Pediatric Kidney Transplantation Outcomes in Children with Primary Urological Abnormalities Versus Nonurological Abnormalities: Long-Term Results

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Abbreviations and Acronyms

AA = African American
CAKUT = congenital anomalies of the kidney and urinary tract
CIC = clean intermittent catheterization
DDKT = deceased donor kidney transplantation
ESKD = end stage kidney disease
FSGS = focal segmental glomerulosclerosis
KT = kidney transplant
LDKT = living donor kidney transplantation
LUTD = lower urinary tract dysfunction
NB = neurogenic bladder
PUV = posterior urethral valves
UPJ = ureteropelvic junction
UTI = urinary tract infection
VUR = vesicoureteral reflux

Purpose: We assessed renal function, graft survival rates and the risk of graft loss in children based on etiology with a focus on differences between urological causes from congenital anomalies of the kidney and urinary tract vs other causes of end stage kidney disease.

Materials and Methods: A retrospective chart review was performed including patients younger than 18 years who underwent kidney transplantation at our institution from December 1984 to November 2010 with the last followup recorded in March 2018. Patient clinical characteristics, demographics and end stage kidney disease etiology were recorded. Patients were divided into the 2 groups of urological (congenital anomalies of the kidney and urinary tract) vs nonurological based on end stage kidney disease etiology, and survival analysis was performed.

Results: Of 112 kidney transplant cases 90 (80.4%) were associated with nonurological causes and 22 (19.6%) with urological causes. Median (IQR) patient age at transplantation was 12 (7-15) years. Median graft survival time was not statistically different according to end stage kidney disease etiology (nonurological 12 years 95% CI 10.01–13.99 vs urological 16 years 95% CI 7.59–24.41, p=0.532). There was a significant risk of graft loss in patients with urinary tract infections after transplantation (HR 3.15, 95% CI 1.59–6.25, p=0.001).

Conclusions: Children requiring transplantation due to urological causes have no disadvantage in graft survival compared to children with end stage kidney disease with other causes. Patients with urinary tract infection after transplantation had a higher rate of graft loss.

Key Words: kidney transplantation; pediatrics; kidney failure, chronic; causality; urologic diseases

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KIDNEY transplantation is the preferred treatment modality for end stage kidney disease in the pediatric population, affording patients the opportunity for an improved quality of life compared to dialysis, with a significant impact on productivity and growth.[1,2] However, the etiology of ESKD in this population appears to be a factor that impacts management before vs after transplantation, as well as postoperative complications and outcomes.[2]

In children the leading causes of kidney failure are congenital anomalies of the kidney and urinary tract such as aplastic, hypoplastic or dysplastic kidneys (15.8%) and obstructive uropathy (15.3%).[2,3] Some children with CAKUT have bladder dysfunction that can affect kidney function in the post-transplant period. Approximately a third of children with ESKD due to CAKUT have lower urinary tract dysfunction with a significant proportion due to posterior urethral valves or neurogenic bladder.[4,5] Patients with a dysfunctional lower urinary tract have an increased incidence of complications after transplantation including UTIs and symptomatic VUR.[6] Thus, optimal management strategies include surgical correction of the underlying anomalies, drug therapy with medications such as anticholinergics, timed voiding and catheterization depending on the etiology and severity of bladder dysfunction.[5]

On the other hand, FSGS remains the most common nonurological cause for kidney transplantation in the pediatric population.[7] It has also been associated with poor graft outcomes and high recurrence rates affecting 15% to 40% of patients.[8,9] Other nonurological causes of ESKD include chronic glomerulonephritis and interstitial nephritis.[5] As surgical techniques have improved and urological intervention is now standard for patients with LUTD, we expect patients with a urological etiology of ESKD to have improved outcomes. Additionally, with the risk of disease recurrence in the nonurological group we would expect improved graft survival in the urological group overall when the 2 groups are compared.

The data are insufficient regarding long-term transplantation outcomes in patients with CAKUT. Despite substantial research in the pediatric kidney transplantation population, few studies have evaluated the differences and outcomes in children who underwent kidney transplantation for urological vs nonurological causes. We present data from pediatric renal transplant procedures completed during a period of 26 years to evaluate and compare renal function, graft survival rates and risk of graft loss based on ESKD etiology, patient demographics and clinical characteristics.

MATERIALS AND METHODS

Participant Selection and Clinical Variables Assessment

An institutional review board approved retrospective chart review (IRB No. 20080141) was performed at Jackson Memorial Hospital, comprised of patients less than 18 years old at the time of transplantation who underwent kidney transplantation between December 1984 and November 2010, followed at the authors' institution with the last followup recorded in March 2018. A total of 226 patients underwent transplantation. Patients with followup less than 6 months, insufficient identifiable data and those with multivisceral transplants, including liver-kidney and heart-kidney transplants, were excluded from analysis.

Patient clinical characteristics such as age at transplantation, gender, recipient ethnicity/race, transplant source from living donor kidney transplantation or deceased donor kidney transplantation, and documented UTI before vs after transplantation were recorded. UTI diagnosis required patient reported symptomatology consistent with UTI (eg fever, dysuria or graft tenderness) as well as a positive urine culture (greater than 100,000 colony-forming units). Primary etiology of ESKD was noted and categorized as urological (CAKUT including LUTD) vs nonurological. Graft survival was defined as "the time period from the date of transplant to the date of graft failure resulting in renal replacement therapy or death with a functioning graft."[10] The different causes of graft loss were recorded. Of those causes nonadherence was included and determined by provider notation based on patient admittance of nonadherence or low/absent calcineurin inhibitor levels.

Statistical Analysis

Statistical analysis was performed with SPSS® version 24.0 software. For patients with more than 1 renal transplantation event, each graft transplanted was considered an independent event and assessed from the statistical standpoint as a single case. Means (±SD) or medians and IQR (25–75) were calculated according to the data distribution. Comparison of numerical variables between groups was performed using the Mann-Whitney U test or Student's t-test as required. Categorical variables were analyzed with a chi-square or Fisher's exact test as required. Median years of graft survival and 95% CIs were obtained through a Kaplan-Meier analysis and a log rank test was used to assess differences in graft survival between groups. An adjusted proportional hazards regression (Cox regression) was performed to obtain the risk of graft loss and $p < 0.05$ was considered statistically significant.

RESULTS

A total of 112 kidney transplantions were eligible to be analyzed from 103 patients (5 patients underwent 2 transplantations and 2 patients underwent 3). Of those transplantations the underlying etiology was nonurological in 90 (80.4%) and urological in 22 (19.6%). In the urological group 8 patients (7.1%) had PUV, 5 (4.5%) NB, 5 (4.5%) reflux

nephropathy and 4 (3.6%) bilateral UPJ obstruction. Median age at transplantation was 12 (range 2 to 18) years (table 1). There were no statistically significant differences between the urological and nonurological clinical characteristics of gender, transplant type (nonurological 50 [55.6%] LDKT and 40 [44.4%] DDKT vs urological 16 [72.7%] LDKT and 6 [27.3%] DDKT, p=0.142) or race/ethnicity (p=0.130). However, the frequency of pre-transplantation UTI was higher in the urological group (95.5%) than the nonurological group (20%) (p <0.001). This trend of UTI frequency persisted after transplantation as well (urological 54.5% vs nonurological 16.7%, p <0.001, table 1), with a median followup period of 10 (5-12) years. In the urological group the use of CIC before vs after transplantation was 15 (68.2%) and 4 (18.2%), respectively.

Table 1. *Clinical and demographic characteristics and outcomes*

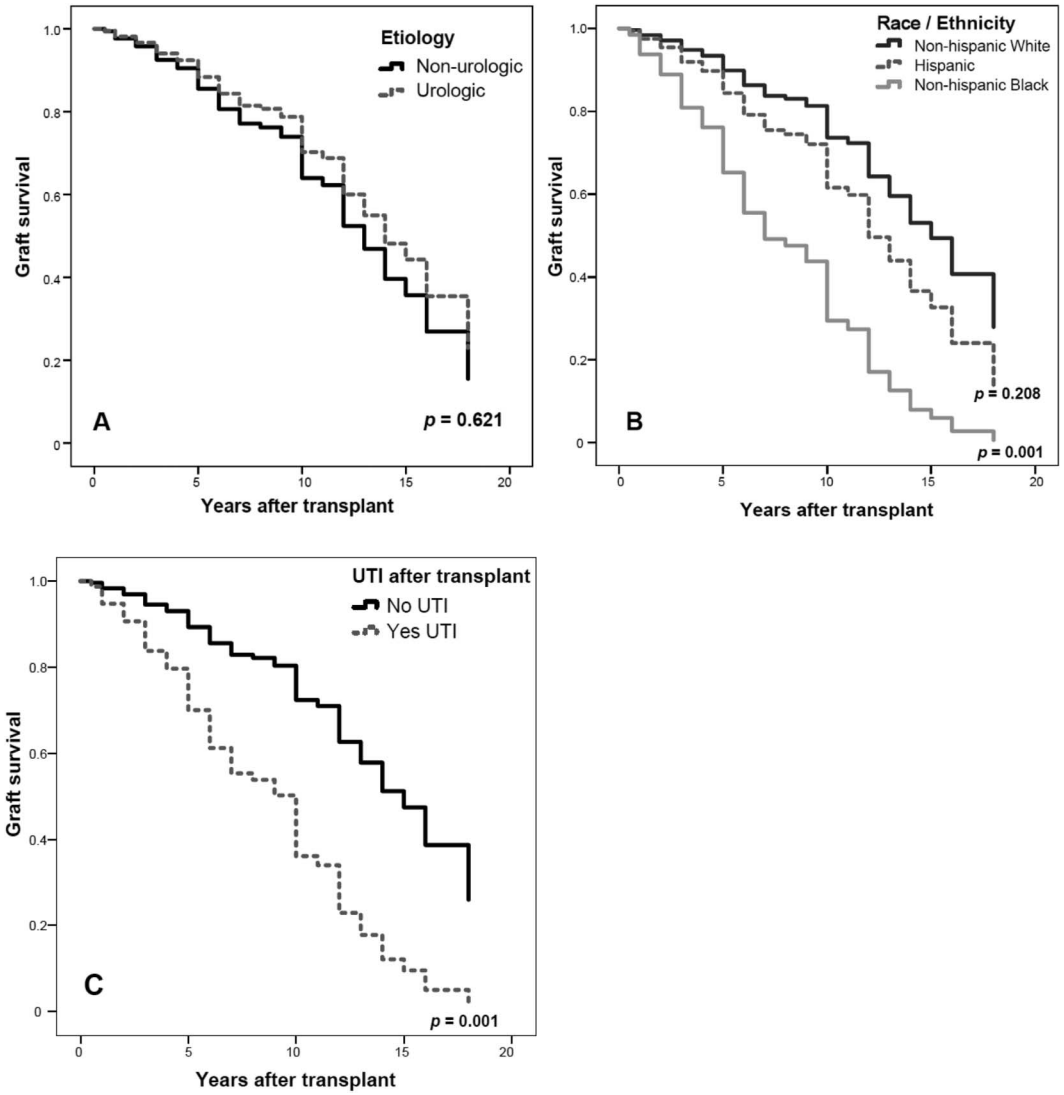
	Nonurological Etiology		Urological Etiology		p Value
No. female (%)	49	(54.4)	8	(36.4)	0.128
Median age at transplantation (IRQ)	12	(7–15)	11	(3.8–14.3)	0.300
No. race/ethnicity (%):					
NonHispanic white	28	(31.1)	7	(31.8)	
Hispanic	33	(36.7)	13	(59.1)	
NonHispanic black	27	(30)	2	(9.1)	
Asian	2	(2.2)	0		0.130
No. transplant type (%):					
LDKT	50	(55.6)	16	(72.7)	
DDKT	40	(44.4)	6	(27.3)	0.142
No. CIC (%):					
Before transplantation	0		15	(68.2)	-
After transplantation	1	(1.1)	4	(18.2)	-
UTI before transplantation:					
Median (IQR)	0	(0–0)	3	(1–5.3)	<0.001
Mean ± SD	0.5 ± 1.3		3.7 ± 2.8		
No. (%)	18	(20)	21	(95.5)	<0.001
UTI after transplantation:					
Median (IQR)	0	(0–0)	1	(0–2)	<0.001
Mean ± SD	0.5 ± 1.5		1.8 ± 2.9		
No. (%)	15	(16.7)	12	(54.5)	<0.001
Mean ± SD creatinine clearance:					
0	95.4 ± 30.4		105.6 ± 24.1		0.140
6 Mos	89.2 ± 27.3		85.7 ± 40.7		0.708
1 Yr*	76.5 ± 30		90.9 ± 20.9		0.035
2 Yrs†	76.4 ± 31.3		84.8 ± 20.6		0.134
3 Yrs‡	73.7 ± 30.7		73.5 ± 25.9		0.976
4 Yrs§	69.9 ± 31.2		80.6 ± 27.9		0.164
5 Yrs‖	65.9 ± 30.1		70.9 ± 29.8		0.511
No. death (%)	3	(3.3)	1	(4.5)	1.000
No. graft loss (%)	47	(52.2)	10	(45.5)	0.569
Median (IQR) yrs followup (range)	9 (5–12) (0.5–23)		10	(5–12) (3–18)	0.591

* Nonurological 89, urological 22.
† Nonurological 86, urological 22.
‡ Nonurological 83, urological 22.
§ Nonurological 79, urological 20.
‖ Nonurological 75, urological 20.

Many of the urological patients required additional surgical interventions before transplantation. The most frequent pre-transplantion procedures were valve ablation performed in patients with PUV, confirmed in 6 of 8 patients with PUV, and bilateral ureteral reimplantation performed in 2 patients with PUV and in 1 with reflux nephropathy. Three patients with bilateral UPJ obstruction underwent bilateral nephrostomy tube placement and 1 patient with bilateral UPJ obstruction underwent native nephroureterectomy. Only 1 patient with the diagnosis of NB underwent bladder augmentation. In the nonurological group the only procedure performed before transplantation was native nephroureterectomy (supplementary table 1, https://www.jurology.com).

The overall graft survival rate was 96% at 1 year (nonurological 96%, urological 100%), 80% at 5 years (nonurological 80%, urological 81%), 56% at 10 years (nonurological 52%, urological 71%) and 35% at 15 years (nonurological 32%, urological 49%) after transplantation. The overall median graft survival was 12 years (95% CI 10.20–13.80). After performing a multivariable adjusted risk analysis there was not a statistically significant increase in the risk of graft loss when analyzing etiologies leading to ESKD (urological etiology HR 0.79, 95% CI 0.31–2.01, p=0.621, part *A* of figure). Comparing race/ethnicity among all the patients with adjustment for multiple variables including etiology, nonHispanic black patients had a significantly higher risk of graft loss compared to nonHispanic white patients (HR 4.00, 95% CI 1.74–9.15, p=0.001, part *B* of figure). Patients with a documented UTI after transplantation had a significant risk of graft loss (HR 3.15, 95% CI 1.59–6.25, p=0.001, part *C* of figure). Interestingly, patients with a DDKT did not show an increased risk of graft loss compared to LDKT (HR 0.90, 95% CI 0.49–1.63, p=0.724, table 2). When analyzing the reason for graft loss the most common etiology was chronic allograft nephropathy and recurrent disease (50.9%), followed by poor medication adherence (24.6%) (table 3).

A subanalysis was performed to determine the variables associated with an increased risk of graft loss in the urological and nonurological groups. Although the incidence of UTI after transplantation in the nonurological group was lower, it was strongly associated with increased graft loss (HR 3.52, 95% CI 1.66–7.47, p=0.001). In contrast, in the urological group the diagnosis of UTI after transplantation demonstrated no association with increased graft loss (HR 1.35, 95% CI 0.19–9.69, p=0.764), nor did the use of CIC before or after transplantation



Adjusted survival curves for Cox proportional hazards model in overall cohort, including etiology leading to ESKD (*A*), recipient ethnicity/race (*B*) and UTI after transplantation (*C*).

(supplementary tables 2 and 3, https://www.jurology.com). When comparing the 18 patients with LUTD (PUV, NB and reflux nephropathy) to those with nonLUTD the rate of graft loss was not different between the 2 groups (nonLUTD 48 [51.1%] vs LUTD 9 [50%], p=0.934, supplementary tables 4-6, https://www.jurology.com). This analysis was repeated with the FSGS cases removed and yielded a similar percentage of graft loss for 26 nonLUTD cases (49.1%) vs 9 LUTD cases (50%) (p=0.945).

DISCUSSION

When comparing outcomes for children who underwent renal transplantation for nonurological vs urological etiologies, Hussein et al showed female gender and nonurological etiology of renal failure were associated with reduced complications and better long-term graft function.[5] Similar to our study their data set was comprised of 124 patients, with nonurological causes for 82 or 67% of their total population, with a mean age of 13 years for the nonurological group and 10 years of age for the urological group. In contrast our cohort, with a similar sample size and distribution, did not demonstrate a statistically significant difference in overall risk of graft loss according to etiology. This difference may be due to the active participation of the urology team in perioperative management in the urological patient group.

In a recent study of 103 patients, 29 urological (PUV, VUR, NB and prune belly syndrome) and 74 nonurological, undergoing transplantation, there was no statistically significant difference in function or graft survival between the groups at set intervals of followup and no graft was lost as a result of urological complications.[11]

Table 2. *Adjusted multivariable risk analysis (Cox regression, an adjusted analysis) for graft loss in all patients*

	HR	95% CI	p Value
Etiology:			
Nonurological	1		
Urological	0.79	0.31–2.01	0.621
Age at transplant (1 unit increased)	1.05	0.98–1.11	0.157
Gender:			
Female	1		
Male	1.07	0.61–1.90	0.816
Race/ethnicity:			
NonHispanic white	1		
Hispanic	1.59	0.77–3.25	0.208
NonHispanic black	4.00	1.74–9.15	0.001
Transplant type:			
LDKT	1		
DDKT	0.90	0.49–1.63	0.724
UTI before transplant:			
No	1		
Yes	0.70	0.33–1.50	0.362
UTI after transplant:			
No	1		
Yes	3.15	1.59–6.25	0.001

Similar to our findings, Nahas et al showed that 5-year graft survival rate was not significantly different in children with nonurological causes of ESKD compared to those with urological causes.[12] However, in their study all children with LUTD underwent bladder augmentation or urinary diversion. In a study by Otukesh et al lower urinary tract anomalies had no significant effect on graft survival in a set of 48 children with LUTD compared to 168 controls with normal lower urinary tract.[13]

It is crucial to manage LUTD appropriately before KT. Sufficient bladder capacity and compliance as well as appropriate drainage of the bladder are essential components for KT.[14] Additionally, patients with LUTD should be evaluated with videourodynamics and bladder ultrasound before KT.[12,14,15] We routinely evaluate our urological patients with videourodynamics and treat bladder dysfunction before KT to ensure a low pressure reservoir.

Table 3. *Etiology of graft loss*

	No. Overall (%)	No. Nonurological (%)	No. Urological (%)
Overall	57	47	10
Chronic allograft nephropathy	29 (50.9)	24 (51.1)	5 (50)
Poor medication compliance (nonadherence)	14 (24.6)	11 (23.4)	3 (30)
Acute T cell mediated rejection	4 (7)	3 (6.4)	0
Recurrent FSGS	4 (7)	4 (8.5)	0
Acute antibody mediated rejection	3 (5.3)	3 (6.4)	0
Chronic transplant glomerulopathy	1 (1.7)	0	1 (10)
Severe ureterovesical junction obstruction	1 (1.8)	0	1 (10)
Early post-transplant lymphoproliferative disease	1 (1.8)	1 (2.1)	0
Reflux nephropathy	1 (1.8)	1 (2.1)	0

The unexpected finding of no significant difference in graft survival in the LDKT and DDKT groups is difficult to explain but may be influenced by the small sample size. Previous studies in the adult population have predominately shown LDKT to have improved graft survival compared to DDKT[16] with similar findings demonstrated in the pediatric population.[17,18]

Our results indicated a higher risk of graft loss in nonHispanic black patients compared to nonHispanic white patients. These results are consistent with prior data demonstrating ethnicity/race as a significant factor in graft survival. Survival analysis of renal transplantation in the adult population assessed variables of related, unrelated and deceased donors showing improved graft survival in white vs black recipients for all categories.[19] A previous study performed at our center indicated an overall poor renal graft survival time in African American children, attributed partly to low socioeconomic status in the AA group as well as the increased likelihood of receiving a deceased donor allograft.[10] However, certain biological factors in the AA population might have a key role in increasing the risk of graft loss. Brown et al further suggested this by demonstrating that the increased incidence of acute rejection, cytomegalovirus infection and FSGS may account for a significantly higher fraction of renal graft loss in the AA population.[20] In a study by Hardy et al nonadherence was higher in adolescents and teens than in younger children and this difference was more pronounced in AA recipients than other groups.[21]

Patients who undergo renal transplantation have an inherently higher risk of UTI due to underlying urological abnormalities, immunosuppression, placement of stents and other manipulations of the urinary tract. UTI after transplantation may affect "long-term graft survival due to scarring and interstitial injury."[22] In our cohort the incidence of UTI before and after transplantation was significantly higher in the urological group. However, in the subanalysis a negative outcome for graft survival was observed only in the presence of UTI after transplantation in the nonurological population. This finding may be due to more frequent use of daily antibiotic prophylaxis in the urological population. Our results are consistent with those reported by Herthelius and Oborn that graft function deteriorated at a faster rate in pediatric posttransplant patients with recurrent UTI compared to those with a single UTI or no UTI.[23] Saad et al found that the incidence of UTI was higher in patients with LUTD.[11] In contrast to our results Nahas[12] and Pereira[14] et al demonstrated that although UTI is more common in patients with LUTD, their long-term graft function is similar to

that of other patients with a normal lower urinary tract. Nevertheless, patients with recurrent UTI after KT should be evaluated for VUR, stones and urinary retention.[24]

Despite the long followup the present study is not without limitations, including a limited sample size and an inherent lack of randomization. Additional data points of transplant ischemia time, postoperative complications, immunosuppressive therapies and the use of prophylactic antibiotics to prevent UTI after transplantation were not included in the analysis. We recognize that due to the relatively long span of the study, some aspects of renal transplantation perioperative management and medication regimens may evolve over the years due to advancements and changes in standards of care. There were many challenges with data collection, specifically the medical record for the older transplant cases, possibly due to conversion from paper charts to electronic medical record. The results of the urodynamic studies were not available in the electronic medical record. In addition, the subanalysis was underpowered due to the relatively small sample size of the subgroups. However, while this is statistically underpowered, we thought this was a valuable component as UPJ obstruction would have no bearing on this aspect of transplantation. Additionally, these results are similar to the urological group as a whole and, as such, we thought important to include.

CONCLUSION

Children requiring transplantation due to nonurological etiologies appear to have similar graft failure rates as children with underlying urological etiologies. NonHispanic black patients have a reduced graft survival time. Patients with UTI after transplantation have a higher rate of graft loss. However, this risk was most evident in the nonurological group despite higher rates of UTI in the urological group. While many factors may have a role in allograft survival, including etiology, medication adherence, ischemia time and LDKT vs DDKT, additional studies with larger sample sizes are required to assess these differences.

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EDITORIAL COMMENTS

Having been actively involved in renal transplantation for the last 30 years, an underlying message with nonurological transplant team members is that pediatric urology patients or those with lower urinary tract dysfunction do not fare as well as nonurological patients. However, because of my involvement with extensive preoperative and postoperative management in patients with LUTD, the programs that I have been involved in have not seen worse outcomes in our urological patients. In fact, an internal review conducted just before I left a transplant program that I was involved in for 20 years demonstrated that patients with LUTD had improved 1 and 5-year graft survival compared to nonurological patients (unpublished data). My failure to publish these data has increased my support of the current study.

The authors present an excellent study demonstrating success in pediatric urological patients with lower urinary tract dysfunction. Those programs with active involvement by pediatric urology need to continue to champion this message. It is my hypothesis that when pediatric urology is closely intertwined in a pediatric transplant program, improved outcomes for patients with LUTD would be obtained. I challenge these authors, as well as our own leadership in pediatric urology, to further expand on these findings by developing a white paper that would set the gold standard evaluation and followup for all pediatric urology patients undergoing renal transplantation and further debunk the myth that pediatric urology patients do not fare as well as nonurology patients.

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The authors report on long-term outcomes from a busy transplant center, describing similar graft survival statistics in pediatric patients with different underlying conditions (ie urological vs nonurological abnormalities). Although somewhat disadvantaged by relatively small numbers, lack of adjustment for important covariates and retrospective study design, this study provides reassuring information. To maintain these outcomes urologists should remain critical members of the transplant team, tasked with multiple aspects of care including interventions to ensure optimal lower urinary tract function and reconstruction.[1]

A renal allograft is an invaluable gift and every effort should be made to maximize its survival. This is important for all transplant recipients, but perhaps more so for younger individuals who face the high probability of requiring dialysis or a second transplant at some point down the road. Thus, strategies to mitigate chronic rejection and primary disease recurrence are among the top priorities. Thankfully, advances in organ preservation, immunosuppressive protocols, perioperative and postoperative care, and surgical technique promise a progressively more favorable outlook for our pediatric and adolescent patients.[2]

Multiple insults to the allograft can have devastating long-term consequences. This study also reminds us that urinary tract infections are important culprits in avoidable allograft damage. Along with addressing issues related to medication adherence, prevention and early treatment of infections are paramount to our goal. Similarly, we are reminded that ethnicity and socioeconomic differences impact renal replacement therapies.[3] A better understanding of how these factors influence organ survival is bound to help us implement more individualized preemptive interventions.

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