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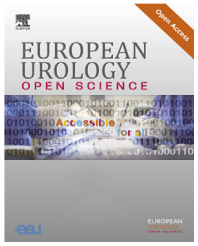

European Association of Urology

Renal Disease

Incidence of and Risk Factors for Recurrent Urinary Tract Infections in Renal Transplant Recipients

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Article info

Article history:
Accepted April 12, 2023

Associate Editor:
Véronique Phé

Keywords:
Renal transplantation
Urinary tract infections
Recurrent infections

Abstract

Background: Recurrent urinary tract infections (rUTIs) are common after renal transplantation (RTx), and the impact on graft and patient survival remains controversial.
Objective: In this study, we investigate the incidence and risk factors for rUTIs in a cohort of RTx recipients and evaluate the effect on graft and patient survival.
Design, setting, and participants: A retrospective cohort of adult patients who underwent RTx at Rigshospitalet, Denmark, between 2014 and 2021 was evaluated in this study.
Outcome measurements and statistical analysis: Risk factors for rUTIs were explored with a multivariable cause-specific Cox proportional hazard analysis. The Kaplan-Meier estimate was used to assess overall survival.
Results and limitations: A total of 571 RTx recipients were included. The median age was 52 yr (interquartile range: 42–62 yr). Of the cases, 62% were deceased donor RTx. A total of 103 recipients experienced rUTIs. We found increasing age (hazard ratio [HR]: 1.02 per year increase, 95% confidence interval [95% CI]: 1.00–1.04, $p = 0.02$), female gender (HR: 2.1, 95% CI: 1.4–3.3, $p < 0.001$), history of lower urinary tract symptoms (HR: 2.3, 95% CI: 1.4–3.5, $p = 0.001$), and a UTI within 30 d of surgery (HR: 3.5, 95% CI: 2.1–5.9, $p < 0.001$) were associated with rUTIs. No influence of rUTIs on overall or graft survival was observed.
Conclusions: One in six patients experience rUTIs after RTx. Pre- and postoperative variables affect the risk of rUTIs, but none are easily modifiable. In this cohort, rUTIs did not affect the graft function or survival. The etiology of rUTIs remains poorly understood, and there is a continuous need to study how rUTIs can be reduced and treated optimally.
Patient summary: In this study, we looked at the risk factors for recurrent urinary tract infections in patients after kidney transplantation. We conclude that 21.5%

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https://doi.org/10.1016/j.euros.2023.04.001

of patients experience recurrent urinary tract infections 5 years after kidney transplantation. Multiple risk factors were found and should be taken into consideration by clinicians.

1. Introduction

Renal transplantation (RTx) is the most clinically effective and cost-effective method to treat end-stage renal disease (ESRD) [1]. Long-term mortality is 55% lower for ESRD patients who undergo RTx than for dialysis patients on the waiting list [2].

Successful RTx for lasting graft function depends on multiple factors. Surgical factors such as bleeding and vessel thrombosis may lead to acute deterioration of graft function, whereas other complications such as uroplania and ureteric obstruction with hydronephrosis are more subtle complications that affect long-term graft function [3,4]. The most reported long-term complication is urinary tract infections (UTIs) that occur in 47–71% of patients after RTx [5,6]. UTIs have a large impact on the patient's quality of life and the health care system, as these are estimated to account for up to 31% of all sepsis hospitalizations in RTx recipients [7]. In a recent Danish cohort, 72% of secondary blood stream infections in RTx patients derived from the urinary tract [8]. Nevertheless, there is conflicting information regarding the association between UTIs and graft function, graft survival, and overall patient survival [9–11].

Whereas single episodes of UTIs in RTx recipients are frequently reported, recurrent UTIs (rUTIs) in RTx patients are poorly understood. Between 2.9% and 27% of RTx recipients have been reported to experience rUTIs [12]. The definition of an rUTI is not clear in the literature, but commonly defined as three or more UTI episodes within a 12-mo period, or two or more within a 6-mo period [9,10]. Some studies have reported an association between rUTIs and graft rejection, antibiotic drug resistance, and decreased graft and patient survival [13–16]. Given these considerations, it remains important to study risk factors for rUTIs and identify whether there are modifiable factors that could prevent infections for future patients.

The primary aim of this study was to investigate the risk factors for rUTIs in a single-center Danish RTx cohort and investigate the associations of rUTIs with graft survival and overall patient survival.

2. Patients and methods

We included all adult (>18 yr) patients who underwent RTx at Rigshospitalet, Denmark, between November 2014 and August 2021. Two patients with immediate rejection and graftectomy within 24 h were excluded. All transplanted recipients had a urinary anastomosis by ureteroneocystostomy using the Woodruff technique.

The national electronic patient record, including the national microbiology register (includes community-acquired UTIs), was reviewed. Information regarding symptoms and microbiology of UTIs was assessed to evaluate whether the criteria of rUTIs were met.

A UTI was defined as bacteriuria with a significant culture of $>10^3$ microbes and symptoms. Symptoms were reviewed through the electronic patient record and include fever, lower abdominal and flank pain, increased frequency, urgency, dysuria, foul-smelling urine, and/ or hematuria. An rUTI was defined as three or more culture-verified UTIs in a 1-yr period after RTx, following the European Association of Urology guidelines [17]. The date of the third UTI was registered as the rUTI date and could be registered only once. The urine cultures in this cohort were indication based and not only taken routinely. If two positive cultures with the same microbe were taken a few days apart, corresponding to the approximate length of antibiotic treatment, it was considered an unsuccessful treatment and was not registered as a new UTI.

Graft failure was defined by the permanent start of dialysis or graftectomy, whichever occurred first. Comorbidities were scored using Charlson comorbidity index on the day of transplantation—disregarding the 2 points given for renal failure. The complete list of collected variables and their detailed definitions are available in Supplementary Table 1. In our cohort, all RTx recipients received sulfamethoxazole/trimethoprim prophylaxis for 6 mo after transplantation for pneumocyst infections. The standard immunosuppressive regimen induction therapy included prednisone (250 mg), basiliximab (20 mg), tacrolimus (0.075 mg/kg × 2), and mycophenolate mofetil (MMF; 750 mg × 2) as stated in the guideline by Kidney Disease: Improving Global Outcomes [18]. Maintenance doses were prednisone 20 mg (downregulated to 5 mg after 6 mo), tacrolimus until serum level is 5–10 μg, and MMF 1500 mg daily. The standard treatment of acute graft rejection was 500 mg intravenous methylprednisolone, once a day for 3 d. For borderline rejections, 250 mg intravenous methylprednisolone was used instead. The study has been approved by the Danish Patient Safety Authority (3-3013-3232/1) and the Danish Data Protection Agency committee (P-2019-661).

2.1. Statistical analysis

Categorical variables are described as frequencies, and continuous variables by median and interquartile range (IQR) or mean and a standard deviation. A multivariable cause-specific Cox proportional hazard analysis was used to assess the association of included covariates and rUTIs.

The cumulative incidence of rUTIs was assessed by the Aalen-Johansen estimator, with any cause of death being a competing risk. The association between rUTIs and patient survival was assessed by the delayed-entry Kaplan-Meier estimate, and the association between rUTIs and graft loss was assessed by competing risk time-dependent Cox regression with delayed entry, with death as a competing risk. The underlining timescale was from the time of transplantation until the time of death, rUTI, loss of graft, migration, or end of follow-up (December 31, 2021). To account for the immortality bias in the delayed-entry models, patients with rUTIs entered the analysis at the date of the third UTI. Time point 0 was defined as the time of transplantation. Median follow-up time was defined as the median time to censoring.

A statistical analysis was performed using IBM SPSS statistics version 25 and RStudio version 1.2.5001, and $p < 0.05$ was considered statistically significant.

3. Results

A total of 571 RTx patients were included. The median follow-up time was 44 mo (IQR: 21–67 mo). During the observational period, 103 recipients experienced rUTIs. The median time to an rUTI was 8 mo (IQR: 4–20 mo) after RTx. The cumulative incidence of rUTIs is 21.5% (95% confidence interval [95% CI]: 17.5–25.5) 5 yr after RTx. The clinical characteristics are presented in Table 1.

Table 1 – Clinical characteristics of the cohort, stratified for patients with or without rUTIs

	No rUTI (*n* = 468)	rUTI (*n* = 103)
Preoperative characteristics		
Age at transplantation, median (IQR)	50 (41–61)	56 (43–65)
Female gender, *n* (%)	156 (33)	57 (55)
DM, *n* (%)	77 (17)	19 (18)
History of LUTS, *n* (%)	71 (15)	30 (29)
Charlson comorbidity index, *n* (%)		
0	257 (55)	54 (52)
1	110 (24)	21 (20)
2	58 (12)	17 (17)
3	29 (6.2)	7 (6.8)
4	9 (1.9)	2 (1.9)
6	1 (0.2)	0 (0)
Missing	4 (0.9)	2 (1.9)
Pretransplantation dialysis, *n* (%)	393 (84)	90 (87.4)
Months in dialysis, median (IQR)	23 (10–50)	34 (14–55)
Patients with pretransplantation urinary production, *n* (%)	331 (71)	64 (62.1)
Nephrological diagnosis, *n* (%)		
Unidentified	115 (24.6)	30 (29.1)
Diabetic nephropathy	41 (8.8)	9 (8.7)
Hypertension	36 (7.7)	6 (5.8)
Chronic glomerulonephritis	121 (26)	15 (15)
Cystic kidney disease	78 (17)	19 (18)
Other	77 (17)	23 (22)
Graft-related characteristics		
Graft from deceased donor, *n* (%)	280 (60)	71 (69)
Graft on perfusion machine, *n* (%)	118 (25)	24 (23)
Cold ischemic time (min), mean ± SD		
Living donor	182 ± 58	169 ± 44
Deceased donor	1049 ± 394	1084 ± 397
Incompatible AB0 blood type, *n* (%)	48 (10.3)	9 (8.7)
Postoperative characteristics		
Urinary catheter >5 d postoperatively, *n* (%)	74 (16)	32 (31)
Days with JJ stent, median (IQR)	25 (18–33)	25 (19–35)
Postoperative LUTS, *n* (%)	38 (8.1)	47 (46)
UTI first 30 d postoperatively, *n* (%)	25 (5.3)	24 (23)
Immunosuppressive medicine, n (%)		
Prednisone	452 (96.6)	103 (100.0)
Azathioprine	1 (0.2)	1 (1.0)
Mycophenolate mofetil	451 (96.4)	102 (99.0)
Cyclosporine	7 (1.5)	4 (3.9)
Tacrolimus	442 (94.4)	98 (95.1)
mTOR	4 (0.9)	1 (1.0)
Acute rejections 1 yr after transplantation, n (%)		
One	109 (25.8)	29 (29.3)
Two or more	5 (1.1)	0 (0.0)

DM = diabetes mellitus; IQR = interquartile range; LUTS = lower urinary tract symptoms; *n* = number of patients; rUTI = recurrent UTI; SD = standard deviation; UTI = urinary tract infection.
History of LUTS was not available for one patient in each group. Ten patients in the no-rUTI group had unavailable data regarding perfusion machine. Ten patients in the no-rUTI group had unavailable data regarding LUTS postoperatively.
Immunosuppressive medicine: Immunosuppressive medication was continued at discharge after transplantation. Following outpatient changes were not registered.

3.1. Risk factors

In a multivariable analysis, increasing age, female gender, and a preoperative history of lower urinary tract symptoms were significantly associated with rUTIs compared with the rest of the transplant recipients (Table 2). Experiencing a UTI within the first 30 d postoperatively was the risk factor that had a strong association with an rUTI, with the highest hazard ratio. Pretransplantation urinary production, defined as <100 ml of urine production per 24 h prior to transplantation, was a protective factor against rUTIs. No significant associations were found between rUTIs and pretransplantation diabetes, previous dialysis, duration of JJ stent, extended urinary catheter (<5 d), or previous RTx. No donor-related variables were associated with rUTIs.

3.2. Pathogens

The distribution of microbes in the three urine cultures necessary for the rUTI diagnosis is shown in Figure 1, the most common being *Escherichia coli* (41%).

3.3. Treatment and further examination

In the rUTI patient group, 39 (38%) were started on prophylactic antibiotic treatment after the rUTI diagnosis to prevent further UTIs. The most used were pivmecillinam (64%), trimethoprim (15%), nitrofurantoin (7.7%), and ciprofloxacin (7.7%). Local estrogen was given to 22 (39%) of female recipients as a prophylactic measure for rUTIs.

A total of 57 of 103 patients were referred for a urological workup for further examination of their underlying pathophysiology. Male patients (33 of 46) with rUTIs were referred to a urologist more often than females (24 of 57). Fifteen of 57 female recipients with rUTIs were referred to a gynecologist. Thirty of the total 57 female recipients with rUTIs were referred to a urologist and/or gynecologist, and some were referred to both.

The urological examinations included cystoscopy (79%), flow and residual urine test (71%), computed tomographic urography (32%), and urodynamic test (21%).

Urological workup resulted in a diagnosis of 26 patients, of whom 16 (28%) were diagnosed with residual urine although no strict definition was used, five (8.8%) with benign prostatic hyperplasia, two (3.5%) with urethral stricture, two (3.5%)

Table 2 – Multivariable cause-specific Cox proportional hazard analysis of the risk of rUTIs

Characteristics	HR (95% CI)	*p* value
Age at transplantation	1.02 (1.00–1.04)	0.02
Female gender	2.1 (1.4–3.3)	<0.001
Pretransplantation diabetes	1.1 (0.6–1.8)	0.82
Pretransplantation urinary production	0.5 (0.3–0.9)	0.01
History of LUTS	2.3 (1.4–3.5)	<0.001
Pretransplantation dialysis	0.9 (0.5–1.7)	0.72
Previous RTx	1.03 (0.5–2.0)	0.92
Graft from deceased donor	0.9 (0.5–1.5)	0.56
ABO incompatible	1.1 (0.5–2.6)	0.76
UTI first 30 d postoperatively	3.5 (2.1–5.9)	<0.001
Extended duration of urinary catheter	1.5 (0.98–2.4)	0.06
Duration of JJ stent (d)	1.0 (1.0–1.0)	0.85

CI = confidence interval; HR = hazard ratio; LUTS = lower urinary tract symptoms; RTx = renal transplantation; rUTI = recurrent UTI; UTI = urinary tract infection.

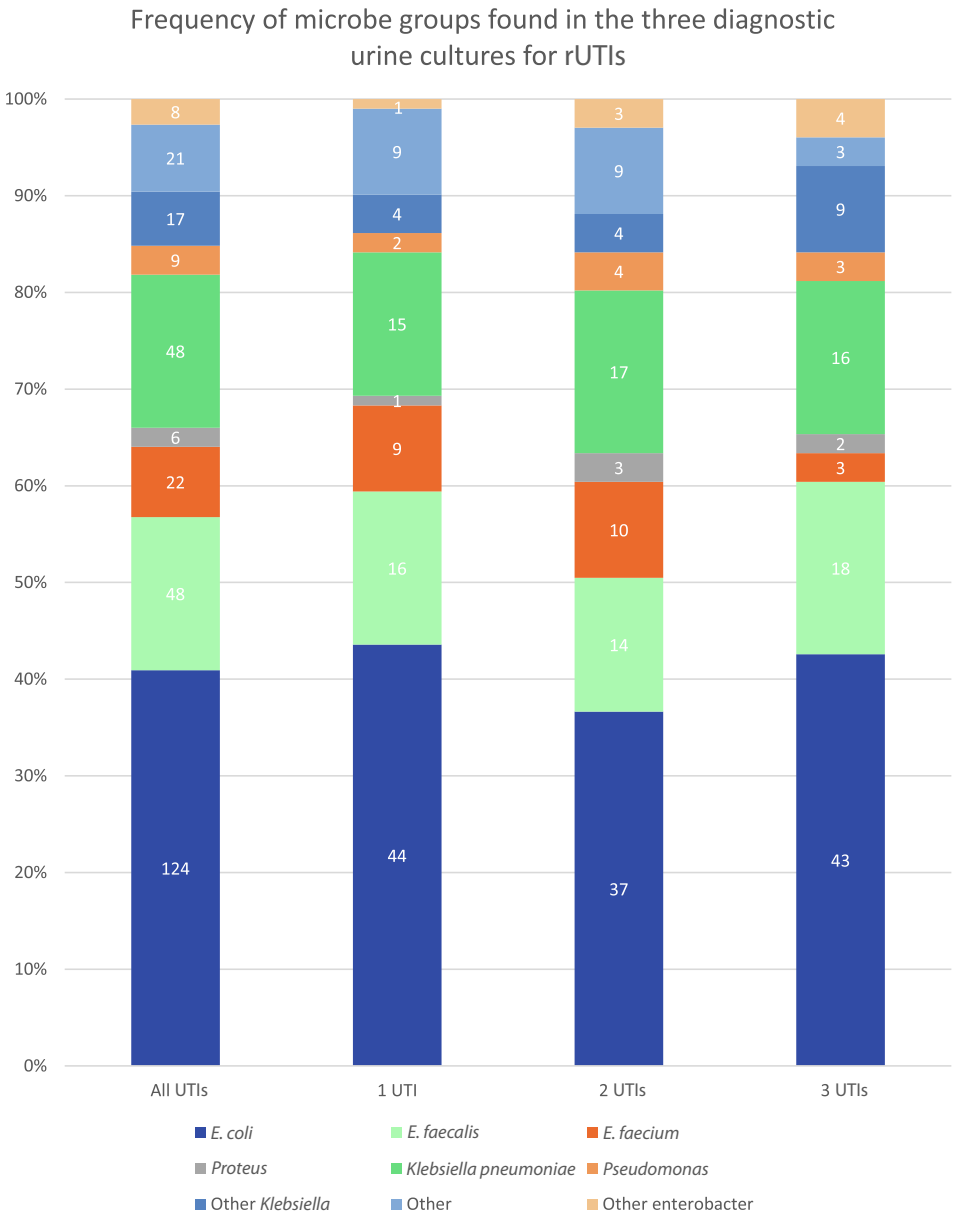

Fig. 1 – Frequency of microbe groups found in the three diagnostic urine cultures for rUTI. The numbers in bars represent the absolute numbers. rUTI = recurrent urinary tract infection; UTI = urinary tract infection.

with renal calculi, and one (1.8%) with ureteric stenosis. Three recipients with rUTIs (5.3%) were never seen by the urologist after referral, four (7.0%) recipients were seen due to other urological complications (such as the need for nephrostomies or JJ stents), and three (5.3%) had other diagnoses. Intermittent clean self-catheterization was advised for nine (16%) patients with residual urine, one patient was operated for urethral stricture (1.8%), and all five patients with benign prostatic hyperplasia were referred for transurethral resection of the prostate (TURP). Of the recipients with rUTIs who were referred to a urologist, 21 (37%) had no pathological findings.

3.4. *Long-term graft survival and overall patient survival*

During follow-up, 48 recipients experienced loss of graft function. The cumulative incidence of graft loss for all patients was 12.8% (95% CI: 9.1–16.6) over a 5-yr period. Ten and 38 recipients experienced graft loss in the rUTI and the no-rUTI group, respectively. The cumulative incidence of graft loss or death in patients with and without an rUTI is demonstrated in Figure 2A. No statistical difference was found.

A total of 34 recipients died during the follow-up. Overall survival after 5 yr was 85.6% (95% CI: 81.6–89.7). No difference in 5-yr survival rate between patients with rUTIs (79.0%, 95% CI: 68.5–89.6) and no rUTIs (86.4%, 95% CI: 81.9–90.9, p = 0.8; Fig. 2B). No difference in cause-specific death was observed between the rUTI and no-rUTI groups.

4. Discussion

In this single-center study, we found that one in six patients experienced an rUTI after RTx. We identified risk factors for developing an rUTI that could be considered for patient

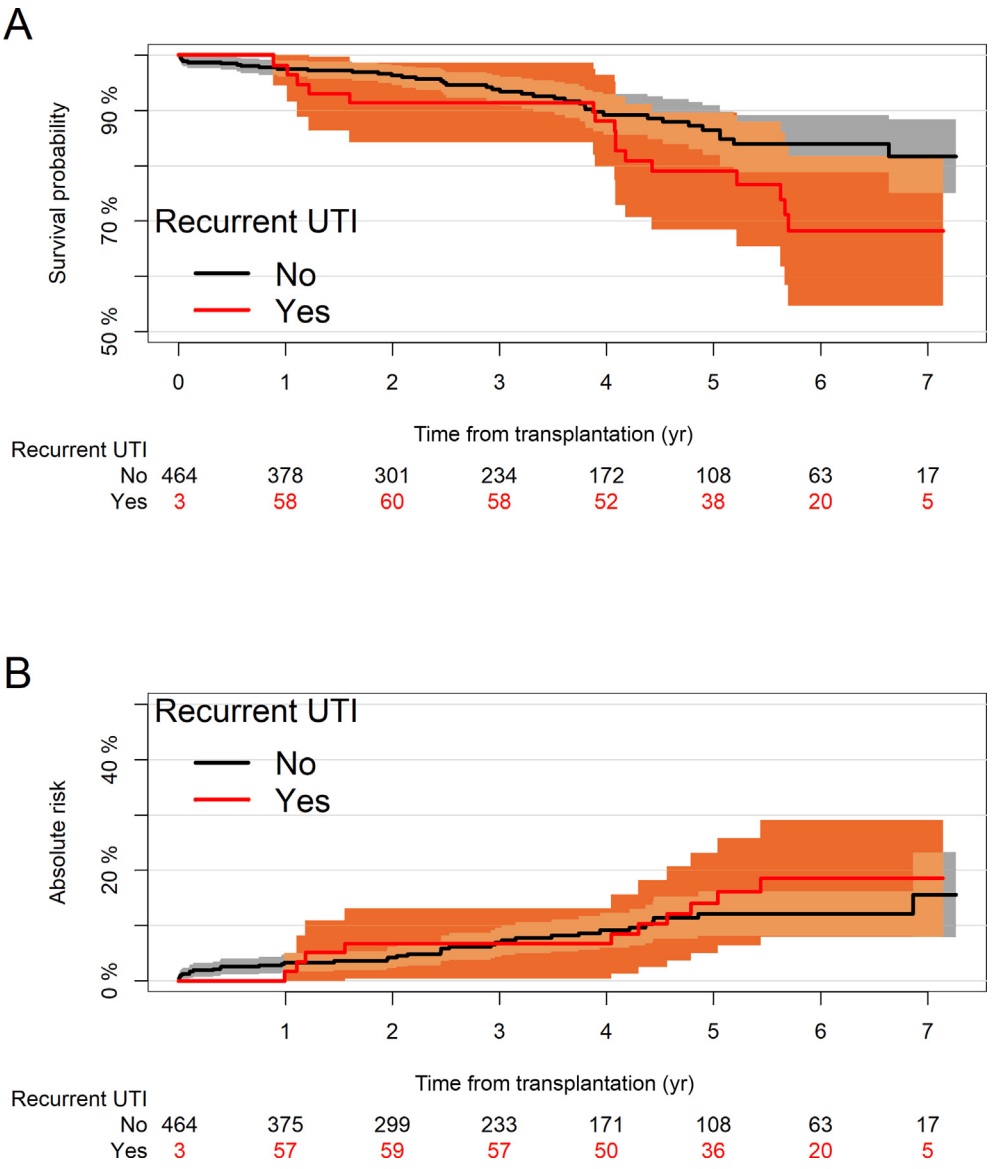

Fig. 2 – (A) Cumulative incidence of graft loss, with death as a competing risk. (B) Kaplan-Meier plot on overall patient survival comparing patients having rUTI with those having no rUTI. The analysis is adjusted for the immortality bias by delayed entry in the recurrent UTI group. Be aware that the *Y* axis shows a limit of 50%. rUTI = recurrent urinary tract infection; UTI = urinary tract infection.

counseling, although these are not easily modifiable. We demonstrated that UTIs within the first 30 d have the strongest association with an rUTI. Having a UTI as a short-term complication can therefore predict the patients' tendency for long-term infections, and can be used as a warning sign for rUTIs and should lead to increased awareness about future infections in the patient. We did not find a correlation between rUTIs and long-term graft function or patient survival, which is contrary to other studies.

Recurrent UTIs remain of interest as these constitute the most reported long-term complication after RTx, have major economic impact on the health care system in terms of outpatient visits and hospitalizations, and impact the patients' quality of life [9]. In the general population, studies show that the identification of risk factors for rUTIs among women improves quality of life and reduces antibiotic use, which could also have relevance for RTx patients [19].

In our study, the frequency of rUTIs was 18%, which seems in concordance with other studies using the same definition, where the frequency ranges from 6.3% to 18%. The pathophysiology for rUTIs in RTx patients is not well studied [12]. Many ESRD patients suffer from bladder dysfunction [20], and pretransplantation bladder atrophy, typically a consequence of anuria, has been linked to an increased risk of urological complications after RTx [21]. Although we do not know how many patients had bladder atrophy before or after RTx, we demonstrated that preoperative urinary production reduced the risk of rUTIs in our study population. It is assumed that these patients have better bladder function than the patients with anuria. After RTx in anuric patients, they regain urinary production. There may be bladder dysfunction initially, increasing the risk of a UTI. It remains unknown whether bladder function should be evaluated with urodynamic studies prior to trans-

plantation. The use of a urodynamic investigation in anuric patients is controversial and should be explored further. It has been shown that more simple urological examinations, such as flow, residual urine, and LUTS questionnaires prior to transplantation, can predict voiding dysfunction after RTx [22]. On the contrary, it remains uncertain whether all RTx patients would benefit from urological workup prior to surgery.

Urodynamic investigations after RTx seem to have high sensitivity for diagnosing bladder outlet obstruction in male patients after RTx. A study of 233 male RTx patients showed that 67% of men referred for urodynamic investigation after RTx were diagnosed with obstruction and TURP significantly relieved their lower urinary tract symptoms, using the International Prostate Symptom Score questionnaire before and after TURP [23]. Five patients in our study received TURP, of whom three still suffer from rUTIs after TURP.

Bladder and urinary tract function could also be screened using simple lower urinary tract assessment, for example, with questionnaires or even a thorough medical history. One study showed that a preoperative assessment with a validated overactive bladder questionnaire predicted the risk of postoperative urinary tract symptoms [24]. In our study, we assessed urinary tract symptoms from the medical history and found that this simple assessment was also associated with an increased risk of rUTIs. Conclusively, patients with a history of LUTS should be informed of the increased risk of urinary problems after RTx.

Overall, we observed that 56% of the patients with rUTIs were referred for a urological workup to explore the possible pathophysiology. The urological workup was not systematic, which should be criticized, although it revealed treatable diseases in a few patients. The most common diagnosis was residual urine, but no systematic definition was used, and repeat testing or even further urodynamic studies were used rarely, and thus the diagnosis should be interpreted with caution. Most patients with residual urine were offered clean intermittent catheterization. We observed that voiding cystourethrography was not used to explore the role of reflux as a causal mechanism for rUTIs in this cohort, which is a limitation. There was no systematic evaluation of the treatment effect and we do not know what the level of compliance was, which is problematic.

Female gender is the most consistent risk factor for rUTIs in previous studies of RTx [12,15]. It is uncertain whether age is a risk factor, as we demonstrated it to be [12,14,15,25]. The combination of increasing age and female gender for the risk of rUTIs is known in postmenopausal women in the general population [26]. The etiology is suspected to be caused by the shorter urethral length and estrogen-deprived atrophic mucosa. The use of local estrogen treatment was relatively common among our patients, but the effect on UTIs was difficult to evaluate.

Given the use of immunosuppressive therapy following RTx, it could be suspected that patients are susceptible to a wider range of microbes, but the distribution of microbes in this study seems to be equivalent to common cystitis among elderly women in the general population [27].

We were surprised to find that factors such as pretransplantation diabetes or other comorbidities were not associated with rUTIs. A study of 127 patients showed diabetes to be a significant risk factor for rUTIs [5], but this could not be found in a case-control study of 100 patients [14]. A review found diabetes to be associated with rUTIs in two out of seven studies [12]. We believe that no clear association can be concluded currently.

There has also been an interest in foreign bodies such as JJ stents and urinary catheter in relation to UTIs [5,28]. Our study did not find the duration of urinary catheter or JJ stent to be a risk factor for rUTIs. A large US study showed that intraoperative JJ stent placement was a risk factor for UTIs within the first 3 mo of transplantation [28]. In our cohort, prophylactic antibiotics were given 3 d before the removal of JJ stent, likely reducing the risk of infections, at least on a short term. However, it seems unlikely that short-term JJ stent or urinary catheter should increase the risk of rUTIs in the long term.

Here, a numerically higher number of patients with graft loss and death were found in the rUTI group than those without UTI, but the risk at 5 yr after transplantation was not statistically significantly different. The association between rUTIs and graft loss or death is a much-debated topic [15,25,29,30]. A retrospective cohort of 2469 renal RTx patients with a median follow-up of 5.7 yr found a two-fold increased risk of graft failure and a three-fold risk of death over a 10-yr observational period in rUTI patients compared with those without [15]. On the contrary, another retrospective study of 1019 RTx recipients showed no significant effect of rUTIs on graft or patient outcomes, but the lack of reporting the length of follow-up and missing a time-dependent analysis must be criticized [25]. A future analysis including other risk factors should elucidate the association between rUTIs, graft loss, and survival. In conclusion, due to the discrepancy in the literature, whether rUTIs are associated with graft loss and survival remains uncertain [10].

As this is a retrospective study, it is subject to bias due to missing data and can result in underdiagnosing rUTIs, especially considering that the definition of a UTI includes symptoms. Owing to the thorough follow-up and documentation in the Danish health care system, which has a nationwide electronic patient record system, we believe that the risk of missing infections is low. As all transplanted recipients had the same urinary anastomosis technique, we could not evaluate its effect on rUTIs. The incidence of rUTIs may be different in centers using different types of urinary anastomosis. Data regarding cytomegalovirus infections were not collected and were therefore not included in the risk factor analysis. Another limitation of the study is that only the UTI microbe with the largest count was included as a UTI agent. If all agents were included, the micro pattern may have appeared differently. This is a single-center study, which may impact the generalizability to other RTx cohorts.

Some studies show that the type of immunosuppressive treatment has not been found to affect the risk of rUTIs; we acknowledge that we did not analyse these data due to unknown dosage and treatment length, which could have given further insight into this association or the treatment of acute rejection [14]. Our transplantation center has strict protocols on immunosuppressive medicine regulation, and

every RTx recipient receives 6-mo prophylactic sulfamethoxazole/trimethoprim antibiotics.

The strengths of this study included the large sample size, long follow-up, and that we had access to complete data using the national Danish electronic medical chart system.

5. Conclusions

In conclusion, rUTIs are common after RTx, and there are several risk factors that can guide early detection and management. We could not demonstrate an effect of rUTIs on graft or patient survival. The pathophysiology of rUTIs in RTx patients is underexplored, also in this cohort, but is not necessarily different from the background population. There is an unmet need for urological investigations to explore both preventive and treatable options for RTx patients affected by rUTIs.

Author contributions: Anna C. Lin Halskov had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Halskov, Dagnæs-Hansen, Stroomberg, Sørensen, Røder.
Acquisition of data: Halskov, Dagnæs-Hansen.
Analysis and interpretation of data: Halskov, Dagnæs-Hansen, Stroomberg, Sørensen, Røder.
Drafting of the manuscript: Halskov, Dagnæs-Hansen, Røder.
Critical revision of the manuscript for important intellectual content: Halskov, Dagnæs-Hansen, Stroomberg, Sørensen, Røder.
Statistical analysis: Dagnæs-Hansen, Stroomberg.
Obtaining funding: Dagnæs-Hansen, Røder.
Administrative, technical, or material support: Halskov, Dagnæs-Hansen, Stroomberg, Sørensen, Røder.
Supervision: Dagnæs-Hansen, Stroomberg, Sørensen, Røder.
Other: None.

Financial disclosures: Anna C. Lin Halskov certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This project was partially funded by the Danish Kidney Association. The sponsor played a part in the design and conduct of the study, collection and management of the data, and analysis and interpretation of the data.

Data sharing: Owing to patient confidentiality, no patient sensitive data will be made available. The corresponding author can be contacted if further information is needed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.04.001.

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