registry of Transplant Recipients (SRTR) databases to examine the allograft survival and sensitization rates of HLA-DR matching in children undergoing deceased donor kidney transplantation.

Methods

As reported to the OPTN, between January 1, 1996, and December 31, 2004, 2292 pediatric patients aged 0 to 17 years received a first deceased donor kidney-only transplant. Among these, 1585 (69%) received kidneys from deceased donors who were 35 years of age or younger. Adult recipients aged 18–45 (n = 9535) who received a first deceased donor kidney transplant from a donor aged 35 or younger during the same period were examined for comparison. Zero HLA antigen-mismatched kidneys and multiorgan and previous organ transplant recipients were excluded from analysis (except in Table 1, where zero mismatched transplants are listed for comparison of their frequencies). Log-rank testing was used to compare the Kaplan–Meier graft survival curves of HLA-DR-antigen-matched and HLA-DR-antigen-mismatched kidneys in this pediatric population. Waiting time was defined as the number of days between the date the patient was added to the waiting list and the transplant date for the analyses shown in Figure 5.

Table 1: A comparison of primary HLA-A, -B, -DR and HLA-DR-matched kidney transplants to pediatric or young adult recipients of deceased donors aged 35 or younger

	HLA mismatches				
	0 ABDR		0 DR[1]		
Ages	n	%	n	%	Total
<5	6	2.1	31	11.2	276
6–10	15	4.5	31	9.6	322
11–17	42	4.1	139	14.1	987
18–45	1557	14.0	2174	22.8	9535

[1]Excluding 0 HLA-ABDR mismatched grafts.

In separate analyses of the SRTR database, pediatric recipients aged 0 to 17 who received their first deceased donor kidney-only transplant between January 11, 1995 and December 31, 2000 were analyzed using a Cox regression model. The relative rate of graft failure was calculated as the time from transplantation until graft failure or death, censoring at the earliest of last known follow-up date, or December 31, 2005. The model included indicators for donor age groups (0–10, 11–17, 18–34, 35–49, >50). The model was adjusted for recipient sex, recipient race, recipient body mass index (BMI), year transplanted, panel-reactive antibody **(**PRA), recipient ABO blood type, diagnosis group, time on dialysis, donor sex, donor race, cold ischemic time, donor cause of death, number of HLA mismatches, number of pretransplant transfusions, double kidney transplant and donor history of diabetes or hypertension.

An additional model was constructed using a logistic regression to determine the odds of sensitization following first graft failure among pediatric patients (measured PRA as reported to the OPTN at the time of second waitlisting), based on HLA mismatches with the first transplant donor. This model was adjusted for PRA at time of first transplant, length of first transplant survival, time since failure of the first transplant, and the recipient's race/ethnicity, sex, age, blood type, previous transfusions and year of transplant.

Results

The distribution of HLA-DR-matched grafts according to recipient ages is shown in Table 1 for the unadjusted comparisons. During the 8-year period from 1996 to 2004, very few pediatric transplant recipients received zero HLA-A,-B,-DR

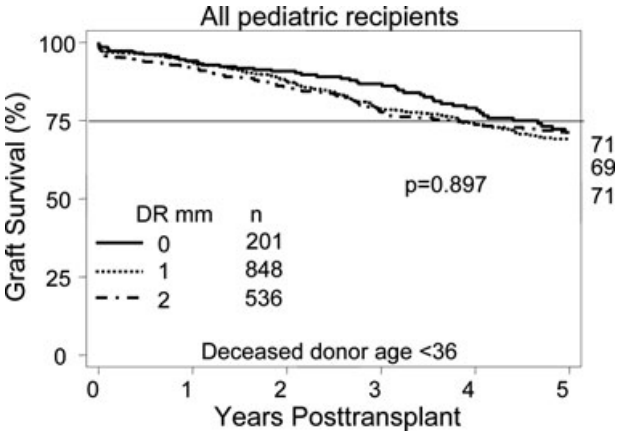

Figure 1: Actuarial 5-year graft survival rates among all pediatric recipients by number of HLA-DR mismatches. The p-value is reported as well as the total number of recipients in each group (n). This analysis was of pediatric recipients who received their first kidney transplant from deceased donors 35 years of age or younger.

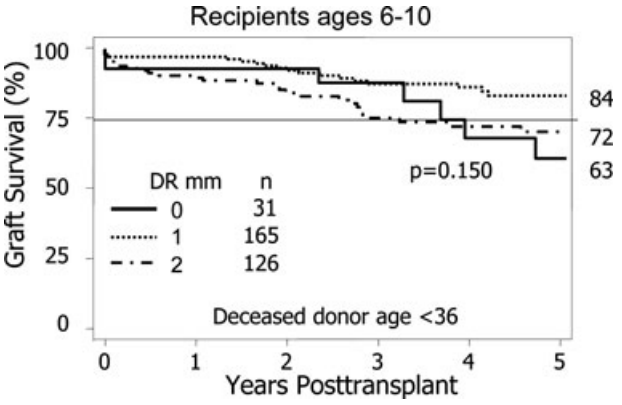

Figure 3: Actuarial 5-year graft survival rates among pediatric recipients aged 6–10 by the number of HLA-DR mismatches. The p-value is reported as well as the total number of recipients in each group (n). This analysis was of pediatric recipients 6–10 years old who received their first kidney transplant from a deceased donor 35 years of age or younger.

(range 2.1–4.5% depending on age and number of transplants) or zero HLA-DR (range 9.6–14.1%)-mismatched transplants. In contrast, 14.0% and 22.8% of adult recipients between the ages of 18 and 45 years received zero HLA-A,-B,-DR or zero HLA-DR-mismatched transplants, respectively.

Compared to 1-DR-mismatched or 2-DR-mismatched kidneys, zero HLA-DR-mismatched matches produced no statistically significant difference in the 5-year pediatric allograft survival rates (Figure 1). After 5 years, 71% of the zero- and 2-DR-mismatched grafts survived compared with 69% of those with one HLA-DR mismatch ($p = 0.897$). Furthermore, among the subpopulations of pediatric recipients aged 0–5, 6–10 and 11–17 years, there was no apparent benefit of HLA-DR matching (Figures 2–4).

The analysis of waiting time for pediatric recipients transplanted in each DR-match category shown in Figure 5 suggests that within the constraints of the allocation system during the study period, waiting longer for a kidney did not result in better-matched transplants. In fact, HLA-DR-matched kidneys tended to be transplanted into pediatric recipients sooner than DR-mismatched kidneys.

As shown in Figure 6, the overall 5-year graft survival rate for adult recipients aged 19–45 years was superior to that for adolescent recipients (75% vs. 65%, $p < 0.001$), but

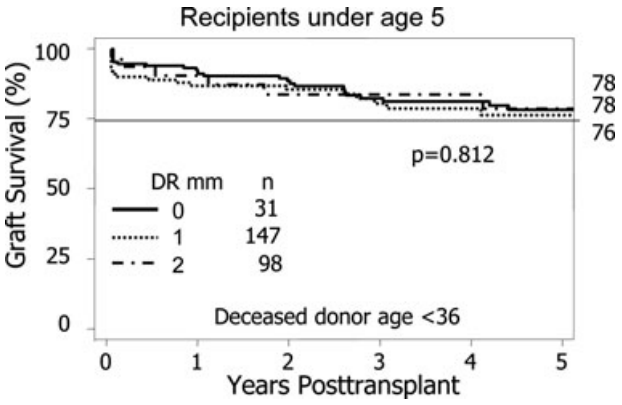

Figure 2: Actuarial 5-year graft survival rates among recipients under age 5 by the number of HLA-DR mismatches. The p-value is reported as well as the total number of recipients in each group (n). This analysis was of pediatric recipients 5 years old or younger who received their first kidney transplant from a deceased donor 35 years of age or younger.

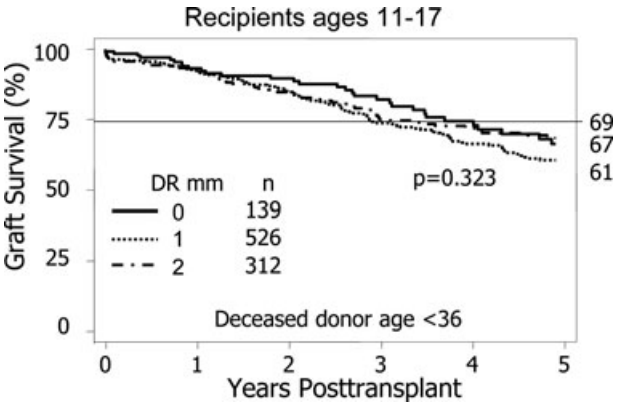

Figure 4: Actuarial 5-year graft survival rates among adolescent recipients by the number of HLA-DR mismatches. The p-value is reported as well as the total number of recipients in each group (n). This analysis was of pediatric recipients 11–17 years old who received their first kidney transplant from a deceased donor 35 years of age or younger.

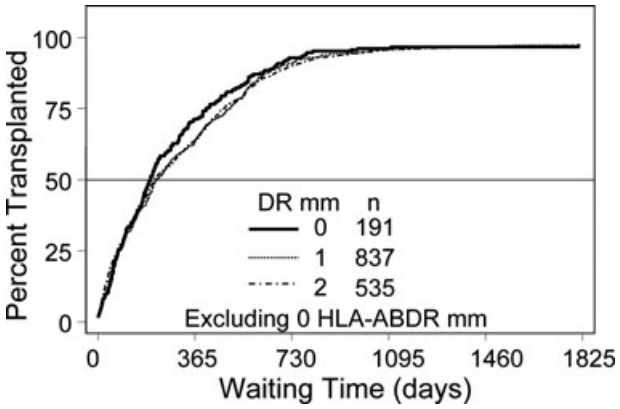

Figure 5: Time to transplant for pediatric recipients by level of HLA-DR mismatch, the time to transplant was defined as the difference between the transplant date and the date the patient was added to the waiting list. The total number of recipients is reported in each group (n). This analysis was of renal transplant recipients who received their first kidney transplant from a deceased donor 35 years of age or younger and excludes recipients of zero HLA-A, -B and -DR-mismatched transplants.

not significantly different from that observed of recipients aged 0–5 years (80%) or 6–10 years (77%).

In the adjusted model, 1470 pediatric patients received kidney transplants during the study period. Of these, 933 (63.5%) were in the 10- to 17-year-old age range. There were 365 graft failures and 31 deaths during the study period. The mean age of the donors was 26.4 and the age range was from <1 to 73 years. Eighty-five percent of donors were between 6 years and 48 years, and 65% were between 16 years and 48 years. When compared to donors less than 35 years of age, the relative rate of allograft failure was 1.32 ($p = 0.033$) for donor age $\geq$35 (Figure 7).

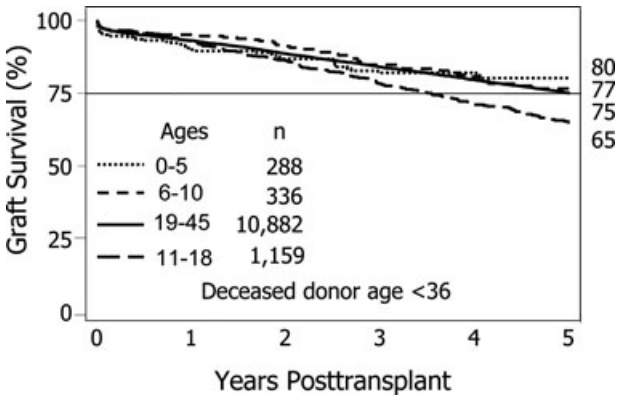

Figure 6: The 5-year graft survival rates of adult, adolescent and pediatric renal transplant recipients from donors under age 35.

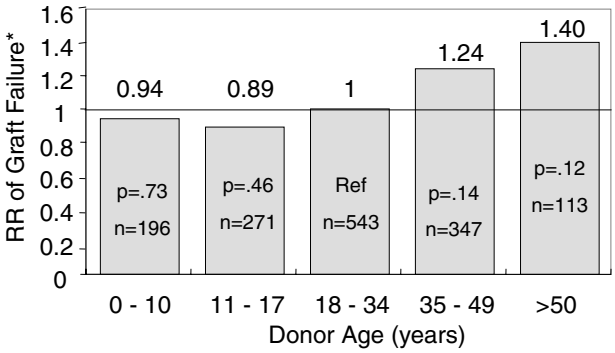

Figure 7: Relative risk of graft failure for pediatric first transplant recipients according to donor age group. Adjusted for recipient sex, recipient race, recipient BMI, year transplanted, PRA, recipient ABO blood type, diagnosis group, time on dialysis, donor sex, donor race, cold ischemic time, donor cause of death, number of HLA mismatches, number of pretransplant transfusions, double kidney transplant and donor history of diabetes or hypertension.

Also available for analysis were 313 second waitlisted candidates whose PRA at the time of first transplant was less than 30%. This number excluded patients whose PRA at first transplant or second waitlisting were not available. Only seven patients received a zero ABDR mismatched kidney at first transplant, and they were_included in this analysis. There was no statistical increase in the odds of developing a PRA greater than 30% at the time of second waitlisting, based upon the degree of HLA-A, -B or -DR mismatch of the first transplant (Table 2), nor was there a 'dose effect' when more HLA antigens were mismatched between the donor and recipient.

Discussion

Living donor kidney transplants have superior allograft survival compared with even the best-matched deceased donor kidney transplants (5). However, controversy remains regarding the importance of HLA matching among renal allograft recipients who do not have a suitable living

Table 2: The odds of sensitization (PRA >30%) at second waitlisting, based upon HLA mismatch of the first transplant

	N	OR	p-Value
Mismatch at first Tx			
0 A	32	1	Ref
1 A	138	0.72	0.56
2 A	143	1.02	0.972
0 B	19	1	Ref
1 B	105	3.66	0.129
2 B	189	2.28	0.329
0 DR	72	1	Ref
1 DR	158	0.4	0.021
2 DR	83	0.56	0.202

Tx = transplant; Ref = reference.

donor. Adult recipients of zero HLA-A, -B, -DR-mismatched deceased donor kidney transplants have a 3–4% improvement in 5-year graft survival compared to those with any HLA mismatch. Adult recipients with a zero HLA-DR mismatch have significantly fewer rejection episodes in the first year (6) and, as a result, may receive less cumulative immunosuppression during the life of their transplant. Similarly, adult patients who experience graft failure are less likely to become broadly sensitized if the allograft had fewer mismatched HLA antigens (7).

These considerations may be important for pediatric renal transplant recipients, who may require repeat transplantation at some time during their life. Thus, living donor and HLA-matched transplants for pediatric patients would seem to be the best options for transplantation when feasible. Unfortunately, the extensive polymorphisms of the HLA antigen system make finding well-matched deceased donor kidneys difficult, even among very large numbers of potential donors and waitlisted candidates. When we consider the added limitations of smaller local donor pools and populations of waitlisted pediatric candidates and further restrictions imposed by the requirement for ABO compatibility and technical requirements for pediatric transplantation, the small numbers of pediatric recipients of HLA-A, -B, -DR and HLA-DR-matched grafts shown in Table 1 are easily understood. More pediatric patients might receive HLA-matched grafts if they waited longer, but waiting results in prolonged dialysis exposure that is associated with impaired growth and social and physical development, and increased risk of dialysis access failure.

The literature concerning the beneficial effect of DR matching for pediatric recipients has been inconclusive. A single-center study by Barocci and associates (8) suggested that matching of HLA-DR antigens leads to improved graft survival, while another single-center study by El-Husseini et al. (9) reported that HLA-DR matching had no significant impact on graft survival. A very large multivariate analysis of 8442 pediatric kidney transplant recipients reported to the OPTN/UNOS database between October 1987 and December 1998 also failed to show a statistically significant 1- and 5-year graft survival benefit with HLA-A, -B or -DR matching (10).

The three analyses reported here of OPTN and SRTR data were prepared separately and used for OPTN policy development. The analysis is of pediatric patients during a period when the organ allocation policies for pediatric recipients were stable. They are reported here to provide data to the transplant community explaining the rationale for the change in pediatric organ allocation policy so that patients can be informed of the risks and benefits relating to acceptance of donor organs. Our retrospective analysis of more recent nationwide cohorts of pediatric recipients of primary deceased donor kidney transplants confirms that pediatric candidates for kidney transplantation are not penalized in terms of allograft survival or subsequent sensitization by accepting a mismatched kidney from a deceased donor. We were unable to demonstrate allograft survival improvement among pediatric recipients who received better HLA-DR-matched kidney transplants during the 10-year study period. This was true regardless of the pediatric age group studied.

Of course, even these larger studies are hampered by the paucity of well-matched grafts in the pediatric population. Thus, it may be speculative to conclude that closer-matched grafts would not fare better than poorly matched grafts in the long term. However, it is clear that under the previous allocation system, pediatric patients rarely received well-matched grafts. The notion that it benefits pediatric kidney transplant candidates to remain on the waiting list in order to receive a better HLA-matched kidney allograft is also refuted by the results in Figure 5. The lack of a clear survival benefit for pediatric recipients of HLA-DR-matched kidneys, and the observation that HLA-DR-matched transplants tend to be performed at least as quickly as mismatched transplants, suggests that there is no advantage for pediatric patients to remain on the waiting list in the hope of obtaining a better HLA-DR-matched transplant.

The new pediatric deceased donor kidney allocation policy attempts to improve long-term patient survival by minimizing time spent on dialysis. The policy also has the potential to decrease the exposure to HLA antigens due to blood transfusion and subsequent sensitization. This policy may also facilitate deceased donor transplantation before the initiation of dialysis. Deceased donors less than 35 years of age are more likely to have died as a result of trauma rather than from consequences of vascular disease, another significant determinant of improved graft survival (10).

Some concerns have been raised regarding the impact on living donation of giving near-absolute local allocation priority to pediatric patients for *donors less* than 35 years of age. It has been argued that providing very rapid deceased donor kidney transplantation to pediatric recipients may reduce the incentive for their loved ones to donate. It is important to emphasize to patients and their families the significant benefits of living donor compared to deceased donor renal transplantation. Nevertheless, if there were a decline in initial live donation as a result of this policy change, family members who might have donated initially would still be available should retransplantation be necessary for that individual in the future.

Another concern that has been raised is that prioritizing 'ideal' kidneys to the pediatric population may severely disadvantage adult candidates and transplant centers lacking pediatric programs. However, because the proportion of pediatric candidates on the waiting list is stable and nominal (approximately 700–800 per year) in comparison to the adult population, the new pediatric priority policy will only marginally shift the mean age of the donor, and will not

markedly decrease the volume of kidneys transplanted into the adult population (10).

The adolescent recipient population might theoretically pose a problem for this new policy. This population has decreased 5-year graft survival when compared to 19–45 year olds. New trials to carefully monitor immunosuppressive pharmacology and adherence to treatment will hopefully improve the outcomes. Allotment of 'ideal' kidneys to the adult population rather than adolescents might have a greater societal benefit (1,10–13). Ultimately, however, it is up to the individual transplantation teams to ensure that each pediatric recipient is a suitable candidate to receive this valuable organ. This includes appropriate social and financial support. Numerous efforts are underway to improve medication compliance and physician follow-up in this higher risk group.

The strongest modifiable risk factor for renal transplant outcomes is waiting time on dialysis (14). In fact, the best outcomes occur in recipients who preemptively receive a kidney transplant before dialysis becomes necessary (15,16). Based on the current data, pediatric transplant recipients with HLA-DR-mismatched kidneys enjoy essentially the same graft survival as their HLA-DR-matched counterparts. Therefore, transplant centers should not hesitate to accept HLA-DR-mismatched kidneys from deceased donors less than 35 years of age in order to expedite the transplantation process for the majority of nonsensitized pediatric candidates for first transplants.

Conclusion

OPTN policy now prioritizes kidneys from deceased donors less than 35 years of age to pediatric candidates. This policy should improve the allocation of this scarce resource while minimizing the morbidity associated with prolonged exposure to dialysis for children. There is no demonstrable allograft survival benefit for HLA-DR-matched pediatric kidney transplantation. Therefore, pediatric transplant programs should not hesitate to accept HLA-DR-mismatched kidneys from deceased donors less than 35 years of age. It is expected that this policy will lead to shorter pediatric waiting time. As the pediatric waiting list begins to shorten, it will be important that pediatric transplant programs optimize their patients prior to listing for deceased donor transplantation. The long-term effects of this change in allocation policy will need to be monitored to ensure the best outcomes for children with end-stage renal disease.

Acknowledgments

The authors would like to thank the OPTN and SRTR for allowing the use of data prepared for the Pediatric, Kidney-Pancreas, and Minority Affairs Committees. We also appreciate the expertise of the SRTR staff in the preparation of the statistical analysis for the OPTN/UNOS committees to guide policy development. This study was supported by contract number 234–2005-37009C from the Health Resources and Services Administration, US Department of Health and Human Services. The views expressed herein are those of the authors and not necessarily those of the US government. This study was approved by HRSA's SRTR project officer. HRSA has determined that this study satisfies the criteria for the IRB exemption described in the 'Public Benefit and Service Program' provisions of 45 CFR 46.101(b) and HRSA Circular 03.

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