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Original Research

A Retrospective View of Post Renal Transplant Urinary Tract Infections: An Experience of A UK Transplant Centre

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Abstract

Urinary tract infections (UTIs) are prevalent post renal transplant complication. These infections are most common in renal transplant recipient's contrary to their incidence in general healthy population as shown by previous studies. Though the frequencies of occurrences are different in renal transplant patients. There is general lack of consensus on the risk factors associated with development of UTIs in renal transplant patients as well as effects posed by them and occurrence of mortality in patient group. This retrospective cohort study investigated and included adults' patients who were operated for renal transplant in a single transplant center in UK from Jan 2014 to December 2023. The number of patients were 604 with two hundred and fifty-nine developed one or more UTIs in 42 months follow-up period. Significant risk factors for post-transplant UTIs were advanced age, female gender, reflux kidney disease, use of azathioprine and cadaveric donor. UTIs did not increase risk for renal graft loss, but were associated with increased mortality (3.5 odds ratio, 95% confidence interval 1.68–7.23). We conclude UTIs may be associated with an increased mortality risk in renal transplant recipients. Prevention of UTIs in high-risk renal transplant patients or those with recurrent UTIs may possibly decrease post-transplant mortality.

Keywords

Renal Transplant Recipients, Urinary Tract Infections, Bacterial Infections

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1. Introduction

Urinary tract infections (UTIs) after renal transplant in patients are common. The incidence of UTIs is more frequent in transplant population as compared to healthy and other populations [1-3]. Although there is lack of consensus on the frequency of incident and the reporting diverge in one study compared to other. The number of transplant receipts who suffered from at least one case of UTI was 94 out of 363 in 4 years follow-up while 31 out of 50 consecutive renal transplant patients suffering from UTI while followed up for one year. There was a difference of 30% in reporting follow up studies in these cases [4, 5]. The exact patient characteristics which perpetuate risk for developing UTIs after renal transplant are not cleared much until now. conflicting reports by previously conducted studies represents difficulties to point out patients' characteristics attributes as risk factors. Even incidence of post graft UTI is still debated and doubted. It may be attributed to graft rejection or chronic rejection or some other unknown valid reasons as the former reasons are refuted by some studies [1, 5-8]. Post graft complications are difficult in tackling and UTI is finest example of complications. The infectious nature of UTIs makes them lethal increasing risk of mortality and morbidity in renal transplant patients albeit UTIs are not directly associated with increase in kidney transplant patients [4, 9-12]. In our large population cohort in a single study center where renal transplantation is performed under a single surgical team. Primary objectives of this study are to identify causative factors leading to development of UTIs in renal transplant patient and analysis of UTIs on patients' survival and effects on graft inserted.

2. Materials and Methods

We performed a retrospective cohort study in University hospitals Coventry and Warwickshire (UHCW), NHS trust. Electronic medical records of renal transplant patients age ≥ 18 years at the time of renal transplantation were included with effect from Jan 2014 to December 2023. The occurrence of UTI after renal transplant was primary objective which was indicated with a positive urine culture and consistent urine analysis. The number of colonies forming units of pathogenic agent and positive urinary leukocyte esterase or nitrate was positive indicator of UTI. Follow up of each renal transplant patient was conducted to source urinalysis with microscopic examination coupled with urine culture when they presented symptoms typical of UTI consistently. Post renal transplant UTI, loss of renal graft or subsequent patient's mortality was second objective of this study. the loss of renal graft meant the presence of requirement for dialysis or loss of functioning graft when patient expired. Consequently, following variables were acquired after careful collection including patient demography, type of donor viz. cadaveric or living, etiology of end stage renal disease (ESRD), microorganism isolated from the site of infection or maintenance of immunosuppressant therapy. Then pathogens thus obtained were categorized as Escherichia, enterococcus, staphylococcus, streptococcus, klebsiella, pseudomonas or fungal species. The immunosuppressant regimen used for renal transplant included calcineurin inhibitors (tacrolimus or cyclosporin A), corticosteroid like prednisolone (500 mg intravenous followed by 30 mg oral tabs on day 1 which was tapered slowly as 7.5 to 10 mg each day), and anti-metabolites like azathioprine or mycophenolate mofetil). Sirolimus was prescribed in patients intolerant to traditional drugs. All patients received anti-thymocyte globulin intravenously for induction or IL blockers depending on the immunological risks independently assessed for each patient by surgically operating team in research center. The standard procedure for transplantation was followed including urethral catheterization each patient pre-operatively and was removed 3-5 days after transplant procedure. Patient received prophylactic doses of antibiotics on the day of surgery. They included cefazoline or clindamycin, penicillin allergic patients.

It was individually decided to insert urethral stent in each patient by operating surgeons and were removed after 4-7 weeks of transplant procedure. Sulfamethoxazole-trimethoprim or sulfisoxazole (TMP-SMX) were prescribed for 6 months after transplant prophylactically. Patients who were allergic to TMP-SMX were prescribed dapsone for the same period of time.

Table 1. *Patients' demographics in association with incidence of UTIs.*

Demographics		Patients with No UTI	Patient with UTI	P-Value
Age (Mean age in years)		45 ±15.3	46 ±13.2	0.45
Gender	Male	79 (253)	73 (138)	< 0.45
	Female	22 (54)	69 (159)	
Race	White	89	78	<0.01
	Black	22	16	0.15
	Asians	9	4	0.02

Demographics	Patients with No UTI	Patient with UTI	P-Value
Clinical Profile			
Cadaveric donor	58	49	0.04
Causes of ESRD			0.32
Diabetes (129)	59	41	0.78
Glomerulonephritis (94)	59	63	0.76
Hypertension (93)	61	39	0.40
Reflux (31)	34	69	0.01
Other (69)	56	44	0.82
Immunosuppressants			
Cyclosporine A	85	88	0.73
Tacrolimus	11	9	0.74
Sirolimus	7	4	0.29
azathioprine	12	9	0.21
Clinical Outcomes			
Loss of graft	13	13	0.96
Death of patient	12	4	0.1

Categorical variables were statistically analyzed with chi-square testing while continuous variables were inferred with student t-test. Multivariate analyses were processed with conditional logistic regression using Microsoft Excel and R Programming. This study was reviewed and approved by UHCW ethical review board. The article should be written in English. An article should be between 6 and 25 pages, and exceed 2000 words. For original research articles, it should include the headings Introduction, Materials and Methods, Results, Discussion and Conclusions. Other types of articles can be written with a more flexible structure.

3. Results

A total of 604 consecutive adult patients underwent renal transplantation at a single center (UHCW) between January 2014 and December 2023. The recipient population included 391 males and 213 females, with a mean age of 44 ±12.6 years at transplantation (range 18-79 years). Patient characteristics are summarized in Table 1.

Among the 604 patients, 43% (259 patients) experienced at least one UTI during a mean follow-up of 48 months (range 6–78 months). Of these, 27% (137 patients) had more than one UTI post-transplantation. The number of UTIs per patient ranged from 1 to 13, with a mean of 2.8 UTIs over the study period.

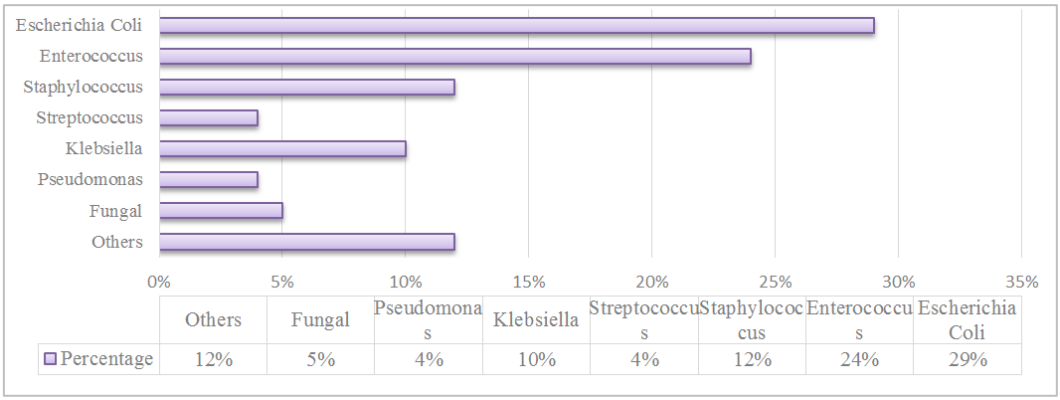

Figure 1. *Relative frequencies of Organisms isolated from Urinary Culture samples.*

During the study period, 37 of the 604 transplanted patients died. The cause of death could only be determined for 23 patients using their medical records and/or the United Network of Organ Sharing (UNOS) database (Table 2). Sepsis was the leading cause of death (43%, 11 patients), followed by malignancies (5 patients).

Table 1. *Causes of death in renal transplant patients.*

Causes of death	Number of patients	Percentage with UTIs
Septicemia	11	45%
Malignancies	6	26%
Cardiovascular events	4	50%
Others[a]	4	50%
Unknown[b]	14	79%

[a] the cause of death was determined in 23 of 37 patients who had died over the study period.
[b] suicides, respiratory collapse, diabetic ketoacidosis and hemorrhage.

(22%) and four from cardiovascular events (17%). Nine of the 10 patients who died from sepsis had post-transplant UTIs, while only two of the five patients who died from malignancy and two of the four patients who died from cardiovascular events had post-transplant UTIs respectively. There was a statistically significant higher incidence of UTIs in female patients ($p < 0.01$).

Female transplant recipients had a significantly higher rate of post-transplant UTIs (68%) compared to males (30%). UTIs were also more common in older patients (55% for ≥65 years vs. 38% for ≤30 years). Among patients with four or more UTIs post-transplant, 71% were female. The most frequent causative organisms were Escherichia, Enterococcus, Staphylococcus, and Klebsiella (details in Figure 1).

Table 3. *Adjusted odds ratio for post-transplant urinary tract infections.*

Variable	Adjusted odd ratio	95% Confidence interval
Female gender	5.8	3.79 – 8.89
Age (per year)	0.02	1.0 – 1.04
Pre-transplant reflux disease	3.0	1.05 – 8.31
Azathioprine (Imuran)	1.9	1.02 – 3.58
Living donor	0.67	0.45 – 1.00

Multivariate analysis revealed advanced age, female gender, pre-transplant reflux kidney disease, and azathioprine use as significant risk factors for post-transplant UTIs. Living-donor kidney transplantation offered protection compared to cadaveric donors (Table 1). UTIs did not influence graft rejection or loss, but showed an association with mortality (OR 3.5, 95% CI 1.68-7.23) (Table 3). Notably, Pseudomonas as the main UTI pathogen significantly increased mortality risk (OR 12.5, CI 2.07-75.99), while none with Streptococcus died (Table 3).

4. Discussion

Urinary tract infections (UTIs) are a common and prevalent pathogenic condition affecting the human body, and are considered an undisputed morbid condition in kidney transplant patients [13-15]. The academic literature suggests that UTIs may carry much more significance in these patients than previously recognized, as studies have found an increased mortality risk associated with UTIs in renal transplant patients [16].

Similar to the general population, research has shown that female gender and advanced age are risk factors for developing UTIs in renal transplant recipients [13, 16]. The difference in urinary anatomy, with women having a shorter urethra and the urethral opening being in closer proximity to the vagina and anus, is often attributed as the reason why women are at higher risk for UTIs compared to men [16].

Older patients, particularly those over the age of 65, are at a higher risk for UTIs, presumably due to factors such as impaired mobility, poor hygiene in institutionalized individuals, higher rates of urinary retention secondary to benign prostatic hypertrophy and/or bladder atrophy, and a defective native immune system [13].

This study has identified several additional patient characteristics, beyond advanced age and female gender, that are independently associated with an increased risk of urinary tract infections (UTIs) in the renal transplant population [14]. These findings suggest that UTIs may be an important and underappreciated complication in kidney transplant patients, warranting increased clinical vigilance and targeted preventive strategies.

One key risk factor that has been identified is the type of kidney donor. Recipients of cadaveric kidneys were found to have an increased risk of developing UTIs, which has also been observed in previous studies [17]. Studies that have included a high percentage of cadaveric organ recipients have reported the highest rates of post-transplant UTIs. For example, previous research found a very high incidence of post-transplant UTIs, with 50 renal transplant recipients developing 144 UTIs over a 1-year period, though 98% of the patients in this study received cadaveric organs [4]. In contrast, the incidence of post-transplant UTIs is reported to be much lower in studies that have evaluated renal transplant recipients who primarily receive their grafts from living donors [1, 3, 18].

Our findings suggests that the type of kidney donor may be an important factor in the development of urinary tract infections (UTIs) in the renal transplant population. Specifically, studies have found that recipients of cadaveric kidneys are at a higher risk of developing UTIs compared to recipients of living donor kidneys [4, 17].

The increased risk associated with cadaveric kidney transplants may be attributable to several factors. First, the prolonged ischemia time experienced by cadaveric kidneys during the transplantation process can lead to greater injury and compromise of the renal allograft, which may increase susceptibility to infections, including UTIs [1, 3, 18]. Additionally, the more potent cytotoxic immunosuppressive agents that are routinely used in cadaveric organ transplantation may further contribute to the elevated risk of UTIs in these patients [1, 3, 18].

The need for chronic immunosuppressive medications to prevent rejection is a universal feature of renal transplantation. The suppression of the immune system can intuitively increase the risk of infections, including UTIs, in these patients. Interestingly, the academic literature has also identified differences in the risk of UTIs among various immunosuppressive medications. Specifically, studies have found that the use of azathioprine, when compared to other commonly used immunosuppressive agents, was associated with a higher incidence of UTIs in renal transplant recipients [1, 3, 12, 18].

These findings highlight the importance of tailored prevention and management strategies for UTIs, particularly in recipients of cadaveric kidney transplants and those receiving immunosuppressive regimens that may confer a higher risk of this complication. Increased clinical vigilance and targeted interventions are warranted to mitigate the risk of UTIs and their associated complications in the renal transplant population.

We did not find pre-transplant diabetes to be associated with an increased incidence of UTIs. Diabetic patients, especially women, have been shown to have a higher incidence of significant bacteriuria [15, 19]; therefore, we expected this trend to continue after renal transplantation. The lack of impact by diabetes may be due to the overall high incidence of UTIs in our renal transplant population, as well as the frequent development of post-transplant diabetes mellitus in many of these patients, of which we did not control for in our study. Previous published studies report conflicting results whether a history of diabetes increases [2, 6, 17] or does not influence the renal transplant patient's risk of developing a UTI [1, 5].

Vesicoureteral reflux disease increased the relative risk for development of a UTI in our renal transplant population. This is consistent with the results published by Erturk et al [20] who reported a high incidence of UTIs in these patients: 56% of 36 renal transplant patients with history of vesicoureteral reflux developed at least one UTI over a mean period of 54 months. They recommend ureteral reimplantation in these patients as they found this additional procedure would reduce the incidence of post-transplant UTIs, but cautioned against routine prophylactic nephrectomies. Other causes of ESRD were not found to significantly increase the risk of post-transplant UTIs in our renal transplant patients.

Besides this study also has revealed that uropathogens other than Escherichia coli (E. coli) are frequently isolated in urinary cultures of renal transplant recipients. Previous retrospective studies have also reported a high prevalence of non-E. coli organisms in this patient population [1, 5, 21].

While E. coli remains the most commonly cultured organism, it was isolated in less than one-third of the urine cultures in the studies reviewed. This is in contrast to the general population, where E. coli is reported to be the cause of 80–90% of urinary tract infections (UTIs) [13, 22].

Notably, we also identified Enterococcus species, which are relatively infrequent uropathogens in non-renal transplant patients, as the second most common cause of UTIs in the transplant population. This finding is significant, as the presence of Enterococcus may be suggested by a nitrite-negative but positive leukocyte esterase result on urinalysis, which should accordingly guide the selection of appropriate antibiotic therapy [13].

Importantly, this is the first published study using data obtained from a careful review of patient records to find that UTIs may be associated with a significantly increased mortality risk in renal transplant patients. This finding is perhaps not surprising, as UTIs have been shown to be the most common source of bacteremia in renal transplant recipients, and infectious diseases are currently the second leading cause of death in this population [4, 11, 21].

We also suggest that aggressive treatment and prophylaxis for urinary tract infections (UTIs) may be more important than previously realized in renal transplant recipients [1, 5]. Clinicians should be vigilant in recognizing and appropriately managing these infections, particularly those caused by non-Escherichia coli (E. coli) uropathogens, to mitigate the significant morbidity and mortality associated with this complication in the renal transplant population [22].

However, this study has several limitations. The reported UTI incidence likely underestimates the true incidence, as some locally treated UTIs were likely not identified in the review of patient records. Additionally, the criteria used to diagnose a UTI were primarily based on a positive urine culture, without requiring the presence of typical signs or symptoms [1, 14, 17, 20]. Renal transplant recipients, like other immunocompromised patients, may be more likely to be asymptomatic and not mount the typical inflammatory response to infections.

Furthermore, the study did not have time-dependent information on the post-transplant UTIs, and thus could not answer important questions regarding the effectiveness of the routinely prescribed 6-month antibiotic prophylaxis or the association between the timing of UTIs and increased mortality [21].

Finally, the study did not control for other significant comorbidities that may have been more frequent in the renal

transplant patients with UTIs, suggesting that the increased mortality may have been a marker for patients already at high risk, rather than a direct consequence of the UTIs [11].

5. Conclusion

The present study raises several clinically pertinent questions warranting future investigation. The findings suggest a potential association between urinary tract infections (UTIs) and increased mortality risk in renal transplant patients, but the impact of UTI prevention on survival remains unclear.

This study identified several patient characteristics, including female gender, advanced age, history of vesicoureteral reflux, azathioprine use, and cadaveric donor, as independently associated with increased post-transplant UTI risk. However, these associations require validation in a prospective study. further investigations in this regard can provide better understanding of associations between characteristics of patients as well as validation of results in a prospective study.

Furthermore, the potential benefits and risks of prolonged or lifelong prophylactic antibiotic therapy in patients prone to UTIs or with high-risk pathogens merit investigation. Additionally, the impact of routine screening for asymptomatic UTIs and subsequent treatment on morbidity requires elucidation.

These questions can be addressed through well-designed prospective studies that overcome the limitations of the retrospective data used in the current study, potentially informing improved care for renal transplant patients.

Abbreviations

UTI	Urinary Tract Infections
OR	Odd Ratio
UHCW	University Hospitals Coventry and Warwickshire
SMP-TMX	Sulfamethoxazole-Trimethoprim
UNOS	United Network of Organ Sharing

Author Contributions

All authors contributed to the study conception and design Material preparation, data collection Allan Karim Odoch, Shruthi Katam, and Pooja Bobbiti, analysis were performed by Mirab Singh, Mahlet Alemayehu Mechessa, and Alidjanov Xodjiakbar kashipovich, The first draft of the manuscript was written by Tochukwu Anthony Akwue, Nnamdi Cletus Opara, and Tseganesh Mekonnen Hailemariam. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability Statement

The data is available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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