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Urinary Tract Infections in Children with Kidney Allografts: Risk Factors and Clinical Consequences

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Urinary Tract Infections in Children with Kidney Allografts: Risk Factors and Clinical Consequences

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ABSTRACT

Kidney transplantation is the optimal treatment for children with end stage renal disease (ESRD). Urinary tract infections (UTIs) are the most common bacterial infection post-kidney transplant and are a significant cause of morbidity in this population. Pediatric patients are at increased risk of UTIs due to the etiology of their ESRD. The morbidity of UTIs and their impact on long-term allograft survival has not been studied.

We conducted a retrospective cohort analysis and record review of pediatric kidney transplant recipients to investigate three main aims: determine risk factors for recurrent UTIs; assess the effect of recurrent UTIs on kidney transplant outcomes; and determine the rate of hospitalizations and frequency of AKI secondary to UTI. Inclusion criteria included receiving a kidney transplant at our pediatric tertiary referral center between 2006 and 2016. Patients with less than one year of documented follow-up were excluded. There were 262 eligible patients. Data was collected up to two years following the date of transplantation.

The median age at transplantation for these patients was 12.4 years (interquartile range: 6.5 – 15.8). Thirty patients (11.6%) had recurrent UTIs in the first year post-transplant and 18 (7.5%) had recurrent UTIs in the second year post-transplant. Thirty-eight patients (14.5%) had recurrent UTIs in the two years post-transplant. When comparing patients with obstructive uropathy to patients with glomerular disease, the estimated odds ratio to develop recurrent UTIs in the first or second year post-transplant was 5.6.

Patients with recurrent UTIs during the first year post-transplant had a greater decrease in eGFR than patients without recurrent UTIs (-19.8 vs -1.0 mL/min/1.73 m^2). Of the 60 patients with obstructive uropathy, the hospitalization rate was 0.4 compared to 0.2 among the 202 patients without obstructive uropathy, yielding a rate ratio of 2.7 (CI: 1.5 – 4.8, p-value: 0.0005). AKI was associated with UTI in 19 patients (7.3%) during the first two years post-transplant.

In pediatric kidney transplant recipients, recurrent UTIs cause significant morbidity and are associated with loss of kidney function. Additional prospective studies are needed to further understand this association and develop strategies for decreasing the morbidity from recurrent UTIs in this patient population.

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INTRODUCTION

Children with end stage renal disease (ESRD) can be managed with dialysis or kidney transplantation. Kidney transplantation decreases morbidity and mortality, and improves quality of life compared to dialysis and is considered the preferred treatment for children with ESRD.(1)

Unfortunately, kidney allografts have a limited lifespan due to acute and chronic rejection and other complications, including infections. Children with kidney transplants are at increased risk for urinary tract infections (UTIs). However, there is limited information on risk factors for UTIs, the morbidity of UTIs, and the impact of UTIs on allograft lifespan.

Our goals were to study children with kidney allografts and determine risk factors for recurrent UTIs, describe the morbidity of UTIs, and determine if UTIs are associated with impaired graft function. We conducted a retrospective study of children who received a kidney transplant at Children's Healthcare of Atlanta (CHOA) between 2006 and 2016. We recorded patient demographics, pre-transplant history and transplant outcomes, including UTIs and allograft function. Our central hypothesis was that children with a history of obstructive uropathy or bladder dysfunction have an increased incidence of recurrent UTIs.

The rationale for this research was that identifying pediatric kidney transplant recipients at increased risk for recurrent UTIs, morbidity from UTIs, and accelerated graft loss would identify opportunities for implementation of interventions to improve outcomes. The large cohort of patients at a single center enabled us to address our research question.

BACKGROUND

Kidney transplantation is considered the optimal treatment for pediatric patients with ESRD, as it provides improved quality of life and decreased mortality when compared to dialysis.(2) Since the first pediatric kidney transplant in the 1960s, there have been major advances in immunosuppression, surgical technique, and medical management of transplant patients, resulting in improved kidney function and patient survival.(3) However, urological complications post-kidney transplant remain a significant cause of morbidity, with a reported prevalence that ranges from 2.5% to 35%.(4, 5) The most common urologic complications post-kidney transplant are lymphocele formation, vesicoureteral reflux, UTIs, anastomotic leakage, and ureteral obstruction.(4)

UTIs are recognized as the most common bacterial infection in the immediate post-transplant period, occurring in 32% of pediatric kidney transplant recipients in one study.(6) UTIs commonly occur in patients with lower urinary tract dysfunction and are a leading cause of hospitalization in the pediatric kidney transplant population.(7) This is particularly worrisome since these patients are immunosuppressed and are at greater risk for disseminated infections that could be life threatening, especially since glucocorticoid exposure may diminish their ability to produce stress steroids. Infection was cited as the cause of death in 24-56% of patients post-transplant and remains the leading cause of death in this patient population.(1)

Significant risk factors for developing UTIs in this patient population include a younger age at transplantation, urological causes of renal failure, indwelling catheters and stents, and history of pre-transplant UTI.(7, 8) The occurrence of pre-transplant UTI is

higher in patients with congenital anomalies of the kidney and urinary tract (CAKUT). This is likely secondary to chronic bacterial colonization and introduction of bacteria through clean intermittent catheterization. The increased risk in patients with CAKUT is especially relevant in children since CAKUT is the etiology of ESRD in over 50% of children who receive a kidney transplant.(9) Obstructive uropathy and reflux nephropathy are two of the most common causes of ESRD in children.

The microorganisms that most frequently cause UTIs in children with kidney transplants are *E. coli, Enterococcus, Staphylococcus, Klebsiella, Proteus,* and *Enterobacter or Micrococcus luteus*.(8) Although *E.coli* is the most commonly isolated organism in post-transplant UTIs, it is a less common etiology than in the general pediatric population.(1) Pyelonephritis can result in kidney transplant damage secondary to scarring. Prompt diagnosis and treatment of UTIs can decrease morbidity and preserve long term kidney transplant function. However, prompt diagnosis in an immunocompromised population is challenging secondary to delay in presentation and detection.(6)

Transplant recipients are also at risk to develop complicated or recurrent UTIs due to their chronic immunosuppressed state from anti-rejection medications. Retrospective analyses suggest that symptomatic UTIs occur in 20-60% of pediatric kidney transplant recipients following transplantation.(10) Mueller et al. demonstrated a transient decrease in kidney transplant function post UTI, but the long-term effect of post-transplant UTIs has not yet been fully elucidated.(6)

Although case reports, literature reviews, and retrospective analyses have described the prevalence, some risk factors, and causative organisms of UTIs in the

pediatric kidney transplant population, the impact of recurrent UTIs on long-term graft function has not been well studied.(8) The majority of investigations focusing on post-transplant UTI have concentrated on adults and previous pediatric investigations have studied the occurrence of UTIs.(6) To our knowledge, there is no existing literature that addresses risk factors for recurrent UTIs, which has the potential to be more clinically relevant since these patients are potential targets for interventions. Consequently, it is important to investigate risk factors and long-term sequelae of recurrent UTIs in this population.

It is important to note that there is no universal definition for UTI in children. There remains controversy, as many patients who develop recurrent UTIs may also develop bacterial colonization. In our study, we defined a UTI when a patient had symptoms consistent with a UTI, a positive urine culture, and received antibiotic treatment for the UTI. As our target population is at increased risk to develop multiple infections, we specifically aimed to investigate the effect that repeated UTIs had on pediatric patients post kidney-transplant. We defined recurrent UTIs as two or more symptomatic UTIs occurring within one year, excluding UTIs that occurred while the patient still had a post-transplant stent or catheter in place.

METHODS

This study had three aims and associated hypotheses:

- Aim 1: Determine risk factors for recurrent urinary tract infections (UTIs) in pediatric kidney transplant recipients.
    - Hypothesis: A history of obstructive uropathy or bladder dysfunction increases the risk of recurrent UTIs in pediatric kidney transplant recipients.
- Aim 2: Compare graft function, using estimated glomerular filtration rate (eGFR), in pediatric kidney transplant recipients with and without recurrent UTIs.
    - Hypothesis: Patients with recurrent UTIs would have a greater loss of kidney function compared to patients without recurrent UTI.
- Aim 3: Compare the frequency of hospitalizations and acute kidney injury (AKI) due to UTI between patients with and without a history of obstructive uropathy.
    - Hypothesis: A history of obstructive uropathy or bladder dysfunction increases the risk of hospitalization and acute kidney injury secondary to UTI in pediatric kidney transplant recipients.

To address these aims, we conducted a retrospective cohort analysis of pediatric kidney transplant recipients followed at Children's Healthcare of Atlanta (CHOA), a large tertiary pediatric referral center. Inclusion criteria included receiving a renal transplant at CHOA between 2006 and 2016. Exclusion criteria consisted of having less than one year of documented follow-up at CHOA. During the study period (from 2006-2016), 299 pediatric kidney transplant recipients were transplanted at CHOA. Since 37

patients (12.4%) were excluded due to inadequate follow-up, 262 patients were included in our study.

This study was approved by the Institutional Review Board (IRB) of CHOA (IRB #17-013). The data obtained for this study is presented in **Table 1.** Data was collected up to two years following the date of transplantation. Data was entered into a HIPAA secure, online REDCAP database, and all analyses were conducted using SAS version 9.4 and RStudio version 1.0.153.

The outcomes for the first aim were the development of recurrent UTIs in the first year post-transplant, the development of recurrent UTIs in the second year post-transplant, and the development of recurrent UTIs overall in the first two years post-transplant. Each outcome was dichotomous and was measured separately for each year using logistic regression. Covariates were included based on clinical judgment and prior literature and included the following: patient age at transplantation, race, ethnicity, and etiology of ESRD. ESRD etiology was assessed as the predictor of the outcome and was separated into three groups: glomerular disease, non-glomerular disease without obstructive uropathy, and non-glomerular disease with obstructive uropathy.

Descriptive statistics summarizing outcomes, covariates, and predictors were reported. Numeric variables were reported with a mean, standard deviation, and range. Nominal and ordinal variables were reported using frequency percentages. The development of recurrent UTI was presented with histograms, stratified by age. In regards to inferential statistics, we performed univariate and multivariate regression on both outcomes of this aim. The outcome was modeled three ways: recurrent UTI development in the first year post-transplant, recurrent UTI development in the second

year post-transplant, and recurrent UTI development in the first two years post-transplant. The multivariate model is shown below:

MODEL: ODDS of Recurrent UTI = EXP(B_0 + B_1(Non Glomerular disease) + B_2(Obstructive Uropathy) + B_3(Age: <6 years) + B_4(Age: > 12 years) + B_5(Gender) + B_6(Black) + B_7(Other Race) + B_8(Ethnicity))

For this model, our exposure of interest, etiology of ESRD, had 3 levels: glomerular disease (reference), non-glomerular disease without obstructive uropathy, and non-glomerular disease with obstructive uropathy. For race, our reference group was Caucasian/White. We analyzed age as a categorical variable with 3 levels: < 6 years, 6-12 years, > 12 years (reference). Odds ratios, confidence intervals, and corresponding p-values were reported for each univariate analysis and multivariate model.

This study was designed to have adequate power to detect a difference in the proportion of patients having recurrent UTI stratified broadly by etiology of ESRD. From clinical literature, we assumed 30% (79) of the 262 patients should have a history of obstructive uropathy or bladder dysfunction. Also from the literature, we conservatively estimated a recurrent UTI rate of 15% for patients with obstructive uropathy or bladder dysfunction and 3% for patients without obstructive uropathy or bladder dysfunction. With an alpha of 0.05, the study had a 90% power to detect a difference between these study populations using a two sample two-sided test of proportions.

AIM 2 – The outcome for this aim was loss of kidney function, measured using eGFR, which is the standard approach for describing level of kidney function. eGFR was calculated using the modified Schwartz formula:

Modified Schwartz formula:
eGFR (mL/min/1.73m^2) = 0.413 * Height(cm) / Serum Creatinine(mg/dL)

eGFR was calculated at 1 month, 12 months, and 24 months post-transplant, as these time points occurred at routine post-transplant visits where laboratory monitoring was performed. Descriptive statistics summarizing the outcome were reported. A mean, standard deviation, and range were reported at each time point. A mean, standard deviation, and range were also reported for the change in eGFR between each time point. The exposure of interest was development of recurrent UTIs during the follow-up period. The eGFR values among all patients were stratified into groups with and without a history of recurrent UTI respectively. A two-sample t-test was used to compare differences in change of mean eGFR between these two groups between 1 month and 12 months and 12 months and 24 months post-transplant. The difference in the change of mean eGFR and corresponding t-test statistic and p-value for each analysis was reported.

To account for differing baseline eGFR in the patient population, an analysis of covariance (ANCOVA) was performed comparing the difference between eGFR in patients with and without a history of recurrent UTI from 1 month to 12 months post-transplant. An ANCOVA was also performed comparing the difference between eGFR in patients in these two groups between 12 months and 24 months post-transplant. ANCOVA results were reported in table form and also plotted with axes comparing the change in eGFR between pertinent time points. A p-value reflecting difference in 12 month post-transplant eGFR and 24 month post-transplant eGFR was reported, controlling for differences in baseline eGFR.

AIM 3 – The outcomes for this aim were the number of hospitalizations and episodes of acute kidney injury secondary to UTI. Acute kidney injury (AKI) was defined by the pediatric risk, injury, failure, loss, end stage renal disease (pRIFLE) criteria as an

increase in serum creatinine by 50% from the patient's baseline creatinine level.(11) Each outcome was dichotomous and was measured separately. We only recorded AKI data on patients who were hospitalized secondary to UTI. As such, the patients with AKI were a subset of hospitalized patients. To assess the outcome of AKI, patients were grouped by etiology of ESRD. As in Aim 1, etiology of ESRD was separated into three groups: glomerular disease (1), non-glomerular disease without obstructive uropathy (2), and non-glomerular disease with obstructive uropathy (3).

The number of hospitalizations and the number of AKI episodes were recorded for two years following transplant. Descriptive statistics summarizing outcome and predictors were reported. Numeric variables were reported with a mean, standard deviation, and range. Nominal and ordinal variables were reported using frequency percentages. The number of hospitalizations secondary to UTI was presented with histograms for each etiology of ESRD.

To compare the rate of hospitalizations by etiology of ESRD, a Poisson regression was used to estimate the rate ratio comparing patients with obstructive uropathy or bladder dysfunction to patients without obstructive uropathy or bladder dysfunction. We also compared the proportion of AKI occurrence in patients with glomerular disease, non-glomerular disease without obstructive uropathy, and non-glomerular disease with obstructive uropathy and performed a Pearson's Chi square test to assess whether the proportions were different.

RESULTS

This study followed 262 pediatric patients for one-year post-kidney transplant, of which 240 patients were followed for two years. Based on the exclusion criteria, no patients included in the study were lost to follow-up in the first 12 months post-transplant. However, in the period between 12 months and 24 months post-transplant, 22 of 262 patients (8.4%) were lost to follow-up. The majority of these patients were lost to follow-up due to receiving care in another state post-transplant. Hence, we made the assumption that these patients would not have differing outcomes compared to patients not lost to follow-up and analyzed the dataset using complete case analysis.

Table 2 presents demographic data and clinical characteristics of our study population. The median age at transplantation for these patients was 12.4 years (interquartile range: 6.5 – 15.8). At time of transplantation, 23.7% were less than 6 years old, 23.7% were between 6 and 12 years old, and 52.6% of patients were > 12 years old. 62.2% of patients were male. The etiologies of ESRD were glomerular disease in 92 patients (35.1%), non-glomerular disease without obstructive uropathy in110 patients (42.0%) and non-glomerular disease with obstructive uropathy in 60 patients (22.9%). Thirty (11.6%) developed recurrent UTI in the first year post-transplant and 18 (7.5%) developed recurrent UTI in the second year post-transplant, and thirty-eight patients (14.5%) developed recurrent UTI in both years one and two post-transplant. Mean eGFR trended downwards during the two years post-transplanted, from 73.0 ± 30 to 66.2 ± 27.7 mL/min/1.73m^2.

Figure 1 demonstrates histograms of the age at transplantation for patients with recurrent UTI in the first and second year post-transplant. Fifty percent of patients who

developed recurrent UTIs were between two and six years old, and 22% of patients who developed recurrent UTIs were between fourteen and eighteen years old. As such, we stratified age into three categories: less than six years old, six - twelve years old, and greater than twelve years old in analyses.

For Aim 1, **Table 3** presents the univariate logistic regression for the outcome of recurrent UTI in the first year post-transplant. Obstructive uropathy was estimated to increase the odds of recurrent UTI development by a factor of 5.3 compared to patients with glomerular disease (CI: 1.8 – 15.6; p-value: 0.001). Non-glomerular disease without obstructive uropathy was estimated to increase the odds by a factor of 1.9 compared to patients with glomerular disease (CI: 0.6 – 5.8; p-value: 0.7). **Table 4** presents the multivariate logistic regression for the same outcome. Both history of obstructive uropathy and age at transplantation remain significant in this multivariate regression. **Table 5** presents the univariate logistic regression for the outcome of recurrent UTI in the second year post-transplant. Patient race did not converge in this model and as such, maximum likelihood estimates could not be obtained. **Table 6** presents the multivariate logistic regression for the outcome of recurrent UTI in the second year post-transplant. The results remain similar compared to the first year outcomes. However, it should be noted that in the multivariate analysis for the second year outcome, female gender was estimated to increase the odds of recurrent UTI development by a factor of 5.4 (CI: 1.3 - 22.9; p-value: 0.02). **Table 7** and **Table 8** present the univariate and multivariate logistic regression, respectively, for the outcome of recurrent UTI in either first or second year post-transplant and present similar results, with obstructive uropathy and age remaining significant.

For Aim 2, **Table 9** presents the change in eGFR in the first two years post-transplant, comparing patients with and without recurrent UTI development. The mean eGFR in patients with recurrent UTI decreased more compared to the mean eGFR in patients without recurrent UTI in the first year post-transplant (-19.8 ± 33.9 vs. -1.0 ± 24.6mL/min/1.73m^2; p-value: 0.005). This was not observed in the second year post-transplant (-7.0 ± 24.0 vs. -4.7 ± 16.9mL/min/1.73m^2; p-value: 0.7). When performing the same comparison investigating during the first two years post-transplant combined, a significant decrease in mean eGFR was observed in patients with recurrent UTI development (-19.1 ± 28.4 vs. -6.3 ± 28.0mL/min/m^2; p-value: 0.02).

Figure 2 and **Figure 3** present the results from the ANCOVA analyses in the first and second year post-transplant respectively. In the ANCOVA analyses, which adjust for baseline differences in eGFR, patients with recurrent UTI in the first year post-transplant had a significantly lower eGFR at 12 months compared to patients without recurrent UTI in the first year post-transplant (Figure 2). However, patients with recurrent UTI in the second year post-transplant did not have a significantly different eGFR at 24 months post-transplant compared to patients without recurrent UTI in the second year post-transplant (Figure 3).

For Aim 3, **Figure 4** presents histograms of the number of hospitalizations secondary to UTI in patients, stratified by etiology of ESRD. This included repeated hospitalizations if the patients were hospitalized for than once during the follow-up period. Patients with history of obstructive uropathy had increased hospitalizations compared to the other two etiologies of ESRD. **Table 10** demonstrates results of a Poisson Regression comparing the rate of hospitalizations, presenting etiology of ESRD

as the exposure of interest. In the analyses, patients with obstructive uropathy were directly compared to patients without obstructive uropathy. Of the 60 patients with obstructive uropathy, the hospitalization rate was 0.42 compared to 0.15 among the 202 patients without obstructive uropathy, yielding a rate ratio of 2.7 (CI: 1.5 – 4.8, p-value: 0.0005).

Table 11 presents AKI frequency secondary to UTI for the first two years post-transplant, stratified by etiology of ESRD. As mentioned previously, we only collected AKI data during the time of a UTI. Nineteen of 262 patients (7.3%) developed AKI. Fifteen percent of patients with obstructive uropathy developed AKI secondary to UTI compared to 6.5% of patients with glomerular disease and 3.6% of patients with non-glomerular disease without obstructive uropathy. A Pearson's chi square test analysis demonstrated that patients of obstructive uropathy developed AKI secondary to UTI more frequently (Chi square statistic: 6.9; p-value: 0.008).

DISCUSSION

Children with end stage renal disease (ESRD) can be managed with dialysis or kidney transplantation. However, mortality is increased and quality of life is decreased for children managed with dialysis.(12) Therefore, kidney transplantation is considered the preferred treatment for children with ESRD.

Infections are the most common cause of mortality post-transplant.(1) UTIs are the most common bacterial infection post-kidney transplant and are a significant cause of morbidity in this population. Pediatric patients are at increased risk of UTIs due to the etiology of their ESRD. Previous literature is inconclusive regarding the long term effects of UTIs on transplant function.(10) Our goals for this investigation in children with kidney allografts were to determine the risk factors for recurrent UTIs, describe the morbidity of recurrent UTIs, and determine if recurrent UTIs are associated with decreased eGFR in the post-transplant period.

Recurrent UTIs occurred in 14.5% of our patients. In the literature, UTIs were reported in 17-38% of children following renal transplant (8, 13), and there are no prior studies describing the risk of recurrent UTIs. It should also be pointed out that we intentionally excluded UTIs that occurred while the post-transplant catheter was in place, as the post-transplant instrumentation was a likely cause of these isolated infections, and the aim of our investigation was to investigate the long-term effects of recurrent UTIs.

Urological anomalies increase the risk of UTI development in children without transplantation, but little data has been published specifically looking at pediatric kidney transplant recipients.(10) Hogan *et al*. determined several risk factors for UTI in this population: female sex, presence of uropathy, prolonged cold ischemia time, and

cyclosporine as first calcineurin inhibitor used post-operatively.(14) Our findings also support that etiology of kidney failure (obstructive uropathy) significantly increases the risk of recurrent UTI. Obstructive uropathy remained significant in all univariate and multivariate analyses for multiple outcomes: development of recurrent UTI in first year post-transplant, development of recurrent UTI in second year post-transplant, and development of recurrent UTI overall in first two years post-transplant. This result is of increased importance since obstructive uropathy is a common cause of ESRD in the pediatric population.(15)

Age less than 6 years also remained significant in all univariate and multivariate regression analyses. We chose to stratify age into sub-groups, as there was an increased frequency of recurrent UTI development noted in the younger age group. Our analyses demonstrated that a younger age at transplantation increases the risk of recurrent UTI development.

From our data, the eGFR decreased significantly more during the first year post-transplant in patients with recurrent UTIs compared to patients without recurrent UTIs (19.8mL/min/1.73m^2 decrease vs. 1.0mL/min/1.73m^2 decrease; p-value: 0.005). The change in eGFR during the second year post-transplant was not significantly different in patients with or without recurrent UTIs that developed during the second year post-transplant. However, when looking at the first two combined, the eGFR decreased significantly over the first 24 months post-transplant (19.1mL/min/1.73m^2 decrease vs. 6.3mL/min/1.73m^2 decrease, p value: 0.02). Overall, this is suggestive of long-term kidney transplant morbidity secondary to recurrent UTI, the development of which may be secondary to obstructive uropathy. This is significant, as there is a paucity of data in

the literature regarding the long term, detrimental affects of recurrent UTIs in this patient population.

A recent study by Alkandri *et al.* demonstrated that AKI post-kidney transplant is common, occurring in 30% of pediatric kidney transplant recipients.(16) We demonstrated that the frequency of AKI and rate of hospitalizations secondary to UTI were significantly different between patients with different etiologies of kidney failure. Specifically, 15% of patients with obstructive uropathy developed AKI in association with UTI, which was a larger percentage when compared to patients with other etiologies of kidney failure (6.5% in patients with glomerular disease and 3.6% in patients with non-glomerular disease). This increased frequency of AKI is significant, as AKI has been known to be associated with increased morbidity and mortality in adults and children.(16) Specifically, there is an increased risk of graft failure in patients who develop AKI.(16) In addition, our data demonstrated that the rate of hospitalization secondary to UTI was higher in patients with obstructive uropathy (0.42) compared to patients without obstructive uropathy (0.15), yielding a rate ratio of 2.7.

In summary, our investigation demonstrated that patients with obstructive uropathy have an increased risk of recurrent UTI, recurrent UTI is associated with a decrease in eGFR during the first two years post-transplant, and that patients with obstructive uropathy are at increased risk for hospitalization and AKI secondary to UTI.

The strengths of this study include the investigation of a novel outcome (recurrent UTI). Utilization of the outcome of recurrent UTI enabled us to analyze the effect over time of UTIs on kidney transplant function, which is arguably more clinically relevant than investigating a single instance of infection. In addition, we had access to a large

pediatric cohort, which provided adequate power for these analyses. As this investigation was conducted as a detailed record review, we were able to capture information that may have been unavailable in studies using large, multicenter databases. Lastly, our investigation was the first pediatric investigation showing an association between UTI development and eGFR decline in relatively long-term follow-up.

Limitations of the study include a small sample size with respect to the number of patients with recurrent UTIs, especially in the second year post-transplant. Due to the retrospective nature of the study and utilization of secondary data, not all factors and possible confounders were realistic to assess (i.e. cold ischemia time, more frequent eGFR trending etc.). It is also important to note that there is no universal definition of UTI. The definition that we utilized may be provider dependent and thus may have led to bias in the analyses.

In conclusion, there is a need to understand the risk factors and consequences of UTIs in pediatric kidney transplant recipients so that targeted interventions can be implemented to improve the outcome of this vulnerable patient population. Our investigation further elucidated the morbidity of recurrent UTIs. We demonstrated that obstructive uropathy increases the risk for recurrent UTI in pediatric kidney transplant recipients, that there is loss of kidney function in patients with recurrent UTI, and that obstructive uropathy is associated with increased rates hospitalization and AKI due to UTI. Future studies should provide an extended evaluation of the long-term consequences of recurrent UTI in the pediatric kidney transplant population. Additional investigation into possible interventions and prophylaxis therapy in this patient population may improve outcomes.

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Table 1. Data collected (using standard measurements).

Patient Demographics	Gender
	Race, Ethnicity
	Date of birth
Medical History	Etiology of end stage renal disease: -Glomerular disease -Non-glomerular disease without obstructive uropathy -Non-glomerular disease with obstructive uropathy
	Urologic History: -Number of prior urologic operations
	Transplant history: -date of transplant -type of donor (living or deceased) -eventual failure (Yes/No)
Post-transplant history	Date of stent removal
	Development of UTI* (Yes/No) and name of causal organism(s)
	Resistance profile of causal organism for UTI
	UTI prophylactic regimen (name of antibiotic, dates of regimen)
	Date of native nephrectomy if undergone
Kidney function	eGFR** (calculated using modified Schwartz formula) post-transplant at: -1 month -12 months -24 months

*UTI = urinary tract infection.
**eGFR = estimated glomerular filtration rate

Table 2. Demographic Information and Clinical Characteristics of Pediatric Kidney Transplant Recipients, 2006-2016 (total n=262).

Characteristic	**N (%)**	**Mean ± std. deviation (range)**
Patient age at transplant (years)	262	11.3 ± 5.4 (1.6 – 21.3)
Patient age:	262	
Age < 6 years	62 (23.7%)	
Age 6-12 years	62 (23.7%)	
Age > 12 years	138 (52.6%)	
Gender (male)	163 (62.2%)	
Race:	**262**	
-White	143 (54.6%)	
-Black	102 (38.9%)	
-Other	17 (6.5%)	
Ethnicity:	**262**	
-Hispanic/Latino	43 (16.4%)	
-Non-Hispanic/Latino	219 (83.6%)	
Etiology of ESRD:	**262**	
-Glomerular disease	92 (35.1%)	
-Non-glomerular disease w/out obstructive uropathy	110 (42.0%)	
-Non-glomerular disease w/ obstructive uropathy	60 (22.9%)	
Type of Donor:	**262**	
-Living	106 (40.5%)	
-Deceased	153 (58.4%)	
-Deceased (paired)	3 (1.2%)	
Mean UTI post-tx:	262	1.3 ± 2.8 (0 – 16)
Recurrent UTI*:		
-Overall	38 of 262 (14.5%)	
-Year 1 post-tx	30 of 262 (11.6%)	
-Year 2 post-tx	18 of 240 (7.5%)	
eGFR (mL/min/1.73 m²):		
-1 month post-tx	262	73.0 ± 30.0 (4.9 – 190.0)
-12 months post-tx	262	69.7 ± 24.5 (4.1 – 159.1)
-24 months post-tx	240	66.2 ± 27.7 (4.9 – 202.6)
Number of prior Urologic Operations	262	0.8 ± 1.1 (0 – 7)
VCUG prior to transplant (Yes)**	93 (35.6%)	
Started on UTI PPX (Yes)	52 (19.9%)	

*Recurrent UTI is defined as two or more symptomatic UTIs occurring within 1 year, excluding UTIs that occur while the patient still has a post-transplant stent or catheter in place.
**VCUG = voiding cystourethrogram.

Table 3. Risk Factors for Recurrent UTI in First Year Post-Kidney Transplant, Univariate Analyses.

Characteristic	N	Odds Ratio	95% Confidence Interval	P-value
Etiology of ESRD:	**262**			
-Glomerular disease (1)	92	Reference	------	------
-Non-glomerular disease w/out obstructive uropathy (2)	110	1.933 (2 v 1)	0.646 – 5.782	0.6787
-Non-glomerular disease w/ obstructive uropathy (3)	**60**	**5.295 (3 v 1)**	**1.795 – 15.621**	**0.0012**
Age:	**262**			
< 6 years	**62**	**4.986**	**2.061 – 12.061**	**0.0005**
6 – 12 years	62	1.536	0.522 – 4.520	0.4402
> 12 years	138	Reference	------	------
Gender (Male reference group.)	262	0.803 (F v M)	0.360 – 1.795	0.5935
Race:	**262**			
-White (1)	143	Reference	------	------
-Black (2)	102	0.595 (2 v 1)	0.259 – 1.367	0.9486
-Other (3)	17	0.384 (3 v 1)	0.048 – 3.061	0.5080
Ethnicity: (Non-His reference group.)	262	0.761 (His v Non-His)	0.252 – 2.305	0.6296

Table 4. Risk Factors for Recurrent UTI in First Year Post-Kidney Transplant, Multivariate Analyses.

Characteristic	N	Odds Ratio	95% Confidence Interval	P-value
Etiology of ESRD:	**262**			
-Glomerular disease (1)	92	Reference	------	------
-Non-glomerular disease w/out obstructive uropathy (2)	110	1.428 (2 v 1)	0.451 – 4.525	0.3242
-Non-glomerular disease w/ obstructive uropathy (3)	**60**	**5.031 (3 v 1)**	**1.405 – 18.019**	**0.0055**
Gender (Male reference group.)	262	1.617 (F v M)	0.596 – 4.384	0.3450
Age:	**262**			
< 6 years	**62**	**3.843**	**1.480 – 9.982**	**0.0035**
6 – 12 years	62	1.217	0.391 – 3.791	0.3473
> 12 years	138	Reference	------	------
Race:	**262**			
-White (1)	143	Reference	------	------
-Black (2)	102	0.419 (2 v 1)	0.164 – 1.069	0.5524
-Other (3)	17	0.394 (3 v 1)	0.046 – 3.362	0.6491
Ethnicity: (Non-His reference group.)	262	0.579 (His v. Non-His)	0.173 – 1.940	0.3754

Table 5. Risk Factors for Recurrent UTI in Second Year Post-Kidney Transplant, Univariate Analyses.

Characteristic	N*	Odds Ratio	95% Confidence Interval	P-value
Etiology of ESRD:	**240**			
-Glomerular disease (1)	87	Reference	------	------
-Non-glomerular disease w/out obstructive uropathy (2)	98	1.505 (2 v 1)	0.349 – 6.491	0.3776
-Non-glomerular disease w/ obstructive uropathy (3)	**55**	**6.222 (3 v 1)**	**1.629 – 23.764**	**0.0015**
Age:	**240**			
< 6 years	**59**	**4.212**	**1.344 – 13.200**	**0.0191**
6 – 12 years	59	1.702	0.440 – 6.586	0.7526
> 12 years	122	Reference	------	------
Gender (Male reference group.)	240	1.393 (F v M)	0.528 – 3.670	0.5028
Ethnicity: (Non-His reference group.)	240	1.034 (His v Non-His)	0.285 – 3.754	0.9599

*Analyzed using complete case analysis.

Table 6. Risk Factors for Recurrent UTI in Second Year Post-Kidney Transplant, Multivariate Analyses.

Characteristic	N*	Odds Ratio	95% Confidence Interval	P-value
Etiology of ESRD:	**240**			
-Glomerular disease (1)	87	Reference	------	------
-Non-glomerular disease w/out obstructive uropathy (2)	98	1.520(2 v 1)	0.335 – 6.903	0.1647
-Non-glomerular disease w/ obstructive uropathy (3)	**55**	**13.202 (3 v 1)**	**2.214 – 78.718**	**0.0017**
Age:				
< 6 years	59	3.027	0.871 – 10.516	0.05
6 – 12 years	59	1.037	0.239 – 4.497	0.4227
> 12 years	122	Reference	------	------
Gender (Male reference group.)	**240**	**5.434 (F v M)**	**1.291 – 22.872**	**0.0210**
Ethnicity (Non-His reference group.)	240	1.235 (His v Non-His)	0.288 – 5.304	0.7761

*Analyzed using complete case analysis.

Table 7. Risk Factors for Recurrent UTI in First or Second Year Post-Kidney Transplant, Univariate Analyses.

Characteristic	N	Odds Ratio	95% Confidence Interval	P-value
Etiology of ESRD:	**262**			
-Glomerular disease (1)	92	Reference	------	------
-Non-glomerular disease w/out obstructive uropathy (2)	110	1.487 (2 v 1)	0.560 – 3.947	0.2300
-Non-glomerular disease w/ obstructive uropathy (3)	**60**	**5.627 (3 v 1)**	**2.191 – 14.453**	**<0.0001**
Gender (Male reference group.)	262	0.834 (F v M)	0.405 – 1.718	0.6233
Age:	262			
< 6 years	**62**	**5.498**	**2.435 – 12.412**	**<0.0001**
6 – 12 years	62	1.469	0.541 – 3.990	0.3010
> 12 years	138	Reference	------	------
Race:	**262**			
-White (1)	143	Reference	------	------
-Black (2)	102	0.629 (2 v 1)	0.300 – 1.320	0.8095
-Other (3)	17	0.295 (3 v 1)	0.037 – 2.328	0.3454
Ethnicity: (Non-His reference group.)	262	0.558 (His v. Non-His)	0.187 – 1.663	0.2952

Table 8. Risk Factors for Recurrent UTI in First or Second Year Post-Kidney Transplant, Multivariate Analyses.

Characteristic	N	Odds Ratio	95% Confidence Interval	P-value
Etiology of ESRD:	**262**			
-Glomerular disease (1)	92	Reference	------	------
-Non-glomerular disease w/out obstructive uropathy (2)	110	1.059 (2 v 1)	0.372 – 3.013	0.0743
-Non-glomerular disease w/ obstructive uropathy (3)	**60**	**5.281 (3 v 1)**	**1.678 – 16.923**	**0.0008**
Gender (Male reference group.)	262	2.136(F v M)	0.831 – 5.492	0.1152
Age:	**262**	**0.878**	**0.815 – 0.946**	**0.0006**
< 6 years	**62**	**4.687**	**1.907 – 11.521**	**0.0004**
6 – 12 years	62	**1.230**	**0.423 – 3.575**	**0.2394**
> 12 years	138	Reference	------	------
Race:	**262**			
-White (1)	143	Reference	------	------
-Black (2)	102	0.416 (2 v 1)	0.174 – 1.00	0.7109
-Other (3)	17	0.283 (3 v 1)	0.033 – 2.434	0.4506
Ethnicity: (Non-His reference group.)	262	0.401 (His v. Non-His)	0.119 – 1.349	0.1397

Table 9. Change in Mean eGFR in Two Years Post-Kidney Transplant, Comparing Patients With and Without Recurrent UTI.

Characteristic:	**N (%)***	**Mean ± std. deviation (range) (mL/min/1.73 m²):**	**T-test statistic**	**P-value**
Δ eGFR between 1 month and 12 months post transplant:	262			
-Recurrent UTI (yes)	30	-19.77 ± 33.89 (-101.23 – 36.25)	**-2.98**	**0.0053****
-Recurrent UTI (no)	232	-1.04 ± 24.59 (-93.54 – 72.33)		
Δ eGFR between 12 months and 24 months post transplant:	240			
-Recurrent UTI (yes)	18	-6.95 ± 23.97 (-84.18 – 35.97)	-.39	0.700**
-Recurrent UTI (no)	222	-4.69 ± 16.90 (-67.71 – 78.13)		
Δ eGFR between 1 month and 24 months post transplant:	240			
-Recurrent UTI (yes)	34	-19.05 ± 28.40 (-79.50 – 22.48)	**-2.43**	**0.0193**
-Recurrent UTI (no)	206	-6.31 ± 27.97 (-108.21 – 62.87)		

*Analyzed using complete case analysis.
*Satterthwaite method t and p values reported as variances between two groups were found not to be equal.

Table 10. Number of Hospitalizations Due to Urinary Tract Infection in Two Years Post Transplant, Stratified by Etiology of Kidney Failure.

Characteristic:	N (%)	Mean # of Hospitalization ± stdev. (Range)	Rate of Hospitalizations	Rate ratio (95% C.I.)*	P-value
Hospitalization secondary to UTI (Yes), by etiology of ESRD:	**56 of 262**				
-Glomerular disease (1)	12 of 92 (13.0%)	0.2 ± 0.6 (0 – 4)	0.153	2.7 (3 v. 1,2) (1.537 – 4.751)	**0.00053 (3 v. 1,2)**
-Non-glomerular disease w/out obstructive uropathy (2)	19 of 110 (17.3%)	0.4 ± 1.5 (0 – 13)			
-Non-glomerular disease w/ obstructive uropathy (3)	25 of 60 (41.7%)	1.0 ± 1.8 (0 – 9)	0.417		

*C.I. = confidence interval

Table 11. Acute Kidney Injury Frequency Due to Urinary Tract Infection in Two Years Post-Kidney Transplant.

Characteristic:	N (%)	Chi-square value	P-value
AKI secondary to UTI, by etiology of ESRD:	**19 of 262 (7.3%)**		
-Glomerular disease	6 of 92 (6.5%)	0.1124	0.7374
-Non-glomerular disease w/out obstructive uropathy	4 of 110 (3.6%)	3.6850	0.0549
-Non-glomerular disease w/ obstructive uropathy	**9 of 60 (15.0%)**	**6.9460**	**0.0084**

Figure 1. Histograms Depicting Age at Transplantation, Stratified by Development of Recurrent UTI in First or Second Year Post-Transplant.

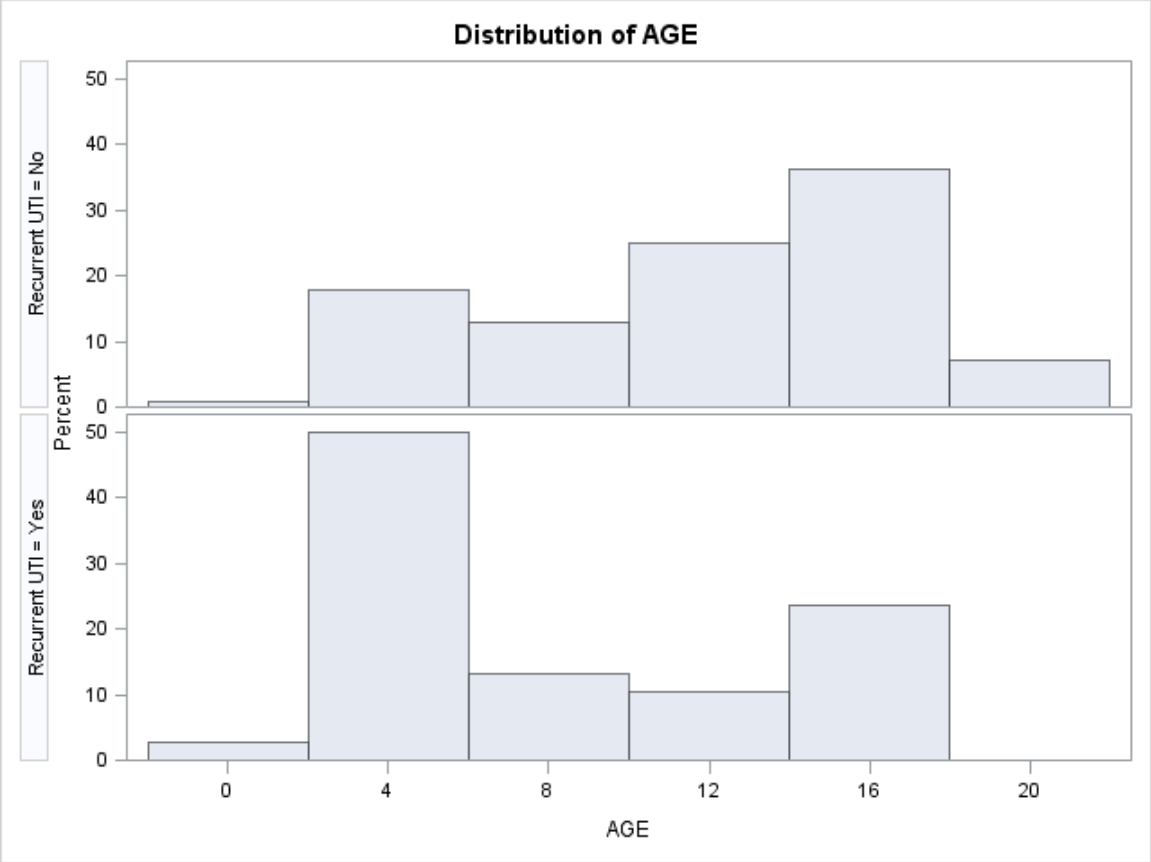

Figure 2. Analysis of covariance (ANCOVA) for eGFR at 12 months Post-Transplant.

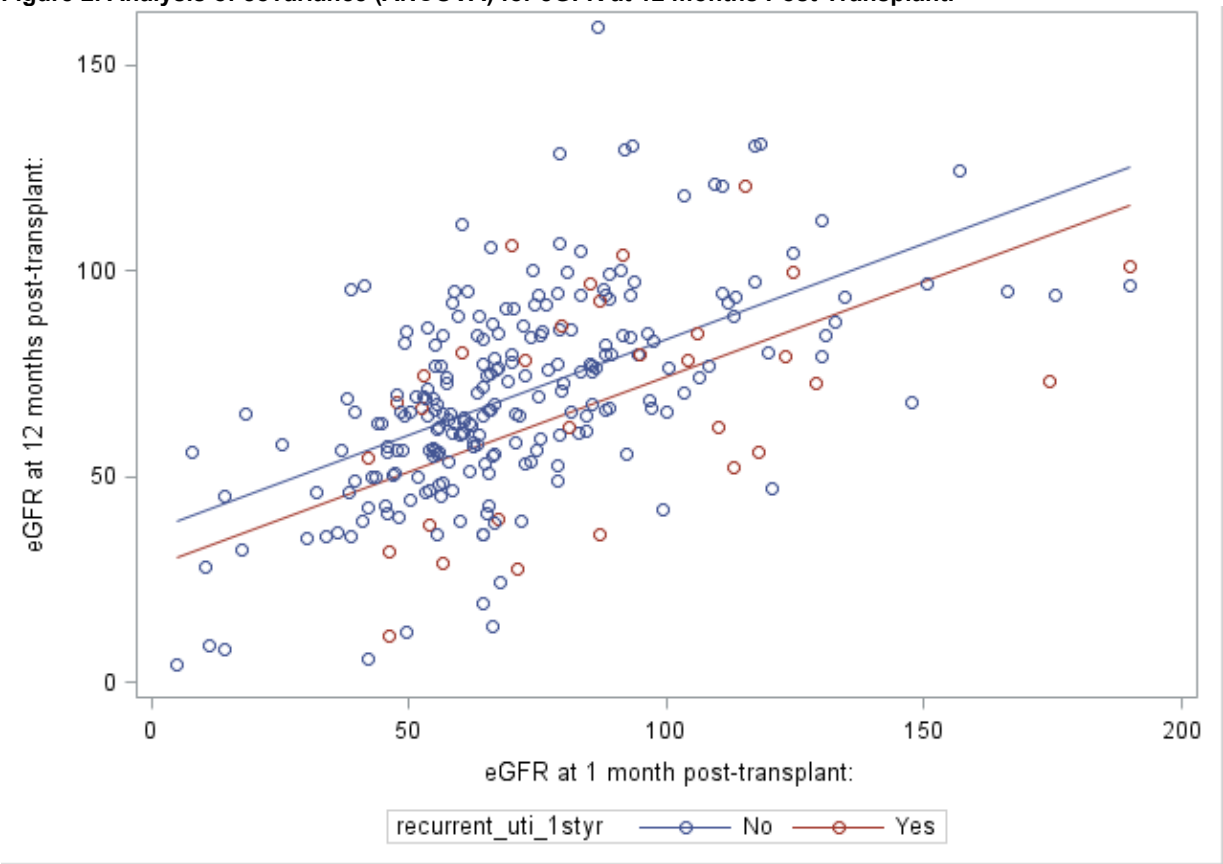

Figure 3. Analysis of Covariance (ANCOVA) for eGFR at 24 months Post-Transplant.

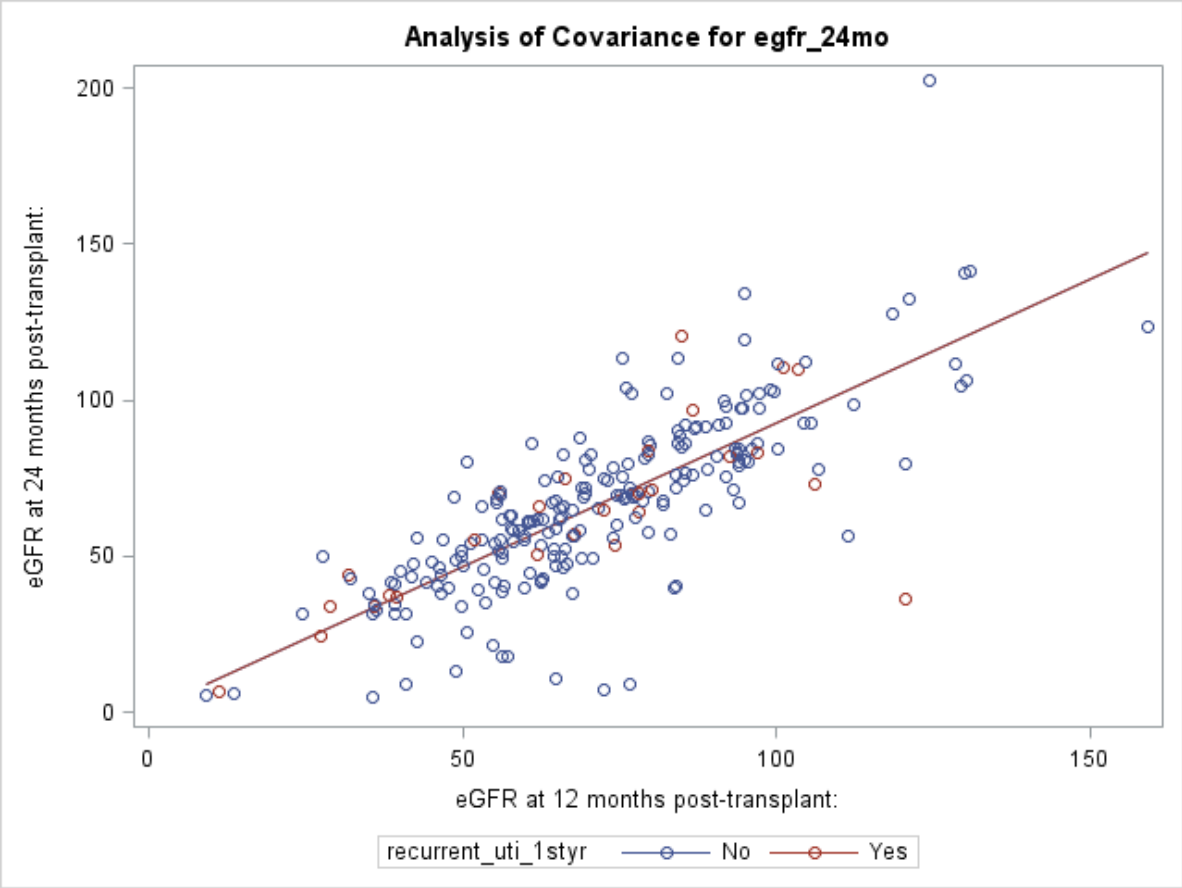

Figure 4. Histograms portraying Number of Hospitalizations Secondary to UTI, Stratified by Etiology of ESRD in Kidney Transplant Recipients.