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Symptomatic Urinary Tract Infections in Renal Transplant Recipients after Cystoscopy for Ureteral Stent Removal

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Abstract

Introduction—Symptomatic urinary tract infection (UTI) is a known complication of cystoscopy with ureteral stent removal. However, little is known about the incidence and risk factors for post-cystoscopy UTI in renal transplant recipients, who likely represent a high-risk cohort. Our aim was to determine the infection rate following cystoscopy with stent removal in this population and identify opportunities for care improvement.

Methods—We performed a retrospective cohort study of office cystoscopies with stent removal in renal transplant recipients performed at a single institution from April 2012 through May 2014. Strict criteria were used to determine presence of symptomatic UTI within one month of the procedure. Fisher's exact tests were completed to examine associations between patient characteristics and post-transplant outcomes with UTI.

Results—A total of 324 patients were included. Mean age was 50.0 (SD 13.1) years, and 187 (57.7%) patients were male. Within this group, 165 (52.5%) patients received a pre-procedural oral fluoroquinolone antibiotic dose prior to the procedure. Nine patients had symptomatic UTIs (2.8%), of which three infections (33.3%) were due to quinolone-resistant organisms. Female sex ($P=0.04$), but no other patient or post-operative characteristic was associated with symptomatic UTI, including the use of peri-procedural antibiotics.

Conclusions—The incidence of symptomatic UTI after cystoscopy with ureteral stent removal in renal transplant recipients is less than three percent and comparable to post-cystoscopy UTI risk in the general population. Female sex is associated with symptomatic UTI. Further investigation is needed to identify groups most at risk for UTI and other complications.

Keywords

Cystoscopy; Ureteral catheterization; Renal transplantation; Urinary tract infection

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Introduction

Cystoscopy for ureteral stent removal after renal transplant is a common reason for urology referral. Placement of stents after renal transplantation serves to decrease the occurrence of post-transplant urologic complications such as ureteral anastomotic leak and obstruction^{1,2}. The transplant stent is typically removed by a urologist 4–6 weeks after transplant.

Urinary tract infection (UTI) is common after renal transplant, and evidence is conflicting regarding whether ureteral stent placement/removal further contributes to an increased incidence of bacteriuria or UTI.^{3,4} Due to the presence of comorbidities, recent genitourinary (GU) manipulation and the use of immunosuppressive medications to prevent organ rejection, renal transplant recipients are likely predisposed to acquiring infections and are commonly prescribed daily antibiotic prophylaxis.⁵

In the general population, cystoscopy is a well-tolerated procedure; however, urinary tract infection (UTI) is a known post-procedural complication. Studies report asymptomatic bacteriuria occurring in 5–25% of patients and symptomatic infection occurring in approximately 5% of patients.^{6–9} Guidelines from the American Urological Association (AUA) and the American Society of Health-System Pharmacists (ASHP) recommend pre-cystoscopy antibiotic administration in patients at increased risk of infection (e.g., advanced age, abnormal urinary tract, indwelling tubes, use of immunosuppression; Appendix) and those undergoing manipulation of their GU tract.^{10,11} Nonetheless, benefits of prophylaxis must always be balanced with risks of antibiotic complications and resistance.¹²

Prior studies have not examined the rate of infection after cystoscopy and stent removal when performed in renal transplant recipients. We performed a retrospective cohort study to determine the rate of symptomatic UTI in transplant patients undergoing cystoscopic stent removal, and the influence of antibiotic prophylaxis in this population.

Methods

Clinic protocol

Between April, 2012 and May, 2014, 5,488 outpatient cystoscopies were performed in the two outpatient urology clinics at our institution. Our cohort included all renal transplant patients who underwent outpatient cystoscopy with stent removal based on CPT and ICD-9 codes. All flexible cystoscopies were performed after genitalia were prepped with povidine-iodine solution. 2% lidocaine jelly was instilled into the urethra prior to the procedure. Ureteral stent removal was performed using a flexible grasper, performed by an attending urologist (no stent had an attached string). After each procedure, cystoscopes were cleaned using an enzymatic cleanser (V. Mueller®), sterile water wash and chemical sterilization with paracetic acid (Steris S40®). Following the procedure, patients were given an informational handout and instructed to notify the clinic if they developed a temperature 101 °F. Neither clinic had a formalized protocol regarding the use of pre-procedure prophylactic antibiotics, and administration of antibiotic prophylaxis was left to clinician

preference. Patients were uniformly on prophylactic dose antibiotics (trimethoprim-sulfamethoxazole or dapsone) prior to removal.

Study Design

After obtaining IRB approval, a retrospective review of medical records was performed and data was collected from electronic medical records. Data collected included patient characteristics (age, race, diabetes, smoking history, prednisone use, and deceased or living donor) and post-transplant outcomes as defined by patients' nephrologist (time to stent removal, readmission, non-genitourinary tract infection, delayed graft function, acute cellular rejection, and major urologic complication [urine leak]). Cases were defined as meeting the criteria for symptomatic UTI within 30 days after cystoscopy. Using prior literature, CDC surveillance definitions, and discussions with our hospital epidemiologist (TT), we developed the following criteria to define patients with symptomatic UTI^{13,14}:

1. One of the following signs or symptoms with no other recognized cause: fever, urgency, frequency, dysuria, prostate tenderness or suprapubic tenderness
AND
Positive urine culture (10^5 microorganisms) with no more than two species present
OR
2. Two of the above signs and symptoms with no other recognized cause
AND
At least one of the following:
 - a. Positive dipstick for leukocyte esterase and/or nitrate
 - b. Pyuria (urine specimen with >10 white blood cell [WBC]/mm³)
 - c. Organisms seen on Gram's stain of unspun urine
 - d. At least two urine cultures with repeated isolation of the same uropathogen (gram negative bacteria or *Staphylococcus saprophyticus*) with 10^2 colonies/mL in nonvoided specimens
 - e. $<10^5$ colonies/mL of a single uropathogen in a patient being treated with an effective antimicrobial agent for UTI
 - f. Physician diagnosis of UTI or prostatitis
 - g. Physician initiation of appropriate therapy for UTI or prostatitis

The student's t-test and Fisher's exact test were used to evaluate patient characteristics and transplant outcomes associated with symptomatic UTI. Chi-squared tests were two-sided and all tests with $P < 0.05$ were considered significant. Statistics were completed using STATA (StataCorp, 2013 *Stata Statistical Software: Release 13.1*. College Station, TX).

As a secondary outcome, we investigated whether the use of prophylactic antibiotics, in addition to daily prophylaxis taken by all transplant patients at our institution for prevention of infectious diseases, was associated with post-procedural symptomatic UTI.

Prior studies indicate that patients undergoing cystoscopy at our institution receive prophylactic antibiotics approximately 75% of the time.¹⁵ With a study cohort of approximately 320 transplant patients, we calculated that we had > 80% power to detect a difference in symptomatic UTI of 2% in those who received antibiotics vs. 10% in those who did not, with a 0.05 type I error probability. Given that transplant patients are already on a daily antibiotic and may receive less prophylactic dosing, we calculate that power approaches 98% if half of the cohort receives prophylactic antibiotics.

Results

A total of 324 renal transplant patients underwent cystoscopy with stent removal during the study time period. Patient characteristics are shown in Table 1. Average age was 50 years. 42.3% of patients were female and 70.4% were white. Stents were removed an average of 28.6 days (SD 6.9) after transplant, and timing was left to the discretion of the referring transplant team. All patients were taking trimethoprim/sulfamethoxazole or dapsone as prophylactic antibiotics. An additional 165 (52.5%) patients received a dose of prophylactic antibiotic prior to cystoscopy to remove ureteral stents. Of these, 163/165 (98.8%) received a fluoroquinolone as pre-procedural prophylaxis. No adverse events related to antibiotic use were noted in patients who received a prophylactic fluoroquinolone.

Nine (2.8%) patients met criteria for symptomatic UTI within 30 days after cystoscopy. Eight of the 9 symptomatic UTIs had a positive urine culture, of which the involved bacteria were *Escherichia coli* (N=3), *Klebsiella pneumoniae* (N=2), *Citrobacter* (2 different species) and *Enterococcus faecalis* (N=1). The one patient with culture negative urine had a UTI diagnosed by a physician due to frequency, incomplete emptying and prostatic tenderness. Three (37.5%) of the 8 bacterial isolates were resistant to fluoroquinolones. Two of the 9 patients with UTI required admission for treatment of pyelonephritis. None required ICU admission. Within the cohort, 21 patients (6.5%) had asymptomatic bacteriuria.

Table 2 shows patient characteristic and post-transplant measures and their association with symptomatic UTI. Female sex was associated with symptomatic UTI ($p=0.04$). No other patient or transplant-related factor was associated with UTI, though and lack of prednisone as an immunosuppressive agent ($P=0.10$) trended toward association with symptomatic UTI. Notably, lack of prophylactic antibiotic use prior to cystoscopy with stent removal was not associated with symptomatic UTI ($p=0.32$, Figure).

Discussion

In this cohort of renal transplant patients undergoing cystoscopic ureteral stent removal, we found a 2.8% rate of symptomatic UTI. Thus, despite multiple factors that may place this group at an increased risk of UTI, including the presence of comorbidities, use of immunosuppressive medications and recent surgical intervention,¹³ the risk of UTI after

stent removal in renal transplant patients may not be different from that found in the general population.

The low rate of symptomatic UTI seen in our cohort differs from that seen in many studies examining infections in the post-renal transplant population. While the majority of these studies examine patients for at least three months after transplant (as opposed to one month post-stent removal in our cohort), the rates of infection are strikingly different. Large studies examining only acute graft pyelonephritis (fever, positive urine culture and urinary symptoms) have shown rates of infection at 13–16.5%.^{16,17} This contrasts with the two out of 324 (0.6%) patients who had acute pyelonephritis in our study, albeit with admittedly shorter observation time. In terms of cystitis, three retrospective cohorts of over 100 patients each demonstrated UTI rates of 34.5%,¹⁸ 44.8%¹⁹ and 33.7%,²⁰ respectively. Importantly, these studies included patients with asymptomatic positive urine culture results in their definition of UTI, representing much less stringent criteria. While some believe that asymptomatic bacteriuria is a reasonable outcome in a transplant population given a possible association with graft related complications,²¹ evidence is lacking as to whether intervention on asymptomatic bacteriuria has any effect on transplant-related outcomes. Furthermore, the role of daily low-dose prophylactic antibiotics on bacteriuria was not established at the time of these studies, as evidenced by the 6.5% rate of asymptomatic bacteriuria seen in our population, among which all patients received daily prophylaxis.

Multiple randomized prospective studies investigating outpatient flexible cystoscopy have demonstrated low rates of UTI in patients randomized to pre-procedural placebo administration. While definition of UTI varied, recent large studies demonstrated symptomatic UTI rates of 3%,²² 2.5%,²³ and 0.8%.²⁴ Notably, patients within these studies did not undergo cystoscopy with urinary tract manipulation such as stent removal. Guidelines place patients at increased risk for infection when manipulation occurs, even though evidence supporting this practice has largely been extrapolated from studies investigating the efficacy of prophylactic antibiotic use prior to trans-urethral resection of the prostate.¹⁰ A number of prior studies, while limited by the above-mentioned broad definition of UTI, have investigated risk factors associated with infection in patients after renal transplant. A retrospective analysis by Camargo et al. demonstrated that older age, acute rejection and deceased donor transplant were associated with UTI (definition unknown, though likely included bacteriuria given a 33.7% rate of infection). A separate cohort showed that immunosuppressive regimen, deceased donor transplant, duration of urinary bladder catheterization and length of hospital stay were associated with symptomatic UTI or bacteriuria.¹⁹ In our contemporary cohort, female sex ($P=0.04$) was associated with symptomatic UTI. This finding is likely valid, as female sex is a known risk factor for UTI,¹⁴ and is mechanistically plausible given the short female urethral length. Further studies are needed, particularly to determine if antibiotics may be safely omitted in select renal transplant patients.

Antibiotics implicitly risk complications such as gastrointestinal distress, opportunistic infections and drug reactions.²⁵ These potential downsides, as well as increasing rates of antimicrobial resistance,^{26,14} have contributed to an increase in awareness of the need for urologists to practice antibiotic stewardship.²⁷ Furthermore, a recent study advocates for

consideration of prophylactic antibiotic omission in patients undergoing outpatient cystoscopy, including those who are at increased risk for infection.⁶ While infectious disease¹¹ and urology¹⁰ guidelines do not advocate for such an approach, a recent study by our group demonstrated that more narrow criteria may be safely used to risk stratify patients undergoing outpatient cystoscopy, especially given high rates of resistance to recommended prophylactics.¹⁵ Interestingly, treatment dose antibiotic prophylaxis was not associated with UTI in this cohort, a group with multiple risk factors for UTI as defined by the aforementioned guidelines, including immune suppression, recent hospitalization and GU tract manipulation.

Given this finding, it may be reasonable to advocate for decreased peri-procedural antibiotic use in this population, especially given the broad use of daily antibiotic prophylaxis in this group. However, a difference in absolute rates of symptomatic UTI was demonstrated in our cohort, with 3.9% of patients in whom prophylaxis was omitted having a symptomatic UTI, compared to 1.8% of those who received pre-procedural medication. These rates of UTI are actually lower than those expected at the onset of the study. A post-hoc power calculation reveals that 640 patients would have been needed to detect a significant difference given the rates of infection and pre-procedural antibiotic use in our cohort. Our study was therefore limited in sample size and the finding that antibiotic prophylaxis is not associated with symptomatic UTI may reflect a type II error. Other limitations of our study, including potential bias related to its retrospective nature which may have limited the number of identified UTIs, make it difficult to definitively conclude that peri-procedural antibiotics do not prevent symptomatic UTI in this population. Additionally, pre-procedural urine cultures were not uniformly available to guide prophylaxis. Given the potential consequences of a severe urinary tract infection in this population, including complications related to graft health or immune suppression, we do not recommend cessation of prophylactic antibiotic dosing in this group until larger, prospective studies have been completed.

To our knowledge, this is the first study to determine the rate of symptomatic UTI after post-renal transplant outpatient cystoscopy and stent pull. The infection rate of 2.8% is comparable to rates of post-cystoscopy symptomatic UTI in the general population, suggesting that UTI risk in this group may be lower than previously expected. We additionally identified sex as a factor associated with symptomatic UTI after stent removal. While the efficacy of full-dose prophylactic antibiotics in prevention of post-procedural UTI remains to be proven, transplant patients represent an at-risk population for which pre-procedural antibiotic prophylaxis should likely continue. Further prospective studies (ideally in the setting of a randomized clinical trial) are needed to determine patients most at risk for symptomatic UTI after renal transplant.

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Key of Definitions and Abbreviations

ASHP	American Society of Health-System Pharmacists
AUA	American Urological Association
GU	Genitourinary
UTI	Urinary Tract Infection

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Appendix. Published Risk Factors for Infection Post-Cystoscopy

AUA *	ASHP**
Advanced Age	Extremes of age
Poor nutritional status	Nutritional status
Smoking	Tobacco use
Distant coexistent infection	Coexistent remote body-site infection
Immunodeficiency	Altered Immune Response
Chronic corticosteroid use	Corticosteroid Therapy
Prolonged hospitalization	Length of Preoperative Hospitalization
Colonized endogenous or exogenous material	Colonization with Microorganisms
Anatomic anomalies of the urinary tract	Anatomic Anomalies of the Urinary Tract
	Obesity
	Diabetes mellitus
	Recent Surgical Procedure
	Urinary Obstruction
	Urinary Stone
	Indwelling or Externalized Catheter

* American Urological Association (AUA) Guidelines.

** American Society of Health-System Pharmacists (ASHP) Guidelines. These were developed jointly by the Infectious Disease Society of America, the Surgical Infection Society and the Society for Healthcare Epidemiology of America.

Figure 1.

Effect of Pre-Cystoscopy Full-Dose Dose Antibiotic Prophylaxis on Symptomatic UTI.

Medical records of renal transplant patients who underwent cystoscopy for stent removal were examined for pre-cystoscopy antibiotic administration and symptomatic UTI criteria 30 days after cystoscopy. Patients who met criteria for UTI are represented in gray and patients who did not meet criteria for UTI were represented in white. Patients who did and did not receive pre-cystoscopy treatment dose prophylaxis in addition to universally administered daily prophylaxis are shown in the upper and lower bars, respectively.

Table 1

Patient Characteristics

Characteristic	Number (%)
Age (mean [STD])	50.0
Sex	
Male	187 (57.7)
Female	137 (42.3)
Race	
White	228 (70.4)
Black	88 (27.2)
Hispanic	2 (0.62)
Asian	6 (1.9)
Diabetes mellitus	
No	220 (67.9)
Yes	104 (32.1)
Smoking history	
No	231 (71.3)
Yes	93 (28.7)
Prednisone	
No	158 (48.8)
Yes	166 (51.2)
Donor kidney type	
Living	114 (35.2)
Deceased	210 (64.8)
Time from transplant to stent removal	
< 4 weeks	199 (61.4)
> 4 weeks	125 (38.6)
Received preprocedure antibiotics	
No	156 (48.1)
Yes	168 (51.9)
Readmission to the hospital one month prior to cystoscopy	
No	233 (71.9)
Yes	91 (28.1)
Non-genitourinary infection one month prior to cystoscopy	
No	294 (90.7)
Yes	30 (9.3)
Delayed graft function	
No	216 (66.7)
Yes	108 (33.3)
Acute transplant rejection	

Characteristic	Number (%)
No	304 (93.8)
Yes	20 (6.2)
Major urological complication	
No	320 (98.8)
Yes	4 (1.2)

Table 2

Post-transplant and Patient Characteristics Associated with Post-Cystoscopy UTI

Characteristic	UTI		P-value
	No	Yes	
Age (mean [STD])	50.0 (13.0)	49.5 (18.0)	0.45
Sex			0.04
Male	185 (58.7)	2 (22.2)	
Female	130 (41.3)	7 (77.8)	
Race			0.73
Caucasian	222 (70.5)	4 (44.4)	
Other	99 (29.5)	5 (55.6)	
Diabetes mellitus			0.15
No	216 (68.6)	4 (44.4)	
Yes	99 (31.4)	5 (55.67)	
Smoking history			0.72
No	225 (71.4)	6 (66.7)	
Yes	90 (28.6)	3 (33.3)	
Prednisone			0.10
No	150 (47.6)	7 (77.8)	
Yes	165 (52.4)	2 (22.2)	
Donor kidney type			0.50
Living	112 (35.6)	2 (22.2)	
Deceased	203 (64.4)	7 (77.8)	
Time from transplant to stent removal			1.0
< 4 weeks	194 (61.6)	6 (66.7)	
> 4 weeks	121 (38.4)	3 (33.3)	
Received preprocedure antibiotics			0.32
No	149 (47.5)	6 (66.7)	
Yes	165 (52.5)	3 (33.3)	
Hospitalized within one month of cystoscopy			0.28
No	228 (72.4)	5 (55.6)	
Yes	87 (27.6)	4 (44.4)	
Non-genitourinary infection one month prior to cystoscopy			0.20
No	287 (91.1)	7 (77.8)	
Yes	28 (8.9)	2 (22.2)	