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ORIGINAL ARTICLE

Febrile urinary tract infection after pediatric kidney transplantation: a multicenter, prospective observational study

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Abstract
Background Febrile urinary tract infections (fUTIs) are common after kidney transplantation (KTx); however, prospective data in a multicenter pediatric cohort are lacking. We designed a prospective registry to record data on fUTI before and after pediatric KTx.
Methods Ninety-eight children (58 boys and 40 girls) ≤ 18 years from 14 mid-European centers received a kidney transplant and completed a 2-year follow-up.
Results Posttransplant, 38.7 % of patients had at least one fUTI compared with 21.4 % before KTx ($p = 0.002$). Before KTx, fUTI was more frequent in patients with congenital anomalies of kidneys and urinary tract (CAKUT) vs. patients without (38 % vs. 12 %; $p = 0.005$). After KTx, fUTI were equally frequent in both groups (48.7 % vs. 32.2 %; $p = 0.14$). First fUTI posttransplant occurred earlier in boys compared with girls: median range 4 vs. 13.5 years ($p = 0.002$). Graft function worsened ($p < 0.001$) during fUTI, but no difference was recorded after 2 years. At least one recurrence of fUTI was encountered in 58 %.
Conclusion This prospective study confirms a high incidence of fUTI after pediatric KTx, which is not restricted to patients with CAKUT; fUTIs have a negative impact on graft function during the infectious episode but not on 2-year graft outcome.

Keywords Children · Kidney transplantation · Urinary tract infection · CAKUT · Outcome

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Abbreviations

AR	Acute rejection
CAKUT	Congenital anomalies of the kidney and urinary tract
CRP	C-reactive protein
DMSA	Technetium-99m dimercaptosuccinic acid
ESRD	End-stage renal disease
eGFR	Estimated glomerular filtration rate
fUTI	Febrile urinary tract infection
GPN	Gesellschaft für Pädiatrische Nephrologie
KTx	Kidney transplantation
SCr	Serum creatinine
VUR	Vesicoureteral reflux
VCUG	Voiding cystourethrography

Introduction

Kidney transplantation (KTx) is the preferred mode of renal replacement therapy (RRT) in children [1]. However, immunosuppressive treatment to prevent rejection comes at a price, and most transplant patients experience different kinds of infections, especially during the first year after transplantation. Studies of adult and pediatric cohorts have revealed that the most common forms of bacterial infection after KTx are urinary tract infections (UTIs) [2, 3], which seems to be lower after pediatric KTx compared with adults (15 – 33 % vs. 30 – 79 %) [4, 5]. The definition of UTI is inconsistent and ranges from asymptomatic bacteriuria to symptomatic, febrile UTI (fUTI) [6]. In particular, episodes with fever (fUTI) seem to be of relevance, as they can cause acute graft loss, result in renal scarring, and even lead to increased mortality of the transplanted patients [5, 7, 8].

Female gender, higher age, reflux kidney disease, and days of bladder catheterization have been shown to be relevant risk factors in adults [8, 9]. In children and adolescents, acknowledged risk factors for fUTI posttransplant are: urological causes of renal failure, indwelling catheters and stents, and history of pretransplant UTI [10–13]. As most data on UTIs after KTx are from retrospective single-or two-center studies, we conducted a multicenter, prospective observational study on fUTI within 14 centers of the German Society for Pediatric Nephrology (GPN) to obtain reliable data on incidence, risk factors, and outcome.

Methods

Patients

The study enrolled 137 patients awaiting KTx aged 1–18 years from 14 GPN centers at time of listing for Eurotransplant after parental informed consent. Baseline demographic and epidemiological data (e.g., primary renal disease, gender, history of fUTI, operations on the urinary tract) were collected retrospectively using a standardized questionnaire. Between November 2006 to 2009, 98 of these patients received a KTx and had a complete follow-up over 24 months. Only prospective data are presented. During the study period, clinical data were collected at 1, 6, 12, and 24 months. To evaluate the acute effect of fUTI on graft function, serum creatinine (SCr) values of the last visit before the fUTI, the highest level during infection, and level at first visit after the infection were recorded. Due to the study design, we could not determine whether antibiotic chemoprophylaxis had been given directly before or restarted after fUTI. The 6-, 12-, and 24-months visits provided information of dosage of immunosuppression either before or after an episode of fUTI. In five cases, no detailed data on antibiotic prophylaxis were available. Patients were divided according to primary renal disease into a group with congenital anomalies of kidneys and urinary tract (CAKUT) ($n = 39$; boys 32/girls 7) and a non-CAKUT ($n = 59$; boys 26/girls 33) group.

Study definitions

Febrile UTI was defined as leukocyturia (white blood cells > 20/μl urine in clean-catch midstream urine or any number of white blood cells obtained from suprapubic aspiration or via urethral catheterization) in combination with fever > 38.5 °C or an increased C-reactive protein (CRP) > 25 mg/L. In the absence of leucozyturia, bacterial growth of at least 10^5 bacterial colony forming units(cfu)/ml in combination with fever or increased CRP was specified as fUTI.

Statistical analysis

Data analysis was performed with SPSS software (Statistical Package for the Social Sciences, version 21.0, SPSS Inc, Chicago, IL, USA) using two-sided tests. Kaplan–Meier statistics were used to describe fUTI-free survival rate after KTx. For statistical analyses with Wilcoxon signed-rank test, only data from the first fUTI were used. Univariate analysis of variance (ANOVA) was employed for variables believed to be associated with delayed graft function. To analyze the relationship between estimated glomerular filtration rate (eGFR) at months 1, 6, 12, and 24; fUTI; absence of fUTI; and complications, such as acute rejection or viral infection, multivariate analysis with post hoc analysis was applied.

Results

Study population

The study followed 98 patients for 24 months (boys 58/girls 40); two children were excluded due to graft loss caused by acute rejection and death related to chronic neutropenia.

Clinical characteristics of the study population including primary immunosuppression and antibiotic prophylaxis at 1-month follow-up are summarized in Table 1. A detailed description of the CAKUT group is shown in Table 2.

fUTI posttransplant

There were 38/98 patients (38.7 %) with at least had one fUTI; 4/38 (10.5 %) had their first fUTI within 4 weeks posttransplant, 14/38 (36 %) in months 2–6, 10/38 (26 %) in months 7–12, and 10/38 (26 %) in the second year. During the first 6 months, the risk for developing fUTI was the highest ($p = 0.024$) compared with the remaining 18 months of the observation period. The primary renal disease had no influence on time lag between KTx and first fUTI (Fig. 1). In the group of children without antibiotic chemoprophylaxis, fUTI rate was not different from the group with chemoprophylaxis [6/16 (37.5 %) vs. 28/77 (36.4 %)], $p = 0.93$).

Recurrent fUTI

A total of 59 fUTI episodes were recorded. Within the observation period, fUTI recurred at least once in 22/38 (58 %) patients. Of these 22 children, 12 (55 %) had more than two episodes, and 15 (68.2 %) had fUTI recurrence despite receiving antibiotic prophylaxis. The incidence of recurrent fUTI episodes was independent of primary renal disease (non-CAKUT 10/22 vs. CAKUT 12/22), gender (male 12/22 vs. female 10/22), surgery on the urinary tract pretransplant (no surgery 15/22 vs. surgery 7/22), and fUTI pretransplant (no fUTI 14/22 vs. fUTI 8/22). No differences were observed within the CAKUT group.

Microbial spectrum

In 55 patients (83 %), urine was collected by the clean-catch method, in four (6 %) via bladder catheterization, and in seven (11 %) the method was not documented. The most frequently isolated microorganisms in urine culture from patients with first fUTI posttransplant were *Escherichia coli* (8/38, 21.1 %), *Enterococcus* (5/38, 13.2 %), *Staphylococcus* sp. (4/38, 10.5 %), *Klebsiella* (3/38, 7.9 %), *Proteus* sp. (2/38, 5.3 %), and *Enterobacter* or *Micrococcus luteus*, respectively, in one case. Mixed bacterial growth was observed in 5/38 (13.2 %); in 7/38 (18.4 %), urine culture remained negative.

Treatment of fUTI

Treatment of fUTI was performed according to local guidelines. The majority of fUTI episodes (47/59, 79.6 %) resulted in inpatient treatment with antibiotics administered IV: 23/47 (48.9 %) received a combination of cephalosporin with ampicillin, amoxicillin/clavulanic acid, ciprofloxacin, or tobramycin. Two patients (4.2 %) were treated with ciprofloxacin in combination with tobramycin or vancomycin. Two patients were treated with gentamycin/tazobactam or vancomycin/meropenem, seven (14.9 %) received triple antibiotic therapy, 13 of 47 patients (27.6 %) were treated with a single dose of antibiotic IV [4/13 (31 %) cefuroxime, 4/13 (31 %) ciprofloxacin, 2/13 (15 %) ceftazidime, 3/13 ceftriaxone, cefotaxime or linezolid, respectively]; 12/59 (20.3 %) fUTI episodes were treated with antibiotics orally [ciprofloxacin 4/12 (33.3 %) and cefixime 2/12 (16.6 %)].

Risk factors for fUTI

Positive history for fUTI and underlying disease

Prior to KTx, 21.4 % of patients had fUTI. It was more frequent in patients with CAKUT than in those without (37.8 vs. 11.9 %, $p = 0.005$). The incidence did not differ between boys and girls (24.6 vs. 17.9 %). Patients with a positive history for fUTI developed posttransplant fUTI more frequently than those who did not (15/21, 71 % vs. 23/77, 29 %, $p = 0.001$). In the CAKUT group (boys 32/girls 7), the incidence of fUTI remained unchanged when comparing pretransplant [14/39 (37.8 %)] vs. posttransplant [19/39 (48.7 %)] $p = 0.01$). Within the CAKUT group, patients with posterior urethral valves more frequently developed posttransplant fUTI did than those without ($p = 0.004$). In the non-CAKUT group (boys 33/girls 26), the incidence of fUTI increased significantly, from 7/59 (11.9 %) pretransplant to 19/59 (32.2 %) posttransplant ($p = 0.01$).

Gender and age

Patients of both genders showed increased rates of fUTI posttransplant—20/58 boys (34.5 %) and 18/40 girls (45 %)—compared with the pretransplant period: 14/58 boys (24.1 %) and 7/40 girls (17.5 %). In the CAKUT group, 4/7 girls (57.1 %) and 15/32 boys (46.9 %) had fUTI ($p = 0.46$), compared with 14/33 girls (42.4 %) and 5/26 boys (19.2 %) in the non-CAKUT group ($p = 0.05$). The age at transplantation did not differ between boys and girls (median 10, range 1–18 vs. 12, 1–18 years); however, two different gender-related age peaks of first fUTI posttransplant were observed: median 4 years (range 1–20) for boys and 13.5 (3–18) years for girls ($p = 0.002$; Fig. 2).

Surgical procedures

Prior to KTx, 20/98 (20.4 %) patients underwent surgery on the upper and lower urinary tract. Of these patients, 19/20 (95.0 %) had CAKUT as primary renal disease. More detailed information is shown in Table 3. Antirefluxive ureterocystoneostomy technique was performed in 86/98

Table 1 Characteristics of patients stratified according to presence or absence of febrile urinary tract infection (fUTI) after kidney transplantation (KTx)

	Total	fUTI	No fUTI	*P* value
Number of patients (%)	98	38 (38.8)	60 (60.1)	
Recipient age	9.82 ± 5.7	8.03 ± 6.1	10.95 ± 5.1	0.01
Gender				
Male	58	20 (34.5)	38 (65.5)	0.42
Female	40	18 (47.4)	22 (52.6)	0.30
fUTI prior to KTx	21 (21.4)	15 (71.4)	6 (28.6)	0.001*
Antibiotic prophylaxis prior to KTx	15 (15.3)	11 (73.3))	4 (26.7)	0.004*
CAKUT	11 (11.2)	8 (72.7)	3 (27.3)	0.073
Non-CAKUT	4 (4.1)	3 (75.0)	1 (25.0)	0.094
Primary renal disease				
CAKUT	39 (39.8)	19 (48.7)	20 (51.3)	0.14
Non-CAKUT	59 (61.2)	19 (32.7)	40 (67.8)	0.009*
Glomerulonephritis	22 (22.4)	4 (18.2)	18 (81.8)	0.004*
Nephronophthisis	11 (11.2)	3 (27.3)	8 (72.7)	0.227
HUS	5 (5.1)	3 (60.0)	2 (40.0)	1.0
ARPKD	8 (8.2)	3 (37.5)	5 (62.5)	0.727
Metabolic disorders	2 (2.0)	0 (0.0)	2 (100.0)	**
Other	11 (11.2)	6 (54.5)	5 (45.5)	1.0
Urological surgery prior to KTx	35 (35.7)	19 (54.3)	16 (45.7)	0.74
CAKUT	26 (26.5)	15 (57.7)	11 (42.3)	0.18
Non-CAKUT	9 (9.2)	4 (44.4)	5 (55.6)	0.45
Antirefluxive implantation of ureter				
Modified Lich-Grégoire	66	28 (42.4)	38 (57.6)	0.30
Other	19	13 (68.4)	6 (31.6)	0.64
Immunosuppressive therapy				
Cyclosporine/MMF/prednisone	38	17 (44.7)	21 (54.3)	0.08
Tacrolimus/MMF/prednisone	31	7 (22.6)	24 (77.4)	0.05
Sirolimus/MMF/prednisone	15	8 (53.8)	7 (46.2)	0.09
Other	14	7 (50.0)	7 (50.0)	1.0
Antibiotic prophylaxis 1 months after KTx				
TMP/SMX	53	17 (32.1)	36 (67.9)	0.27
TMP	14	4 (28.6)	10 (71.4)	0.31
Cephalosporine	9	6 (66.7)	3 (33.3)	0.44
Ciprofloxacin	2	1 (50.0)	1 (50.0)	1.0
Patients with acute rejection	35	14 (40.0)	21 (60.0)	0.83
Viral infection (CMV, EBV, BKV)	38	16 (42.1)	22 (57.9)	0.33

CAKUT congenital anomalies of kidney and urinary tract, *HUS* hemolytic-uremic syndrome, *ARPKD* autosomal recessive polycystic kidney disease, *Other primary renal disease*: Townes-Brocks syndrome, nephropathia of unknown origin, complication in the preterm period, feto-fetal transfusion syndrome, Alport syndrome, Denys-Drash syndrome, OEIS complex (omphalozele, bladder exstrophie, imperforate anus, spine defect), *MMF* mycophenolate mofetil, *TMP* trimethoprim, *SMX* sulfamethoxazole, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *BKV* BK virus

*Significant, **not calculated

KTx (87.8 %), with the modified Lich-Grégoire technique in 66/98 (67.3 %). In 12 cases (12.2 %), the surgical procedure was not further specified. Indwelling bladder catheters were used in 80/98 (81.6 %) patients: 54/98 (55.1 %) transurethral, 26/98 (26.5 %) suprapubic; in ten (10.2 %), no catheter was placed; In eight (8.2 %), we had no detailed information. Posttransplant, a double-J ureteral catheter was used in 72/98 patients, 11/98 had no double-J catheter, and 15/98 had no information. The surgical ureteral reimplantation procedure ($p = 0.87$), type of urinary catheterization ($p = 0.48$), or the use of double-J ureteral catheter ($p = 0.33$) did not statistically affect the rate of fUTI.

Table 2 Specified primary renal disease of patients with congenital anomalies of kidney and urinary tract (CAKUT)

Primary renal disease	Total	fUTI after KTx	No fUTI after KTx	*P* value
CAKUT	39 (39.8 %)	19 (48.7 %)	20 (51.3 %9	0.14
VUR	4 (10.3 %)	2 (50.0 %)	2 (50.0 %)	0.60
Renal dysplasia	19 (48.7 %)	6 (31.6 %)	13 (68.4 %)	1.00
Urethral valve	13 (33.3 %)	10 (76.9 %)	3 (23.1 %)	0.004*
Malformation of lower and upper urinary tract	3 (7.7 %)	1 (33.3 %)	2 (66.7 %)	1.00

fUTI febrile urinary tract infection *KTx* kidney transplantation *VUR* vesicoureteral reflux

*Significant

Outcome

Influence of fUTI on allograft function

SCr significantly increased during fUTI, from 74.8 ± 51.8 to 114.7 ± 71.4 μmol/L, ($p < 0.001$) and returned to baseline levels (79.2 ± 57.3 μmol/L) after treatment. During fUTI, there was no significant difference in the change (Δ) of eGFR in patients with or without fUTI (16.2 ± 19 ml/min/1.73 m^2 vs. 20.1 ± 25 ml/min/1.73 m^2) ($p = 0.1$) (Fig. 3). In the entire cohort, eGFR significantly decreased from 79.3 ± 28.7 ml/min/1.73 m^2 at month 1 to 61.3 ± 20.9 ml/min/1.73 m^2 at year 2 posttransplant ($p = 0.04$). This declining renal graft function was statistically independent of fUTI, viral infections, urinary tract surgery, mode of immunosuppressive treatment, or demographic risk factors of gender and age. Using multivariate regression analysis, only the incidence of acute rejection (AR) episodes showed a significant negative impact on graft function (Table 4).

Discussion

This is the first multicenter study prospectively evaluating incidence, risk factors, and outcomes of fUTI after pediatric KTx. We confirm a high incidence of fUTI after KTx, interestingly not only in patients with CAKUT, who traditionally have a higher incidence of fUTI prior to KTx. Febrile UTI was accompanied by acute morbidity and graft dysfunction but did not have a negative impact on the 2-year graft-survival outcome.

Febrile UTIs represent one of the most common complications contracted by renal allograft recipients in the posttransplant period, although prospective multicenter studies have not been published to date. In retrospective investigations, moderate to severe fUTIs are reported in 17–32 % of children following KTx during a follow-up period of 54 and 18 months, respectively [10, 14]. The incidence of fUTI observed in our prospective study was slightly higher, at 38.7 %.

Several studies have shown a predominance of fUTI during the early posttransplant period, which is likely to be caused by more intensive immunosuppressive therapy and postinterventional instrumentation of the urinary tract [11, 12]. Data presented herein are in accordance with these observations and show that almost half of the patients experienced fUTI within the first 6 months posttransplant. The rate of recurrence was lower than described in the retrospective study by Silva et al. (58 % vs. 72 %) [15]. Interestingly, fUTI occurred despite antibiotic prophylaxis in most children investigated, which suggests that antimicrobial prophylaxis has a limited effect on the occurrence of fUTIs. Data available in the literature on this topic are conflicting, and the use of antimicrobial prophylaxis in clinical practice remains a matter of debate [11, 12, 16–18].

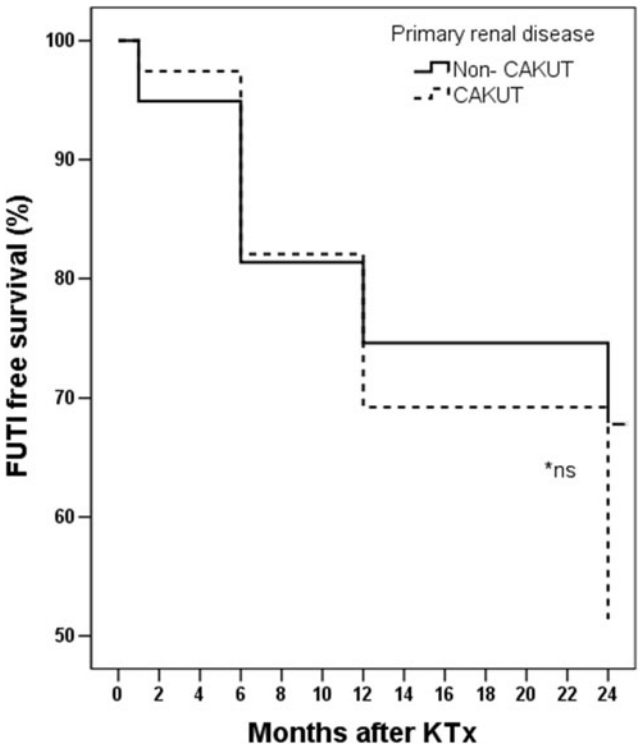

Fig. 1 No significant influence of primary renal disease (CAKUT vs. non-CAKUT) on fUTI after KTx (Kaplan–Meier analysis). *CAKUT* congenital anomalies of kidney and urinary tract, *fUTI* febrile urinary tract infection, *KTx* kidney transplantation, *ns* not significant

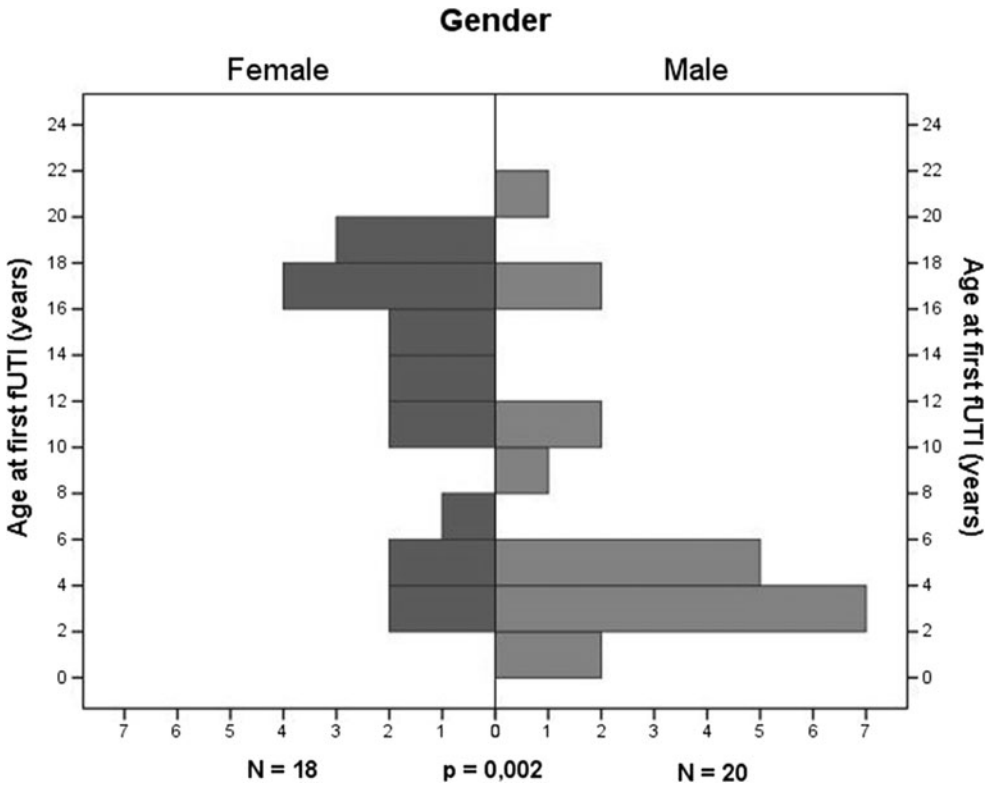

Fig. 2 Gender-specific age peaks at first fUTI are significantly different. *fUTI* febrile urinary tract infection

With our prospective study, we confirm a positive history of fUTI, which occurred more frequently in CAKUT patients, as a risk factor. However, it is an important observation that after KTx, CAKUT itself is not a risk factor for fUTI. Of the CAKUT group, patients with posterior urethral valves were at particular risk, which has previously been described in the retrospective study by Mochon et al. [19].

Regarding gender and age as risk factors, Silva et al. found that girls did not have an increased risk for fUTI posttransplant compared with boys [10]. This is in contrast to John et al., who previously reported a high prevalence of fUTI in children after KTx and especially in girls [13]. We did not observe an overall gender-specific difference; however, it is remarkable that fUTIs in girls occurred significantly later in girls, possibly aggravated by sexual activity. The reason boys experience their first UTI at a younger age might relate to their underlying disease. As no routine assessment of possible dysfunctional voiding or residual postvoid urine was performed in our study, we cannot comment on these as possible risk factors in our cohort [20].

The impact of posttransplant fUTI on graft function in the pediatric population is not well understood [21]. Previous studies suggest that fUTI predisposes the development of acute rejection [22]. However, in our study, although a transient decline in renal

Table 3 Surgery on upper and lower urinary tract prior to kidney transplantation (KTx) in patients with congenital anomalies of kidneys and urinary tract (CAKUT)

Primary renal disease	Total	No surgery	Ureter-neoimplantation/ antireflux surgery	Bladder augmentation	External urinary diversion
VUR	4 (10.0 %)	1 (25.0 %)	3 (75.0 %)	0 (0.0 %)	0 (0.0 %)
Renal dysplasia	19 (48.0 %)	15 (78.9 %)	2 10.5 %)	1 (5.3 %)	1 (5.3 %)
Urethral valve	13 (33.3 %)	3 (23.1 %)	3 (23.1 %)	3 (23.1 %)	4 (30.8 %)
Combined malformation of upper and lower urinary tract	3 (7.7 %)	1 (33.3 %)	1 (33.3 %)	1 (33.3 %)	0 (0.0 %
Total	39 (100.0 %)	20 (51.3 %)	9 (23.1 %)	5 (12.8 %)	5 (12.8 %)

VUR vesicoureteral reflux

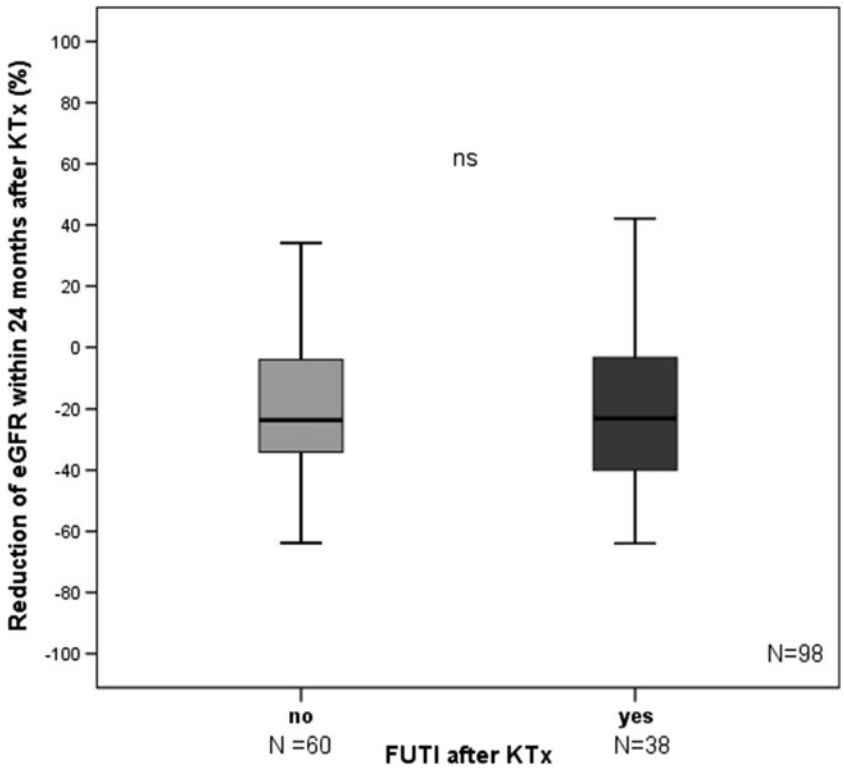

Fig. 3 No significant influence of fUTI on graft function 24 months after KTx. (*fUTI* febrile urinary tract infection, *KTx* kidney transplantation, *ns* not significant

function occurred during infection, fUTIs were not associated with an accelerated decline of graft function, as described previously [7, 23]. It will be interesting to evaluate a longer follow-up of our cohort, as a negative influence of fUTI on allograft dysfunction might still develop later.

Several limitations of this study need to be addressed: Although a standardized data acquisition sheet was used, documentation of medical history—and especially management by the physicians in charge—were heterogeneous. Although a substantial number of children with KTx were included, 98 patients does not provide sufficient power to demonstrate significant changes in the incidence of renal graft dysfunction. Dupont et al. previously showed that patients posttransplant with recurrent fUTI developed renal scarring in up to 43 % of cases [6]. We did not evaluate renal damage after fUTI with, for example, Technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) scans, nor did we perform routine voiding cystourethrography (VCUG). From a methodological point of view, it was possibly inappropriate to include urine samples from patients pretreated with antibiotics, as this may have biased the detection of causative bacteria.

In conclusion, we confirm a high prevalence of fUTI after pediatric KTx, not just in CAKUT patients and independent of microbial prophylaxis. Children with fUTI before transplantation and boys with urethral valves have a higher risk for fUTI. The gender-specific age pattern observed in our study can help define individual risk profiles. Febrile UTI leads to acute allograft dysfunction but does not negatively affect graft function within 2 years after KTx. Long-term data beyond 2 years on renal function after fUTI are needed—ideally in combination with DMSA or magnetic resonance imaging (MRI), VCUG in recurrent fUTI, and functional bladder assessment—to further improve management.

Table 4 Analysis of different events and their influence on estimated glomerular filtration rate (eGFR) 24 months posttransplant.

Events	Standard error	*T* test	*P* value
fUTI	3.754	1.11	0.27
Recurrent fUTI	5.947	−0.16	0.87
Acute rejection episode	4.028	−4.70	0.000*
Viral infection	3.963	0.51	0.60
Surgery on urinary tract	5.567	−0.53	0.96
Change of immunosuppression	5.084	−1.04	0.30
Patient-related risk factors			
Gender	7.928	0.69	0.49
Age at first fUTI	1.594	−1.62	0.11
Age at KTx	1.557	0.46	0.65
Primary renal disease	7.537	−0.89	0.38

ANOVA analysis of variance, *fUTI* febrile urinary tract infection, *KTx* kidney transplantation

*Significant

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Compliance with ethical standards The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Friedrich-Schiller-University Jena and the respective Ethics Committees of each contributing center. All patients were enrolled at time of listing for Eurotransplant after parental informed consent.

Conflict of interests The authors declare there are no conflicts.

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