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Mode of Initial Renal Replacement Therapy and Transplant Outcomes in the Chronic Kidney Disease in Children (CKiD) Study

Meredith A. Atkinson¹, Jennifer L. Roem², Anuradha Gajjar³, Bradley A. Warady⁴, Susan L. Furth⁵, Alvaro Muñoz²

¹Johns Hopkins University School of Medicine,

²Johns Hopkins Bloomberg School of Public Health,

³Weill Cornell Medical College,

⁴Children's Mercy, Kansas City,

⁵Children's Hospital of Philadelphia

Abstract

Background: Kidney transplant is the renal replacement therapy (RRT) of choice for children with end stage kidney disease (ESKD). Only 21.3% of children who initiate RRT receive a preemptive kidney transplant (PKT). We characterized the transition to RRT in children in the CKiD cohort including the prevalence of dialysis as first RRT vs. PKT and graft survival.

Methods: 258 children enrolled in CKiD have initiated RRT, and 202 had post-RRT initiation data collected through phone or in-person follow-up. Characteristics by first RRT modality were compared using Chi-square and Kruskal-Wallis tests. Parametric-accelerated failure time models were fit for transplantation. Graft failure was characterized using Kaplan-Meier methods and log rank tests.

Results: Sixty-one percent received dialysis as first RRT modality and 39% PKT. Those with PKT were less likely to have glomerular disease and to be African-American, and had higher household-income. African-American subjects were nearly twice as likely to undergo dialysis prior to transplant. Those with a living donor and a college-educated mother had 40%-decreased odds of being dialysis experienced. Children with PKT were more likely to receive a living donor transplant. Only 5% of PKT subjects had graft failure by 4 years compared to 16% of those initially treated with dialysis ($p=0.092$); however, after adjustment the effect of dialysis exposure was attenuated ($p=0.206$).

Corresponding Author: Meredith A. Atkinson, MD, MHS, Division of Pediatric Nephrology, Johns Hopkins University School of Medicine, 200 N. Wolfe St., 3rd Floor, Baltimore, MD 21287, Phone: 410-955-2467, matkins3@jhmi.edu.

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Conclusion: CKiD subjects undergo PKT more often compared to nationally-reported rates, and are more likely to receive a kidney transplant within 1 year of starting dialysis. African-American race and lower household-income are associated with decreased access to PKT.

Keywords

pediatrics; graft loss; hemodialysis; peritoneal dialysis; preemptive

Introduction

Kidney transplantation is the renal replacement therapy (RRT) of choice for children with end stage renal disease (ESKD). Preemptive kidney transplantation (PKT), defined as a transplant serving as the initial RRT modality, has been associated with increased graft and patient survival in both adults and children [1][2][3]. PKT also avoids potential morbidities associated with dialysis including placement of a surgical dialysis access with the associated risk for infectious complications, and cardiovascular complications of dialysis related to chronic volume overload and hypertension [4][5]. Despite these recognized benefits, PKT remains the least frequently utilized initial RRT modality in children with incident ESKD. According to the U.S. Renal Data System (USRDS) Annual Data Report 2018 the most common initial RRT modality in children is hemodialysis (HD) (51.2%), followed by peritoneal dialysis (PD) (25.7%) and PKT (20.0%) [6]. Exposure to dialysis prior to renal transplant is associated with decreased graft survival and an increased risk for cardiovascular events compared to PKT recipients in adults, and the risk for adverse outcomes is noted to increase with dialysis duration [2][1].

In children specifically, there have been conflicting conclusions about the association between pre-transplant dialysis experience and transplant outcomes. Retrospective studies in small cohorts of children have failed to demonstrate significant differences in graft survival between PKT recipients and those treated with dialysis [7][8]. Vats et al. conducted a retrospective study with the North American Renal Trials and Collaborative Studies (NAPRTCS) registry examining 2496 children who underwent a primary living donor (LD) renal transplant from 1992–1996. In contrast to other studies, Vats et al. found that the 3-year graft survival was improved in PKT recipients compared to those who received pre-transplant PD or HD. In contrast, graft survival rates did not differ by pre-transplant dialysis status among those who received deceased donor (DD) grafts [9]. Among those with pre-transplant dialysis experience, there was also no difference in graft survival by dialysis modality (PD or HD) [9]. Both the patient- and graft-survival benefit of PKT in children have been confirmed more recently in data derived from the USRDS, with a survival benefit observed regardless of donor source (LD or DD) [3].

Risk factors previously identified by the NAPRTCS for receiving dialysis prior to transplantation include non-white race, female gender, and the presence of an underlying disease with a high risk for recurrence (e.g. FSGS or oxalosis) [9]. In the USRDS, African-American and Hispanic children under the age of 18 were substantially less likely to receive a PKT from a LD compared to white children, even after adjusting for demographic, clinical, and socioeconomic factors [10]. To undergo PKT from any source requires early

access to specialized nephrology care, which some subjects captured in USRDS may not have had due to experiencing a more recent diagnosis of ESKD from previously unrecognized or acute conditions.

In the Chronic Kidney Disease in Children (CKiD) cohort study, children are recruited from and followed longitudinally at pediatric nephrology centers where they receive their ongoing clinical care. Our objective was to utilize data from the CKiD study to determine whether PKT is more commonly used as the initial renal replacement therapy in children with excellent access to pre-ESKD care and whether it is associated with a transplant graft-survival benefit. In addition, we sought to identify risk factors for pre-transplant dialysis, and extended time on dialysis prior to transplant, in this population.

Materials and Methods

Setting and Participants

The CKiD study is a multicenter observational prospective cohort study of children ages 1–16 years at study entry with mild to moderate chronic kidney disease (CKD) recruited from 54 pediatric nephrology centers in North America. Inclusion criteria included an estimated glomerular filtration rate (GFR) between 30 and 90 ml/min/1.73m². The CKiD study design and conduct were approved by an external advisory committee appointed by the National Institutes of Health and the Institutional Review Boards at each participating center. Details of the study design and objectives have been previously published [11]. The primary outcome of interest is CKD progression, defined as a composite endpoint of the earliest of either a 50% reduction in GFR from baseline, an estimated GFR (eGFR) < 15 ml/min/1.73m², or the initiation of RRT (dialysis or transplant) [11]. Estimated GFR at RRT initiation was calculated based on the last serum creatinine obtained at the last study visit prior to initiation; if possible, patients were brought in for an expedited study visit prior to RRT initiation. Whereas subjects reaching ESKD and initiating RRT were dropped from the main study, clinical information was collected annually through the CKiD Phone or In-Person follow-up (PIP) arm in a portion of these subjects when the children were contacted by a CKiD study coordinator either by phone, online, or at a routine nephrology clinic visit. In the initial years of the study, consent for participation in PIP follow-up was separate from the main study consent and was obtained from participants or parents/legal guardians at the time of RRT initiation. Currently, consent for PIP participation is incorporated into the CKiD study consent and participants are given the option at the time of their consent for the main study.

Variables

The primary exposure of interest in our analysis was mode of initial RRT, which was classified as either transplant, HD, or PD. Subjects were observed to initiate RRT in the time span ranging from March 2006 to January 2017. Subjects who underwent dialysis as their first RRT had initial modality (HD vs. PD) and start date collected. The outcome of interest among those whose initial RRT modality was dialysis was whether the subject received a transplant during follow-up. For those who were transplant recipients, their pre-transplant RRT experience (PKT vs. dialysis-experienced) and date of transplant were collected, while

transplant graft failure was the outcome of interest. Donor type was classified as living or deceased. The scale for time on dialysis prior to transplant, time with a transplant prior to graft failure, and the need for dialysis initiation, was years.

Covariates considered as possible confounders included age at RRT, race, sex, underlying cause of kidney disease, GFR, and socioeconomic status. Race was categorized as African-American or non-African-American. The underlying cause of kidney disease was classified as glomerular or non-glomerular. Estimated GFR prior to initiation of RRT was calculated using the 2012 CKiD equation [12]. Socioeconomic status (SES) indicator variables included annual household income (>\$75,000 vs. \$75,000) and maternal education (college graduate vs. some college or high school).

Statistical Analysis

Demographic and clinical characteristics of the cohort by first RRT modality were compared using Chi-square and Kruskal-Wallis tests. Among subjects with dialysis as first RRT, Kaplan-Meier methods were used to estimate the cumulative incidence of transplantation stratified by dialysis modality (HD or PD). In addition, parametric-accelerated failure time models using the generalized gamma distribution stratified by dialysis modality were fit for transplantation as the event, allowing each modality group to modify the location, scale, and shape parameters. Maximum likelihood methods were used to fit the models including using likelihood ratio tests to determine differences in the cumulative incidences of transplant among those with HD vs PD [13].

To describe transplant failures among transplanted subjects, and to control for multivariable differences between PKT and dialysis-experienced participants at the time of the transplant, we used inverse probability of treatment weighting based on propensity scores to construct a weighted cohort of children who differed with respect to pre-transplant dialysis experience, but were similar in terms of other measured characteristics. We calculated the inverse probability of treatment weights using a logistic regression model to estimate each subject's propensity to undergo dialysis prior to transplantation. The model included predictor variables selected on the basis of their potential to confound the relationship between dialysis experience and transplant graft survival. These variables included age at transplant, race, sex, household income, maternal education, underlying cause of CKD, eGFR prior to any RRT, and donor source. Subjects who were dialysis-experienced prior to transplant were assigned a weight of $1 \div (\text{propensity score})$ and those who underwent PKT a weight of $1 \div (1 - \text{propensity score})$. The weights were scaled to match the original sample sizes of the two groups by multiplying them by the proportion of the full sample who were dialysis-experienced and PKT, respectively. We then characterized transplant graft failure by pre-transplant dialysis experience using Kaplan-Meier methods and log rank tests using the original data (i.e., unadjusted) and weighting by the scaled inverse probability weights to adjust for the multivariable differences of the two groups (PKT vs. dialysis-experienced).

Results

A total of 258 children enrolled in CKiD have subsequently initiated RRT, and 202 had available PIP data to be included in the analysis. Sixty-one percent (n=123) underwent

dialysis as first RRT (66% HD, 34% PD), and 39% (n=79) underwent PKT. Demographic and clinical characteristics of subjects by initial RRT modality are presented in the left 3 columns of Table 1. Compared to children who initiated dialysis first, those who received PKT were less likely to have glomerular disease (17% vs. 39%, $p=0.001$) and to be African-American (13% vs. 30%, $p=0.004$) and of the 47 African-American subjects, 18 (38%) had glomerular disease but of the 155 non-AA, 43 (28%) had glomerular disease. Within the glomerular disease sub-group, the proportions of participants with focal segmental glomerular sclerosis by first RRT modality were: 3% for PKT, 7% for PD, and 17% for HD. Children who received PKT were also more likely to report annual household income $> \$75,000/\text{year}$ (37% vs. 19%, $p=0.004$) and to have mothers who graduated college (38% vs. 20%, $p=0.004$). The last pre-RRT eGFR was slightly higher in those who underwent PKT compared to those who were treated with dialysis (19.1 vs. 17.8 ml/min/1.73m², $p=0.032$). There were no significant differences in age or sex by first RRT modality. When comparing children who underwent dialysis as the first RRT by initial dialysis modality (see right three columns of Table 1), there were no significant differences in age, race, underlying cause of disease, pre-RRT estimated GFR, or socioeconomic status between those initiated on HD vs. PD. Subjects initiated on PD were more likely to be male (74% vs. 54%, $p=0.036$).

The number of transplants observed among the 81 and 42 subjects with HD and PD as first RRT were 56 (69%) and 36 (86%), respectively. Figure 1 shows the cumulative incidence of transplantation for the two groups. Specifically, among subjects initiated on HD, 50% were transplanted by 11 months after dialysis initiation, while 50% of subjects initiated by PD were transplanted by 13 months after initiation. The cumulative incidences crossed at around 15 months since dialysis initiation and generalized gamma distributions provided excellent fit to the KM curves and its associated likelihood ratio test yielded a statistically significant difference ($p=0.028$). Hence, those who initially received hemodialysis were transplanted at higher rates during the first 15 months of RRT, but it reversed afterwards such that the transplant rate in PD patients was greater. Similar proportions of subjects in the two groups received a transplant from a living donor (42% for PD and 46% for HD, $p=0.654$).

To determine the longevity of transplants, we then compared the 79 subjects who were PKT recipients to the 91 who were transplanted after being on dialysis and had follow-up after the transplant; their descriptive statistics are shown in Table 2. Dialysis-experienced children were more likely to be African-American compared to those who underwent PKT (29% vs. 13%, $p=0.011$). In addition, those who underwent PKT were significantly more likely to report annual household income $> \$75,000$ (37% vs. 22%, $p=0.034$) and to have college educated mothers (38% vs. 23%, $p=0.035$) compared to those who received dialysis. Subjects with PKT were also less likely to have glomerular disease (17% vs. 36%, $p=0.004$). Children who underwent PKT were more likely to receive a transplant from a living donor than those transplanted after an initial course of dialysis (63% vs. 45%, $p<0.01$).

In multivariable logistic regression, subjects with glomerular disease were nearly three times more likely to have received dialysis prior to renal transplantation compared to those with non-glomerular causes of CKD (Table 3). Although neither race, sex, income, or the availability of a living donor were significantly associated with odds of receiving dialysis prior to transplant, several trends were noted. African-American subjects were nearly twice

as likely to have experienced dialysis prior to transplant, and those with a living donor source and a mother with college education had a 40% decreased odds of being dialysis-experienced.

The number of transplant failures observed over 48 months among the 79 and 91 subjects with PKT and dialysis-experienced transplant were 3 and 10, respectively. Eleven percent of African-American subjects and 7% of non-African-American subjects demonstrated graft failure during the follow up period. Figure 2 shows the cumulative incidence of transplant failure the two groups both unadjusted (continuous lines) and adjusted (dashed lines) for the differences noted in Table 2 and using inverse probability methods based on the propensities provided by the logistic regression results in Table 3. Only 5% of PKT subjects had graft failure by 4 years post-transplant compared to 16% of those treated with dialysis ($p=0.092$; unadjusted). After adjustment using scaled inverse probability weights, the effect of dialysis exposure was attenuated ($p=0.206$).

Discussion

Our study demonstrates that 39% of children enrolled in CKiD underwent PKT as their first mode of RRT, nearly twice the reported 21.3% rate of PKT in children in the USRDS database. In addition, 50% of CKiD subjects received a kidney transplant within one year of starting dialysis, a substantially higher proportion than the 36.3% reported in USRDS [6]. Children enrolled in the CKiD study are unlikely to be representative of the pediatric incident ESKD population in the U.S. overall, but due to selection bias may represent children from more privileged and potentially adherent backgrounds with an appreciation of the need for participation in clinical studies. Thus, the better-than-national rates of PKT observed in our study cohort could be explained by a select population of children who received regular nephrology care and the benefit of longitudinal GFR assessments provided to both primary nephrology providers and families. While those who received a PKT were more likely to receive a LD transplant than those transplanted after dialysis initiation, there was no differences in proportions of children receiving LD transplants between those initiated on HD vs. PD at the time of incident ESKD.

Despite higher rates of PKT and transplantation within one year of dialysis initiation compared to the general pediatric ESKD population, African-American children enrolled in CKiD were still less likely than non-African-Americans to undergo PKT. African-American patients made up 23% of the total study population, but comprised only 13% of the PKT population. Amaral et al. have previously reported in a large national sample that children receiving PKT were more likely to be white and non-Hispanic, and were also more likely to have private insurance and live in wealthier neighborhoods [3]. Our analysis also demonstrated that socioeconomic status was associated with PKT rates, with preemptively transplanted subjects more likely to report higher household income and maternal college education. Our finding that subjects with glomerular causes of ESKD were less likely to receive PKT was also consistent with prior data from the USRDS, where those with congenital anomalies of the kidneys and urinary tract (CAKUT) were more likely to undergo PKT compared to other diagnoses. This is likely due to longer disease duration and opportunities for care planning among children with congenital causes of disease. In our

multivariable analysis, glomerular disease as the underlying cause of CKD was also significantly associated with being dialysis-experienced prior to transplant; this likely reflects the increased prevalence of glomerular disease in African-American children in CKiD compared to children of other races [14]. Although the trend for non-African-American race to be associated with decreased odds of PKT did not reach statistical significance in the multivariable analysis, the relatively small number of African-American subjects likely limited our ability to detect a significant difference.

In this analysis, subjects with PKT demonstrated marginally decreased rates of graft failure compared to those who were exposed to dialysis prior to transplant (5% vs. 16% at 4 years), with further attenuation of a difference after inverse probability weight adjustment. Improved graft and patient survival for children treated with PKT has been noted previously. In the NAPRTCS registry, 3-year graft survival among children transplanted in the mid-1990s was improved in LD PKT recipients compared to those who received pre-transplant dialysis, although there was no difference in graft survival by initial mode of RRT among patients who received DD transplants [9]. The most common overall causes of graft loss were rejection and vascular thrombosis [9]. In a more recent national cohort of children transplanted from 2000–2012, a consistently lower proportion of graft failures was noted among patients who received PKT compared to non-preemptive transplants regardless of donor source. Although children who received LD transplants had lower rates of graft failure overall compared to DD recipients, LD recipients who underwent PKT still had fewer graft failures compared to LD recipients who were exposed to pre-transplant dialysis [3]. Among DD transplant recipients alone, the benefit for graft survival for preemptive vs. non-preemptive transplants was notably significant as early as 2 years post-transplant and trended to greater significance in a linear fashion with the most marked difference in graft survival noted at 5 years (85.4% vs. 76.4%, $p<0.0001$) [3]. Consistent results have also been observed in adults, in whom PKT from LD has been associated with longer allograft survival compared to recipients who received LD grafts after dialysis [2]. Additionally, a study in Japanese adults found that patients who underwent dialysis prior to transplantation had a significantly increased risk for a composite outcome of transplant graft loss, death with a functioning graft, or cardiovascular events compared to those with PKT, observing a dose-dependent increase in the risk for adverse outcomes per year on dialysis [1].

The morbidity of long-term dialysis in children with ESKD has been well documented and includes cognitive dysfunction, impaired growth, anemia, cardiovascular disease and overall decreased lifespan compared with transplantation [15]–[20]. Amaral et al demonstrated that any dialysis exposure was associated with a 32% higher rate of graft failure in children, even after adjusting for race, cause of kidney disease, and SES indicators [3]. Among subjects in our analysis who underwent dialysis as first RRT, there were no differences in the proportions starting with PD vs. HD by age, race, underlying cause of disease, or SES indicators. Male subjects were noted to be more frequently started on PD vs. HD compared to female patients; this difference is likely due to the increased incidence of CAKUT in male infants and toddlers, who are more likely to be initiated on PD due to the challenges of establishing vascular access for HD in very young children. Given the demand for organs that far outpaces supply, many pediatric patients will face extended dialysis wait times with its attendant risks even though wait times for children are generally shorter than those in

adults [21]. Whether we should be reassured that pre-transplant dialysis exposure is not significantly associated with decreased transplant graft survival in CKiD subjects remains to be seen, but could be attributed to improved continuity of care in CKiD study patients compared to the universe of children with ESKD in the United States. Among those with pre-transplant dialysis experience, we found no difference in graft survival by dialysis modality (PD or HD).

Strengths of this analysis include its prospective cohort design, in which exposures including SES indicators were collected prior to the initiation of RRT. One limitation is the relatively small number of transplant graft failures among CKiD subjects, which may have limited our ability to detect differences in risk for graft failure by initial RRT modality. We also did not have access to granular indicators of donor quality, beyond whether there was a living donor source, which could influence the function of the transplant graft over time. We were unable to explore other clinical factors that could delay time to transplantation or shorten graft survival including human leukocyte antigen (HLA) sensitization or overall health status at the time of incident ESRD. The rate of renal transplant graft failures is fortunately low in children, but with time and as more CKiD subjects progress to ESKD and renal transplantation, our power to detect these differences will increase.

In conclusion, we have demonstrated that CKiD subjects who reach the need for RRT undergo PKT substantially more often compared to overall national rates and are more likely to receive a kidney transplant within 1 year of starting dialysis. However, even for subjects in the CKiD cohort which includes children receiving long-term and consistent nephrology care at tertiary care centers, African-American race and lower SES remain associated with decreased access to PKT. Pre-transplant dialysis exposure may be associated with increased risk for transplant graft failure even after accounting for other demographic and clinical factors.

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Figure 1.

Cumulative incidence of transplantation (solid lines) following dialysis as first RRT event in 123 CKiD subjects. The black lines represent the 81 HD participants of whom 50% were transplanted by 11 months after initiating dialysis. The gray lines are the 42 PD participants of whom 50% were transplanted 13 months after initiating dialysis. The dashed lines represent the generalized gamma curves yielding a likelihood ratio statistic with a p-value= 0.028.

Figure 2.

Cumulative incidence of transplant failure following transplant event in 170 CKiD subjects. Solid lines depict unadjusted functions and dash-dotted lines represent adjusted functions using inverse probability weights. The gray lines are the 79 PKT participants of whom only 5% had transplant failure by 48 months. The black lines represent the 91 dialysis-experienced participants of whom 16% had transplant failure by 48 months. Incidence of transplant failure marginally differs between dialysis-experienced and PKT when unadjusted ($p=0.092$), but attenuates when adjusted by inverse probability weights ($p=0.206$).

Table 1:

Demographic and clinical characteristics of 202 post-renal replacement therapy participants in PIP protocol by initial RRT modality, and of 123 participants with dialysis as initial RRT^a

Characteristic ^a	Dialysis N=123	PKT N=79	p	PD N=42	HD N=81	p
Age at 1 st RRT, yrs	15.5 [13.1, 17.1]	15.1 [12.6, 17.5]	0.837	14.8 [12.5, 17.1]	15.6 [13.3, 17.0]	0.301
African-American race	30% (37)	13% (10)	0.004	24% (10)	33% (27)	0.275
Male	61% (75)	61% (48)	0.975	74% (31)	54% (44)	0.036
Income > \$75,000	19% (23)	37% (29)	0.004	19% (8)	19% (15)	0.943
Maternal education: college	20% (24)	38% (30)	0.004	21% (9)	19% (15)	0.699
Glomerular Dz	39% (48)	17% (13)	0.001	38% (16)	40% (32)	0.879
eGFR prior to RRT, ml/min/1.73m ²	17.8 [13.7, 24.1]	19.1 [16.2, 24.1]	0.032	17.6 [15.1, 21.4]	17.8 [13.3, 24.3]	0.660
Follow-up time, yrs	0.8 [0.4, 1.6]	3.8 [1.8, 5.8]	<.001	1.1 [0.5, 1.6]	0.8 [0.3, 1.5]	0.100

^aContinuous variables described as median [interquartile range] and categorical as percent (n).

PKT, preemptive kidney transplant; eGFR, estimated glomerular filtration rate using the 2012 CKiD equation

Table 2.

Demographic and clinical characteristics among 170 transplanted participants in PIP protocol, by pre-transplant dialysis experience^a

Characteristic ^a	PKT N=79	Dialysis-Experienced N=91	p
Age at transplant, yrs	15.1 [12.6, 17.5]	15.9 [13.4, 17.9]	0.455
African-American	13% (10)	29% (26)	0.011
Male	61% (48)	64% (58)	0.690
Income > \$75,000	37% (29)	22% (20)	0.034
Maternal education: college	38% (30)	23% (21)	0.035
Glomerular diagnosis	17% (13)	36% (33)	0.004
eGFR prior to RRT, ml/min/1.73m ²	19.1 [16.2, 24.1]	17.8 [13.6, 24.1]	0.032
Living donor source	63% (50)	45% (41)	0.017
Original dialysis modality			na
Peritoneal	na	40% (36)	
Hemodialysis	na	60% (55)	

^aContinuous variables described as median [interquartile range] and categorical as percent (n).

PKT, preemptive kidney transplant; eGFR, estimated glomerular filtration rate using the 2012 CKiD equation

Table 3.

Multivariate logistic regression results from propensity score model estimating the odds of being dialysis-experienced (n=170)

Variable	Odds ratio	95% confidence interval
Age at transplant	1.04	(0.95, 1.14)
African American race	1.93	(0.80, 4.67)
Male	1.24	(0.62, 2.47)
Income > \$75,000	0.75	(0.34, 1.64)
Maternal education: college	0.60	(0.28, 1.31)
Glomerular diagnosis	2.79	(1.27, 6.12)
eGFR prior to RRT, ml/min/1.73m ²	0.98	(0.95, 1.02)
Living donor source	0.60	(0.30, 1.20)

Bold indicates p<0.05