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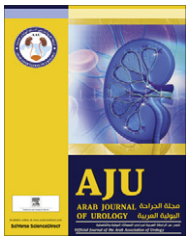

RENAL/TRANSPLANTATION

REVIEW

Urinary tract infection in renal transplantation

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KEYWORDS

Renal transplantation;
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Treatment;
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ABBREVIATIONS

ABU, asymptomatic bacteriuria; KTX, kidney transplantation; EAU, European Association of Urology; CMV, cytomegalovirus; TMP, trimethoprim; SMZ, sulfamethoxazole

Abstract ***Introduction:*** Urinary tract infection (UTI), especially recurrent UTI, is a common problem, occurring in >75% of kidney transplant (KTX) recipients. UTI degrades the health-related quality of life and can impair graft function, potentially reducing graft and patient survival. As urologists are often involved in treating UTI after KTX, previous reports were searched to elucidate underlying causes, risk factors and treatment options, as well as recommendations for prophylaxis of UTI after KTX.

Methods: Pubmed/Medline was searched and international guidelines and recommendations for prevention and treatment of UTI after KTX were also assessed.

Results: Most studies on UTI after KTX have a small sample, and are descriptive and retrospective. Many transplant- and recipient-related risk factors have been identified. While asymptomatic bacteriuria is often treated, even though some studies advise against it, symptomatic UTI should be treated empirically after collecting urine for microbiological analysis, to avoid the development of transplant pyelonephritis with a high chance of urosepsis. The duration of treatment has not been determined in studies and recommendations refer to the treatment of complicated UTI in the non-transplant population. Prophylaxis has not been the focus of studies either.

Conclusion: UTI after KTX is still largely an under-represented field of study, despite many recipients developing UTI after KTX. Prospective studies on this topic are urgently needed.

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Introduction

UTI, especially recurrent UTI, is a common problem in recipients after kidney transplantation (KTX). Acute UTI not only affects a patient's well-being but also gives rise to several issues that must be addressed in a transplant recipient. These include interaction of antibiotic medication with immunosuppression, the isolation of and infection with resistant bacteria, growth of *Candida* spp. due to antibiotic treatment, and finally recurrent UTI. Most importantly, urosepsis with impairment of graft function are potential long-term sequelae of recurrent UTI in KTX recipients. As urologists are often involved in treating UTI after KTX, previous reports were searched with the aim of elucidating the underlying causes, risk factors and treatment options, as well as recommendations for prophylaxis of UTI in this specific subset of patients.

Methods

PubMed/Medline was searched for previous relevant reports, as well as for guidelines on the topic of UTI after renal transplantation.

Types of infection after KTX

According to the guidelines of the European Association of Urology (EAU) [1], UTI after KTX might present either as asymptomatic bacteriuria (ABU) or as symptomatic infection (Table 1). Symptomatic UTI after KTX is defined as a 'complicated' UTI, as are all UTIs (also in the non-transplant population) after surgery of the urinary tract. Furthermore, other criteria defining 'complicated' UTI, such as occurrence in an immunodeficient patient, are fulfilled in the situation after KTX.

The site of infection

The most common site of UTI after KTX is the urinary bladder (>95%), followed by renal transplant pyelonephritis. Occasionally, an infection of the native kidneys can develop. All other urological infection sites are rarely involved, and infection is most often atypical. Nevertheless, these forms must also be considered in a transplant recipient, as prostatitis due to *Cryptococcus* [2], *Aspergillus* [3] or *Salmonella* [4] has been described, as well as epidydimitis with *Klebsiella* [5], *Mycobacterium haemophilum* [6] or due to cytomegalovirus (CMV) [7] or tuberculosis [8]. Also, orchitis due to salmonellosis [9] and CMV ureteritis have been described in the context of renal transplantation [10]. Recipients of a combined pancreas–kidney transplant with drainage of the exocrine pancreas to the bladder might also develop (nonbacterial) urethritis [11].

When and how often?

UTI after KTX is a common event and cumulatively affects >75% of adult and >30% of paediatric transplant recipients [12].While Saemann and Horl [13] found that most UTIs observed in the first year after KTX occurred within the first 3 months, Senger et al. [14], in a prospective study, found that <30% of the

Table 1 Types of urinary tract infection (according to EAU guidelines).

	Type	Clinical appearance	Urine
1	Acute uncomplicated lower UTI, cystitis (woman)	Dysuria, urgency, frequency	• 10^3 cfu/mL • 10 WBC/mm^3
2	Acute, uncomplicated upper UTI: pyelonephritis	Fever, flank pain, no urologic abnormalities	• $>10^4$ cfu/mL • 10 WBC/mm^3
3	Complicated UTI	Symptoms from 1 and 2 plus at least 1 complicating factor: Operative or radiotherapeutic changes of urinary tract Immune deficiency Ureter stent/bladder catheter, intermittent self-catheterisation Diabetes mellitus Residual vol. >100 mLNeurogenic bladder Vesico-ureteral reflux BOO	• 10 WBC/mm^3 • $>10^5$ cfu/mL (female) • $>10^4$ cfu/mL (male)
4	Asymptomatic bacteriuria	No urologic symptoms	• 10 WBC/mm^3 $>10^5$ cfu/mL in two urine samples > 24 h apart
5	Recurrent, uncomplicated UTI	Only female three episodes of uncomplicated UTI/1 year; no structural or functional pathology	$<10^3$ cfu/mL

Cfu, colony-forming units, WBC, white blood cells.

Table 2 Underlying causes and predisposing factors for UTI in transplant recipients.

Type	Factors
Recipient	Female gender
	Age
	Recurrent UTI prior to renal transplantation
	Diabetes mellitus
	Urinary tract abnormalities (reflux, bladder dysfunction, BPH, hydronephrosis)
	Prior urological operations
	Length of dialysis
	Re-transplantation
Organ	Deceased donor
	Duplicated ureter
Transplantation	Foreign material (ureteral stent, bladder catheter)
	Immunosuppressive regimen: MMF, azathioprine, ATG
	Rejection
	Transplant dysfunction
	Instrumentation of the urinary tract

MMF, mycofenolate mofetil; ATG, anti-thymocyte globulin.

recipients developed UTI within 3 months of KTX. A large retrospective cohort study of almost 29,000 transplant recipients in the USA, combining data of the US Renal Data System with Medicare data, found that the cumulative rate of UTI after KTX was 60% for female and 47% for male recipients after 4 years, with only 17% developing an early UTI within the initial 3 months [15].

Clinical presentation of UTI after KTX

As in the non-transplant population, painful voiding, urgency, frequency, and occasional pain of the lower abdomen and haematuria are the leading symptoms of UTI after KTX, at times accompanied by fever. However, as the transplanted organ has been denervated during transplantation, and as the recipient most often is under immunosuppression with cortisone, symptoms can be masked, especially in older recipients. Elevated leucocyte levels and C-reactive protein are apparent in blood samples. Most importantly, transplant dysfunction plus fever in a transplant recipient is highly suggestive of UTI, irrespective of the patient's subjective well-being.

What kind of infection?

The type of infection strongly depends on where it is acquired (community or hospital) and on regional differences. Thus, close cooperation with the local microbiologist is an important prerequisite for an adequate treatment of UTI after KTX. As in the non-transplant population, UTI is most often due to infection with *Escherichia coli* (30–80%) or other Gram-negative bacteria like *Klebsiella* (≈10%), *Proteus* (≈5%) or *Pseudomonas aeruginosa* (≈10%). Gram-positive enterococcus (15–30%) or *Staphylococcus aureus* (≈10%) is found more often than in the normal population. Besides these agents, *Candida glabrata/albicans*, and BK virus and CMV or tuberculosis, must also be included in the differential diagnosis, and e.g. schistosomiasis, depending on the individual situation. Concerning the time after KTX, *Pseudomonas* and *Staphylococcus* infections most often appear in the first month, while enterococci and *E. coli* have been found to appear thereafter [13,16–18].

Underlying causes and predisposing factors

Several underlying mechanisms promote UTI after KTX (Table 2). Recipient-related factors such as female gender and age or history of recurrent UTI, diabetes mellitus, and urinary tract anomalies increase the risk, as does the waiting time before KTX. The influence of recipient age and waiting time underlines that the problem of UTI in KTX will tend to increase in the future, as we will be confronted with even longer waiting times and older recipients. Organ factors (like re-transplantation, duplex ureter, deceased donor) as well as transplantation factors (Foley catheter, ureteric catheter, transplant dysfunction, rejection) might also increase the risk of UTI [15,19–21]. Also, the type of immunosuppression could affect the development of UTI after KTX; while calcineurin inhibitors, irrespective of the type (cyclosporin/tacrolimus) do not make a difference [22], nor does the use of everolimus vs. cyclosporin [23], agents found to increase the risk were azathioprine [24], mycofenolate mofetil [20] and anti-thymocyte globulin [17]. Steroid withdrawal was not found to have an effect on UTI [25].

The consequences of UTI in KTX

UTI after KTX can affect transplant function and transplant survival, as well as recipient survival. For lower urinary tract infections (excluding transplant pyelone-

phritis), early studies found a negative effect on graft function [26], while later studies failed to confirm this effect [27]. The reason might be a change in the immunosuppressive regimen. While simple lower UTI does not seem to affect transplant function, it can develop into transplant pyelonephritis in ≈20% of cases [15,19,21,28]. In these cases, the consequences might not only affect graft function, which was found to be reduced after transplant pyelonephritis, but 10–12% of patients develop urosepsis which can be lethal in almost half [18,24,29]. Chuang et al. [24] reported that nine of 10 transplant recipients who died due to sepsis had UTI.

As to when UTI is observed after KTX, late infection was often referred to as 'benign'. Contrary findings were published by Dupont et al. [30] who, in a cohort with recurrent UTI > 3 years after KTX, found that > 75% of recipients had cortical scarring in a DMSA-single-photon emission CT evaluation, irrespective of ureteric reflux. The large cohort study of almost 29,000 recipients of Abott et al. [15] found that for symptomatic UTI at > 6 months after KTX the relative risk of graft loss was 2.35 times and the risk of recipient death was 1.33 times higher than in the non-UTI recipients. Results were adjusted for cardiovascular complications and were not affected by UTI acquired in the community or in the hospital. Even though UTI in this study might just be a surrogate variable for more morbid patients and graft loss or recipient death not directly linked to UTI, the concept of 'benign' UTI, if it appears late after KTX, does not seem to be realistic. Each symptomatic UTI is potentially dangerous for graft function, graft survival, and even patient survival.

Diagnosis

The diagnosis of UTI after KTX begins with the transplantation itself. Many centres perform a microbiological analysis of the medium in which the deceased donor kidney was transported. If the recipient develops signs and symptoms of UTI, evaluation should include urine analysis (dipstick/sediment) and always a urinary culture. Also, BK and/or CMV infection should be excluded. Infection variables of blood (C-reactive protein, leucocytes) might help in differentiating between infection and rejection in a dysfunctional graft. The level of immunosuppression must be re-evaluated to exclude over-immunosuppression. Also, imaging (ultrasonography) should exclude post-renal causes of infection (urolithiasis, urinary tract obstruction, 'forgotten' ureteric stent, etc.) [1,12,19].

Therapy of symptomatic UTI

The necessity of treating symptomatic UTI derives from a cascade of events leading to the development of transplant pyelonephritis in 20% of cases, with a risk of subsequent life-threatening urosepsis. Symptomatic UTI should first be treated empirically after having excluded BK virus infection, with a subsequent treatment according to the microbiological findings in pretreatment urine. The duration of treatment is not clear, a time of at least 2 (up to 4) weeks has been recommended.

Interaction with immunosuppression must be considered, such as increased nephrotoxicity of trimethoprim-sulfamethoxazole (TMP-SMZ) and gentamicin in recipients taking calcineurin inhibitors. Most importantly, resistance to antibiotics must be considered, e.g. *E. coli*, *Klebsiella* and *Proteus* might be resistant to TMP-SMZ in 60–100% and to ciprofloxacin in > 75% of infections [13]. As mentioned above, cooperation with the local microbiologist is of utmost importance to select the best treatment based on the local resistance spectrum. Fosfomycin, although typically used to treat women with uncomplicated UTI, has been applied successfully in transplant recipients, as has nitrofurantoin. Here, renal insufficiency must be excluded, as otherwise the amount excreted might be too low and the risk of polyneuropathy can be increased [1,12,19].

Surgical therapy of recurrent UTI after KTX must aim at long-term optimization of urinary drainage. This includes (besides early removal of ureteric stents and bladder catheters) treatment of obstructed transplant ureters, urolithiasis, and BOO from causes like BPH. The effect of re-operation of a refluxive transplant kidney is not clear, as despite anti-refluxive ureteric implantation, reflux is common and appears in > 80% of cases [1]. Nephrectomy of native kidneys has been used successfully in refluxive kidneys to reduce recurrent UTI [16] but should (according to the EAU guidelines) rather be seen as the 'last option' treatment [1]. The same holds true for polycystic kidneys. For hereditary polycystic kidneys (autosomal dominant polycystic kidney disease) success after nephrectomy has been described, but not for acquired polycystic kidneys in patients with renal insufficiency [14,31]. Finally, some authors reported successful surgical intervention for resection of a ureteric stump after native kidney nephrectomy [32].

Therapy of asymptomatic bacteriuria

ABU ($> 10^5$ colony-forming units/mL in two urine samples > 24 h apart) is common in renal transplant recipients. Although treatment is often used, it remains unclear whether each ABU must be treated. Studies promoting treatment have found reduced transplant function due to ABU and a higher virulence of *E. coli* [13,16,18,33]. Other studies question the benefit of antibiotic treatment of ABU, as the effect was found to be insufficient [34], the risk of selection of resistance was higher than the expected benefit, and the virulence of *E. coli* was not found to be higher in transplant recipients [35]. Only one prospective study has been published on treating ABU in transplant recipients [34]. Recipients were either treated according to the antibiogram or not

Table 3 Prophylaxis of UTI in transplant recipients.

Early removal of foreign material (catheter)	
TMP 160 mg/SMZ 800* especially in high-risk patients:	Reflux
	Re-transplantation
	Voiding disorder
Vaccination	Inactivated species of *E. coli*, *Morganella morganii*, *Proteus*, *Klebsiella*, *Enterococcus faecalis*
General behaviour	Excretion minimum > 2 L/day
	Urine dipsticks at home, 'home treatment on demand'
	Genital hygiene (wiping after urination: vaginal ⩾ anal)
	Urine pH 5.8–6.5 (vitamin C, methionine)
	Vaginal oestrogen/lactobacillus
	Intermittent self-catheterization for residual urine
	Cranberry products (juice/tablets)

* Double dose of TMPS-SMZ (320 mg TMP/1600 mg SMZ) has been applied more successful in one study.

treated and followed for a year. Recurrent bacteriuria was found in 58% vs. 73% and the development of symptomatic UTI in 21% vs. 31%. Differences were not significant, so that the authors questioned the necessity of treating ABU. The most recent study on this topic is a retrospective analysis by El Amari et al. [36]. Comparing treated vs. untreated ABU with *E. coli* and *Enterococcus faecium* later than 1 month after KTX, these authors found no significant differences for progression to symptomatic UTI (untreated 2%, treated 0%) nor for clearance of ABU (untreated 59%, treated 55%). In the group of treated patients, 78% of the non-responders to antibiotic treatment showed resistance to the antibiotic regimen. Overall, the need for treating ABU in kidney graft recipients remains unclear.

For candiduria, most often caused by *C. glabrata* and *C. albicans*, treatment is always recommended to prevent local fungal complications. Interestingly, asymptomatic candiduria was found to be a risk factor for patient survival. As treatment does not improve patient survival, asymptomatic candiduria (like late bacterial UTI) might rather be seen as a surrogate variable for overall recipient morbidity [37,38].

Prophylaxis

Only few study results are available on the prophylactic treatment of recurrent UTI after KTX (Table 3). Removal of the catheter as early as 36–48 h after KTX was found to be favourable and feasible [39]. The voiding situation must be assessed in recurrent UTI and complete bladder emptying should be achieved, at times with clean intermittent catheterisation. Also, long-term administration of TMP at 160 mg and SMZ at 800 mg for 6 months, especially in high-risk patients with urinary reflux, re-transplantation, and/or voiding disorders, is recommended [1,40]. Concerning the dose of antibiotics Khosroshahi et al. [41] reported a reduction of UTI from 50% to 25% if the TMP-SMZ dose was doubled. Nevertheless, in a recently published review, Green et al. [42] found a reduction of bacteriuria (– 60%) and of bacteraemia (– 87%) in treated transplant recipients, but no effect on graft or patient survival. Although the follow-up was short, it might be discussed whether treatment of asymptomatic UTI in transplant recipients constitutes overtreatment.

Recently published guidelines (Kidney Disease Improving Global Outcome) [43] only recommend prophylaxis for preventing cystitis after KTX with 6 (to 12) months of treatment with TMP-SMZ. Treatment with ciprofloxacin is discouraged due to the risk of *Pneumocystis carinii* pneumonia. Unfortunately, these guidelines fail to cover any other relevant topic of UTI after KTX.

Vaccination and improvement of the protective urothelial glycosaminoglycan sheath (Uropol™, Medac, Germany) are recommended for prophylaxis of recurrent UTI in the non-transplant population. Data for the transplant population are lacking. Nevertheless, in a personal communication with different manufacturers, vaccination with a mix of inactivated organisms (*E. coli*, *Morganella morganii*, *Proteus*, *Klebsiella*, *Enterococcus faecalis*) in an intramuscular vaccination setting (once every second week for 3 times, Strovac®, Sanego, Germany) was not discouraged, while oral vaccination with lyophilised *E. coli* fractions (Uro-Vaxom®, vifor Pharma, France) and chondroitin sulphate bladder instillations were discouraged, due to the lack of studies.

Despite the lack of studies, instruction for nutrition and general behaviour modifications might prevent UTI to some extent after KTX. This includes teaching the patient about genital hygiene (wiping after urination: vaginal ⩾ anal), increasing fluid consumption to > 2 L/day, regularly checking the urine at home with urine dipsticks, and starting early treatment if the urine is pathological, and regularly checking the acidity of the urine (pH should be 5.8–6.5) and acidifying it as needed (vitamin C, methionine). Also, vaginal oestrogenization must be checked and optimised by the gynaecologist. Use of *Lactobacillus* suppositories and cranberry products (juice/tablets) might also help to prevent UTI. For cranberry juice there are no studies for patients after KTX, but for the normal population some authors

reported a reduction of UTIs [1,44] while others found no preventive effect [45].

Conclusion

Although KTX is generally accepted as the best treatment for end-stage renal disease, prevention and therapy of UTI, even though cumulatively occurring in >75% of recipients, have not been studied widely. Recommendations are mostly based on small, retrospective studies or on data obtained from treating complicated UTI in the non-transplant setting. However, some recommendations can be made for this specific patient group. Large prospective long-term studies are desperately needed.

Conflict of interest

I herewith disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, the work.

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