



# Determination of microbiological characteristics and risk factors associated with bacteriuria and symptomatic urinary tract infection in patients with retained ureteral stents: an observational study

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**Background:** The maintenance of ureteral stents is vital in patients with severe ureteral stricture or ureteral obstruction. This study aimed to identify microbiological characteristics and factors associated with bacteriuria and symptomatic urinary tract infection (UTI) in these patients.

**Methods:** This study is an observational cross-sectional study. From August 2018 to January 2021, urine samples from 307 consecutive patients who required stent indwelling and had replaced ureteral stents more than once were collected before the replacement procedure and analyzed by microbiological testing. Patient demographics, laboratory test results, and data on dependent functional capacity and indwelling urethral catheter use were collected from all patients. Additionally, ureteral stenting duration and number of previous ureteral stent replacements were reviewed. The primary endpoint was the incidence rate of bacteriuria and extended-spectrum beta-lactamase (ESBL)-producing bacteria. The secondary endpoint was the factors predisposing patients with ureteral stents to bacteriuria, ESBL-producing bacteria, and the development of symptomatic UTIs.

**Results:** Bacteriuria was observed in 187 patients (60.9%). Among the bacteria identified in urine, *Escherichia coli* was the most commonly isolated microorganism, followed by *Enterococcus*, *Candida* species, *Staphylococcus* species, *Klebsiella*, and *Pseudomonas*. Using multivariate analysis, bacteriuria was significantly associated with old age, female sex, presence of diabetes mellitus, impaired renal function, and longer duration of ureteral stenting. ESBL-producing bacteria were detected in 52 isolates (27.8%). The incidence of ESBL-producing bacteria in urine culture was associated with old age and longer ureteral stenting duration. Additionally, symptomatic UTIs developed in 22 patients (7.2%). Dependent functional capacity, impaired renal function, and longer ureteral stenting duration were significantly associated with symptomatic UTIs.

**Conclusions:** Infections related to ureteral stents showed a specific microorganism profile and resistance pattern compared to community-acquired UTIs. Additionally, we identified the factors associated with bacteriuria and symptomatic UTI in patients with retained ureteral stents and deduced that these may be associated with better outcomes in patients with retained ureteral stents.

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**Keywords:** Bacteriuria; beta-lactamases; ureteral stents; microbiological characteristics; urinary tract infections (UTIs)

Submitted May 06, 2022. Accepted for publication Nov 13, 2022. Published online Dec 22, 2022.

doi: 10.21037/tau-22-331

View this article at: <https://dx.doi.org/10.21037/tau-22-331>

## Introduction

Urinary tract infection (UTI) is one of the most common types of infection in the general population. Symptoms related to UTI have a broad clinical spectrum, ranging from asymptomatic bacteriuria to severe sepsis accompanied by acute pyelonephritis or renal abscess (1). Globally, UTIs constitute the largest portion of healthcare-associated infections, which are potentially serious complications in hospitalized patients, leading to increasing costs, morbidity, and mortality rates (2,3). Mostly, asymptomatic bacteriuria does not require antimicrobial treatment, similar to bacteriuria associated with indwelling urethral catheters (4). However, UTI, with clinical symptoms such as dysuria and suprapubic pain, is differentiated from asymptomatic bacteriuria in that it requires the use of antibiotics, especially when the infection is complicated by catheter-associated sepsis (4).

Ureteral stenting is a widely used method for urinary drainage through the ureter into the bladder to relieve ureteral obstruction due to various etiologies and supports postoperative drainage in urology care. However, stenting can induce various minor complications, such as dysuria, suprapubic pain, and hematuria, as well as major complications such as UTI (5).

Among these complications, UTI related to ureteral stenting is frequently encountered in patients with ureteral stents and requires adequate treatment to prevent progression to more severe conditions (6). A previous study has reported a high incidence of bacteriuria in patients with ureteral stents with the highest reported incidence rate up to 100% in patients with permanent stents (7). In addition, extended-spectrum beta-lactamase (ESBL)-producing bacteria and multidrug-resistant microorganisms have been isolated in patients with ureteral stents requiring specific treatment, as seen in other foreign materials used as prosthetic devices (8,9). ESBL-producing bacteria represent a major concern, especially in the hospitalized patient population, and a costly therapeutic challenge requiring broad-spectrum antibiotics with an increased length of hospital stay with economic consequences (10).

To prevent the development of UTI and resistant microorganisms, indwelling ureteral stents must be removed, if possible, in a short time. Regarding this, several studies demonstrated that the duration time of ureteral stents was significantly associated with bacteriuria occurrence (11-13). However, ureteral stents need to be maintained in patients with severe ureteral stricture or ureteral obstruction due to malignancy. In such circumstances, ureteral stents should be replaced periodically to prevent the development of UTI. Although stents should be replaced periodically, patients with maintained ureteral stents in place might be at a higher risk of developing UTI than other groups of patients.

Considering this, knowing the microbiological profile associated with the use of these devices and their resistance pattern is essential to avoid the indiscriminate broad use of antibiotics and prevent occurrence of multidrug-resistant bacteria in patients with maintained ureteral stents in place. Moreover, the identification of predisposing factors for the development of symptomatic UTI associated with ureteral stents is important to prevent sepsis or other complications following UTI and establish an appropriate strategy for using antimicrobial treatment.

Most previous studies have mainly evaluated the pattern of asymptomatic bacteriuria and the colonization rate of ureteral stents in patients with these medical devices (12,14,15). However, the results reported in the literature are extremely varied. Moreover, these studies did not make clear distinctions between bacteriuria and symptomatic UTI. Additionally, only a few studies have assessed the pathophysiology and risk factors for the development of symptomatic UTI in these patients. Recently, two literature reviews have attempted to clarify the epidemiological characteristics and risk factors for UTI in patients with ureteral stents; however, they could not come to clear conclusions due to discrepancies in methodology and a low level of evidence of the included studies (16,17).

Accordingly, this study aimed to identify the microbiological profile of bacteriuria and the incidence of ESBL-producing bacteria in patients who, in particular,

required retained ureteral stents and to determine the predisposing factors associated with the bacteriuria and ESBL-producing bacteria in these patients. Additionally, we aimed to determine the incidence rate and risk factors for the development of symptomatic UTI, including factors such as the duration and number of previous replacements of ureteral stents. We present the following article in accordance with the STROBE reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-331/rc>).

## Methods

This study is an observational cross-sectional study. From August 2018 to January 2021, 307 consecutive patients who required indwelling and replaced ureteral stents more than once at Sanggye Paik Hospital were evaluated. Patients with age less than 18 years and those with indwelling ureteral stents placed only once and subsequently removed were excluded from the study. Additionally, patients with ureteral stents inserted through a percutaneous nephrostomy site, bilateral stents, large kidney stones (staghorn stones), ureteral stent migration, or current antibiotic treatment were also excluded from the study because they could have affected the incidence of colonization in urine, leading to inadequate analysis. We excluded patients with urinary stasis developed due to various etiologies, including bladder outlet obstruction and impaired bladder function, because this condition predisposes patients to UTI. We evaluated the voiding pattern and residual urine amount regularly to identify patients with urinary stasis.

Data regarding patient characteristics, including age, sex, body weight, and height, were collected. Underlying systemic diseases of the included patients, such as hypertension, diabetes mellitus (DM), cardiac disease, and the reasons for ureteral stent placement were reviewed. Additionally, laboratory test results, such as estimated glomerular filtration rate (eGFR), glucose level, HbA1c level, lipid profile, and data of patient conditional status, including urethral catheter use and dependent functional capacity, were also collected. We used the Modification of Diet in Renal Disease equation to determine the eGFR according to serum creatinine levels (18). Then, we stratified the patients with chronic kidney disease (CKD) stage by using calculated eGFR. The participants were categorized into the following five stages according to their baseline eGFR: stage 1, eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>; stage 2, eGFR of 60–89 mL/min/1.73 m<sup>2</sup>; stage 3, eGFR

of 30–59 mL/min/1.73 m<sup>2</sup>; stage 4, eGFR 15–29 mL/min/1.73 m<sup>2</sup>; and stage 5, eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>. We divided the patients stratified by eGFR into 2 groups: group A (preserved urine amount group) including CKD stage 1, 2, and 3, and group B (decreased urine amount group) including CKD stage 4, and 5, due to a small number of patients with CKD stage 5. Moreover, the duration and number of previous ureteral stent replacements were reviewed.

Urine samples from patients systematically collected before ureteral stent replacement were examined using microbiological testing. The acquired urine samples were inoculated on eosin methylene blue (EMB) agar and blood agar for cultural studies. Plates were incubated for 48 hours at 37 °C. The microorganisms that grew on the agar were evaluated quantitatively [growth of  $>10^5$  colony-forming units (CFU)/mL was considered significant]. Additionally, all microbial isolates were tested for antibiotic susceptibility. The evaluation and analysis of microbiological characteristics and resistance patterns were conducted according to the definitions and recommendations of the National Committee for Clinical and Laboratory Standards Institute (19,20).

A silicone ureteral stent, double J stent type (Boston Scientific Corp., Natick, MA, USA), was used in all the patients. All stents were inserted through a retrograde route using the endoscopic method under fluoroscopic guidance. After the initial placement of the ureteral stents, they were replaced periodically because the patients required maintenance of these ureteral stents for urinary drainage. However, for different patients, ureteral stents were replaced at different intervals due to the different visiting times and medical conditions of the patients.

The patients with ureteral stents were instructed to visit the hospital immediately in case of developing irritative voiding symptoms, such as dysuria and frequency, fever, flank pain, or pelvic pain during the follow-up period. The patients with clinical symptoms suggestive of UTI, including dysuria, fever, or flank pain who showed the presence of  $\geq 10^5$  CFU/mL of a bacterial species isolated from midstream clean urine were diagnosed with UTI (21,22). Additionally, white blood cell (WBC) count, erythrocyte sedimentation rate, and C-reactive protein values were checked to clarify the disease status.

Asymptomatic bacteriuria was defined as the presence of  $\geq 10^5$  CFU/mL of one bacterial species isolated from two consecutive urine culture samples without any clinical symptoms suggestive of UTI (21). The patients with

symptomatic UTI during the study were administered appropriate antibiotics based on microbiological susceptibility results, and the dose and duration of each antibiotic followed clinical practice guidelines (23,24). Subsequently, ureteral stents were removed if the patients' conditions were stable. Symptomatic UTI was considered to be successfully treated if urinary clinical symptoms disappeared with negative urine culture results.

The primary endpoint was the incidence rate of bacteriuria and ESBL-producing bacteria. The secondary endpoint was the factors predisposing patients with ureteral stents to bacteriuria, ESBL-producing bacteria, and development of symptomatic UTIs.

### Statistical analysis

Quantitative data are presented as mean (standard deviation) and categorical data as numbers (n) and percentages. The normal distribution of variables was checked using the Kolmogorov-Smirnov test. Additionally, goodness of fit of logistic regression models was assessed using the Hosmer and Lemeshow test. Univariate and multivariate logistic regression analyses were performed to identify the factors predisposing patients with ureteral stents to bacteriuria, ESBL-producing bacteria, and the development of symptomatic UTI. Results are presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). All tests were two-tailed, and a P value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA).

### Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of Sanggye Paik Hospital, Inje University (committee reference No. 2018-11-011), and informed consent was obtained from each patient after careful explanation of the scope of the study.

## Results

A total of 307 patients [111 (36.2%) men; 196 (63.8%) women] were included in this study. The mean patient age was 59.4 ( $\pm$ 18.1) years. Patient characteristics are presented in *Table 1*. Overall, 13 (4.2%) had dependent functional

capacity, and 23 (7.5%) had indwelling urethral catheters due to persistent bladder distention. The mean duration of placement of ureteral stents was 75.9 ( $\pm$ 39.4) days, and the number of previous replacements of ureteral stents was 5.7 ( $\pm$ 6.3).

Regarding the results of urine culture, bacteriuria was found in 187 patients (60.9%). Regarding the bacteria identified in urine, *Escherichia coli* was the most commonly isolated microorganism (60 patients), followed by *Enterococcus* (44 patients). Additionally, *Candida*, *Staphylococcus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were detected in 25, 17, 13, and 8 patients, respectively (*Figure 1*). Using the multivariate logistic analysis, the occurrence of bacteriuria was significantly associated with old age, female sex, presence of DM. Additionally, a lower glomerular filtration rate (GFR) and longer duration of ureteral stenting significantly increased the incidence of bacteriuria. Moreover, the patients in group B with CKD stage 4 and 5 showed significantly increased occurrence of bacteriuria compared to those in group A. The number of previous replacements of ureteral stents was not significantly associated with the development of bacteriuria (*Table 2*).

Regarding the resistance of bacteria found in urine, ESBL-producing bacteria were found in 52 isolates (27.8%). Moreover, ESBL-producing bacteria were identified in 43 out of 60 patients (71.7%) with *E. coli* and 9 out of 13 (69.2%) with *K. pneumoniae* (*Figure 1*). The incidence of ESBL-producing bacteria in urine cultures was associated with old age (OR 1.04; 95% CI: 1.02–1.06;  $P < 0.001$ ) and longer duration of ureteral stenting (OR 1.02; 95% CI: 1.00–1.03;  $P = 0.048$ ) using multivariate logistic analysis (*Table 3*).

Additionally, symptomatic UTI developed in 22 patients (7.2%) among all patients. Among patients with symptomatic UTI, the most commonly isolated microorganism was *E. coli* (five). The following species were identified: *Enterococcus* (four), *Candida* species (four), *P. aeruginosa* (three), and *Proteus mirabilis* (one). Out of the isolated *E. coli*, four were ESBL.

When comparing the patients with symptomatic UTI with asymptomatic bacteriuria, asymptomatic bacteriuria was identified in 165 (88.2%), while symptomatic UTI developed in 22 (11.8%) patients with bacteriuria, respectively. No significant differences in bacterial frequency were identified between patients with symptomatic UTI and asymptomatic bacteriuria. However, the proportion of ESBL-producing bacteria among overall

**Table 1** Demographic characteristics of the patients

Factors	N (%) or mean $\pm$ SD
Age (years)	59.4 $\pm$ 18.1
Sex	
Male	111 (36.2)
Female	196 (63.8)
Body weight (kg)	59.0 $\pm$ 15.8
Height (cm)	159.4 $\pm$ 10.8
BMI (kg/m <sup>2</sup> )	23.6 $\pm$ 14.7
Comorbid factors	
Diabetes mellitus	71 (23.1)
Hypertension	122 (39.7)
Cardiac disease (CHF, MI)	21 (6.8)
Chronic kidney disease (stratified by CKD stage)	
Group A	
Stage 1	83 (27.0)
Stage 2	102 (33.2)
Stage 3	71 (23.1)
Group B	
Stage 4	38 (12.4)
Stage 5	13 (4.2)
Hyperlipidemia	17 (5.5)
Other malignancy	28 (9.1)
Indications for ureteral stenting	
Ureteral stricture	167 (54.4)
Hydronephrosis due to ureteral stone	75 (24.4)
Ureteral obstruction due to malignancy	65 (21.2)
Dependent functional capacity	13 (4.2)
Indwelling urethral catheter use	23 (7.5)
Ureteral stent duration period (days)	75.9 $\pm$ 39.4
The number of previous replacements of ureteral stent	5.7 $\pm$ 6.3
Bacteriuria	187/307 (60.9)
ESBL-producing bacteria	52/187 (27.8)
Symptomatic urinary tract infection	22/187 (11.8)

CKD stage by using calculated eGFR. Group A including CKD stage 1, 2, and 3. Group B including CKD stage 4, and 5. BMI, body mass index; CKD, chronic kidney disease; CHF, congestive heart failure; ESBL, extended-spectrum beta-lactamase; GFR, glomerular filtration rate; MI, myocardial infarction; SD, standard deviation.

*E. coli* species was higher in patients with symptomatic UTI (80%) than asymptomatic bacteriuria (71%), although it was not significant.

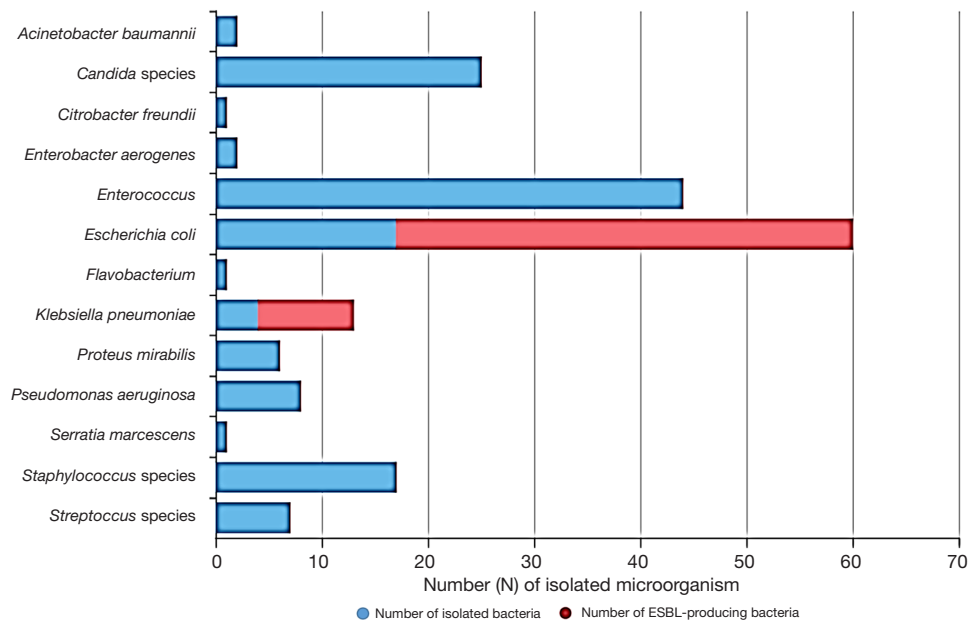
The 22 patients who developed UTI were administered antibiotics according to the urine susceptibility test results. Among them, 15 had their ureteral stent replaced with new stents; subsequently, the UTI symptoms resolved, and bacteriuria was not found in the urine. In the remaining seven patients with symptomatic UTI, ureteral stents were left in place, although they were treated with appropriate antibiotics. Symptoms related to UTI recurred in these patients, and the mean time to symptom recurrence was 10 days. Urine culture obtained in these patients showed positive results. Subsequently, ureteral stents were replaced with new stents after the patients' condition recovered. After the replacement of ureteral stents, the remaining UTI symptoms were relieved.

Dependent functional capacity and impaired renal function were significantly associated with the development of symptomatic UTI. In particular, group B patients with CKD stage 4 and 5 showed significantly increased development of symptomatic UTI compared to those in group A. Additionally, a longer ureteral stenting duration correlated significantly with the development of symptomatic UTI (Table 4). Age, sex, and the presence of DM were not significantly associated with the development of symptomatic UTI. Similar to bacteriuria, the number of previous replacements of ureteral stents was not significantly associated with the development of symptomatic UTI.

## Discussion

In our study, infections related to ureteral stents showed a specific microorganism profile and resistance pattern, in which microorganisms other than *E. coli*, such as *Enterococcus*, *Staphylococcus species*, *Klebsiella*, and *Candida* species, were found more frequently when compared to community-acquired UTI. Additionally, we identified the factors associated with bacteriuria and development of symptomatic UTI in patients with retained ureteral stents.

UTI is one of the most frequent complications in patients with indwelling ureteral stents, occurring in as many as 30% of cases leading to increased treatment costs and higher mortality rates (11,25). To prevent these complications, short ureteral stenting duration, if possible, may be an effective method. However, some patients require ureteral stents in place for longer duration due to various circumstances, such as severe ureteral stricture or



**Figure 1** Microorganisms isolated from urine before ureteral stent replacement procedure. ESBL, extended-spectrum beta-lactamase.

ureteral obstruction due to malignancy.

Several studies have evaluated the relationship between indwelling urethral catheters and development of UTI. However, few studies have reported on UTI development in patients with ureteral stents (12,14,15). Although the guidelines for bladder catheterization were established by the Infectious Diseases Society of America (26), there have been no guidelines for the management of ureteral stents. Infections related to ureteral stents are expected to exhibit microbiological characteristics different from those found in urethral catheters. Therefore, treatment of UTI in patients with ureteral stents should be specified according to the different microbiological patterns found in these patients.

Ureteral stents are associated with a high incidence rate of UTI, particularly the isolation of ESBL and multidrug-resistant microorganisms (8,9). This is known to be due to colonization of ureteral stents by bacteria, which can induce infectious processes.

The bacteria can invade the bladder at the time of ureteral stent insertion or due to its movement during indwelling, both of which have been associated with catheter-associated infections (27). Moreover, indwelling medical devices, such as ureteral stents, facilitate conditioning film formation on the surface of the biomaterial by deposition of host urinary components, including proteins, electrolytes, and unidentified molecules,

which various bacterial species recognize and bind to (28,29). This process by bacterial uropathogens can develop within 24 h after insertion of ureteral stents; up to 90% of indwelling stents when removed from patients contained adherent bacteria (7). The formation of biofilm makes it difficult to achieve significant concentrations of antibiotics. The colonization of the surfaces of materials cannot be prevented, leaving patients at the continued risk of infection or other complications (28). Therefore, once the biofilm is established, eradication of the infection with increased antimicrobial resistance becomes very difficult. Although several studies have been conducted to produce ureteral stents that completely prevent bacterial adhesion and biofilm formation, to date, no such devices exist (30).

Previous studies reported a high incidence of bacteriuria in patients with ureteral stents. Farsi *et al.* demonstrated that the incidence rate of bacteriuria was 30% in their study (11). In other studies, Paick *et al.* reported that the incidence rate of bacteriuria was 21% (31), while Kehinde *et al.* reported that it was 17% (12,32). Similarly, Lifshitz *et al.* reported a bacteriuria rate of 13% in 65 patients with ureteral stents (25). In addition, Yenyol *et al.* reported the presence of bacteriuria in 16% of patients (33) while Akay *et al.* reported bacteriuria in 24% of patients with ureteral stents at the time of ureteral stent removal (34).

In our study, the incidence of bacteriuria was 60.9%,

**Table 2** Univariate and multivariate analysis of risk factors for the occurrence of bacteriuria in the patients with ureteral stents

Factors	Non-bacteriuria, n (%) or mean $\pm$ SD	Bacteriuria, n (%) or mean $\pm$ SD	Univariate		Multivariate	
			OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	54.2 $\pm$ 18.2	62.7 $\pm$ 17.3	1.03 (1.01–1.04)	<0.001	1.02 (1.00–1.03)	0.030
Gender						
Male	61 (50.8)	50 (26.7)	–	–	–	–
Female	59 (49.2)	137 (73.3)	2.83 (1.75–4.59)	<0.001	2.92 (1.74–4.90)	<0.001
Body weight (kg)	62.2 $\pm$ 12.8	56.9 $\pm$ 13.2	0.97 (0.96–0.99)	0.002	1.16 (0.98–1.38)	0.088
Height (cm)	161.4 $\pm$ 10.2	158.2 $\pm$ 9.3	0.98 (0.96–1.00)	0.060	0.90 (0.79–1.02)	0.100
BMI (kg/m <sup>2</sup> )	23.8 $\pm$ 3.7	22.7 $\pm$ 4.4	0.95 (0.90–1.00)	0.033	0.63 (0.40–1.01)	0.053
Comorbid factors						
Diabetes mellitus	17 (14.2)	54 (29.0)	2.48 (1.36–4.53)	0.003	2.09 (1.02–4.28)	0.045
Hypertension	37 (30.8)	85 (45.7)	1.89 (1.17–3.06)	0.010	0.66 (0.34–1.27)	0.212
Cardiac disease (CHF, MI)	7 (5.8)	14 (7.5)	1.31 (0.51–3.36)	0.568	–	–
CKD stage (group A vs. group B)						
Group A	109 (90.8)	147 (78.6)	2.70 (1.32–5.49)	0.006	2.70 (1.20–6.04)	0.016
Group B	11 (9.2)	40 (21.4)				
Hyperlipidemia	4 (3.3)	13 (7.0)	2.17 (0.69–6.81)	0.186	2.92 (0.90–15.2)	0.102
Other malignancy	6 (5.0)	22 (11.8)	2.53 (1.00–6.45)	0.051	1.57 (0.81–10.6)	0.383
Indications for ureteral stenting						
Urethral stricture	59 (49.2)	108 (57.8)	0.94 (0.51–1.71)	0.831	–	–
Nephrolithiasis	39 (32.5)	36 (19.3)	0.74 (0.41–1.92)	0.425	–	–
Obstruction due to malignancy	22 (18.3)	43 (23.3)	–	–	–	–
Dependent functional capacity	0 (0)	13 (7.0)	–	0.003	–	–
Indwelling urethral catheter use	2 (1.7)	21 (11.2)	7.46 (1.72–32.4)	0.007	3.65 (0.66–20.1)	0.137
GFR (mL/min/1.73 m <sup>2</sup> )	78.5 $\pm$ 38.8	65.1 $\pm$ 40.5	0.99 (0.99–1.00)	0.007	0.99 (0.98–1.00)	0.002
Ureteral stent duration (days)	68.4 $\pm$ 43.1	80.7 $\pm$ 36.1	1.01 (1.00–1.01)	0.008	1.01 (1.00–1.02)	0.010
The number of previous replacements of ureteral stents	4.5 $\pm$ 5.0	6.5 $\pm$ 6.9	1.07 (1.01–1.12)	0.011	1.05 (0.99–1.11)	0.090

CKD stage by using calculated eGFR. Group A including CKD stage 1, 2, and 3. Group B including CKD stage 4, and 5. BMI, body mass index; CKD, chronic kidney disease; CHF, congestive heart failure; GFR, glomerular filtration rate; MI, myocardial infarction; OR, odds ratio; CI, confidence interval; SD, standard deviation.

which is higher than that reported in other studies. This may be because the patients included in this study maintained ureteral stents for longer than in other previous studies, although in this study the stents were periodically replaced. Medical devices retained for longer in the urinary tract were found to be vulnerable to bacterial infection (30). Regarding this, Riedl *et al.* have reported

that bacteriuria was identified in 100% of patients with indwelling permanent stent, compared to 45% in patients with temporary stents (7).

Regarding the microbiological pattern, *E. coli* was the most commonly isolated microorganism in urine (60 patients), followed by *Enterococcus* (44 patients). Additionally, *Candida*, *Staphylococcus*, *K. pneumoniae*, and *P. aeruginosa*

**Table 3** Univariate and multivariate analysis of risk factors for the occurrence of ESBL-producing bacteriuria in the patients with ureteral stents

Factors	Non-ESBL-producing bacteriuria, n (%) or mean $\pm$ SD	ESBL-producing bacteriuria, n (%) or mean $\pm$ SD	Univariate		Multivariate	
			OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	60.7 $\pm$ 17.4	67.9 $\pm$ 16.3	1.04 (1.02–1.06)	<0.001	1.04 (1.02–1.06)	<0.001
Gender						
Male	38 (28.1)	12 (23.1)	–	–	–	–
Female	97 (71.9)	40 (76.9)	0.766 (0.36–1.62)	0.484	–	–
Body weight (kg)	57.0 $\pm$ 14.2	56.4 $\pm$ 10.1	0.99 (0.96–1.01)	0.221	–	–
Height (cm)	158.7 $\pm$ 9.3	156.9 $\pm$ 9.3	0.98 (0.95–1.01)	0.106	1.04 (0.96–1.12)	0.316
BMI (kg/m <sup>2</sup> )	22.6 $\pm$ 4.5	23.0 $\pm$ 4.2	1.00 (0.96–1.03)	0.766	–	–
Comorbid factors						
Diabetes mellitus	39 (29.1)	15 (28.8)	1.43 (0.73–2.80)	0.292	–	–
Hypertension	59 (44.0)	26 (50.0)	1.65 (0.90–3.00)	0.104	0.99 (0.48–2.04)	0.971
Cardiac disease (CHF, MI)	7 (5.2)	7 (13.5)	2.82 (0.94–8.50)	0.065	2.17 (0.74–6.39)	0.159
CKD stage (group A vs. group B)						
Group A	105 (77.8)	42 (80.8)	0.83 (0.37–1.86)	0.66	–	–
Group B	30 (22.2)	10 (19.2)				
Hyperlipidemia	8 (5.9)	5 (9.6)	2.15 (0.73–6.40)	0.167	1.92 (0.59–6.28)	0.281
Other malignancy	13 (9.6)	9 (17.3)	1.96 (0.78–4.92)	0.145	2.02 (0.81–5.00)	0.130
Indications for ureteral stenting						
Urethral stricture	72 (53.8)	36 (69.2)	1.51 (0.70–3.26)	0.29	–	–
Nephrolithiasis	30 (22.2)	6 (11.5)	0.48 (0.16–1.40)	0.178	0.67 (0.04–11.5)	0.781
Obstruction due to malignancy	33 (24.4)	10 (19.2)	–	–	–	–
Dependent functional capacity	11 (8.1)	2 (3.8)	0.89 (0.19–4.13)	0.879	–	–
Indwelling urethral catheter use	15 (11.1)	6 (11.5)	1.83 (0.68–4.88)	0.23	–	–
GFR (mL/min/1.73 m <sup>2</sup> )	63.9 $\pm$ 41.2	68.2 $\pm$ 38.8	1.00 (0.99–1.01)	0.694	–	–
Ureteral stent duration (days)	78.2 $\pm$ 36.6	87.1 $\pm$ 34.2	1.01 (1.00–1.02)	0.026	1.02 (1.00–1.03)	0.048
The number of previous replacements of ureteral stents	6.7 $\pm$ 7.7	6.2 $\pm$ 4.3	1.01 (0.96–1.06)	0.712	–	–

CKD stage by using calculated eGFR. Group A including CKD stage 1, 2, and 3. Group B including CKD stage 4, and 5. BMI, body mass index; CKD, chronic kidney disease; CHF, congestive heart failure; ESBL, extended-spectrum beta-lactamase; GFR, glomerular filtration rate; eGFR, estimated GFR; MI, myocardial infarction; OR, odds ratio; CI, confidence interval; SD, standard deviation.

were detected in 25, 17, 13, and 8 patients, respectively.

Several previous studies on bacteriuria in patients with ureteral stents have demonstrated similar results, in which bacteria other than *E. coli*, such as *Enterococcus*, *Staphylococcus* species, *Klebsiella*, and *Candida* species, were found more frequently compared to those in patients with community-acquired UTI (9,21,34). This may be associated with the

longer retention of ureteral stents in patients in the study. Similar to our findings, Akay *et al.* reported that *E. coli* was the most commonly found bacterium in urine (34 of 47 patients); the other samples included *Enterococcus* species (four), *Staphylococcus epidermis* (two), *P. mirabilis* (two), and *P. aeruginosa* (two) (34). In another study, Klis *et al.* reported that *E. coli* was the microorganism



**Table 4** Univariate and multivariate analysis of risk factors for the development of symptomatic urinary tract infection in the patients with ureteral stents

Factors	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	0.99 (0.98–1.02)	0.889	–	–
Gender				
Male	–	–	–	–
Female	1.24 (0.51–3.01)	0.631	–	–
Body weight (kg)	0.98 (0.95–1.01)	0.27	–	–
Height (cm)	1.23 (0.98–1.08)	0.301	–	–
Comorbid factors				
Diabetes mellitus	1.92 (1.06–3.46)	0.031	0.75 (0.23–2.38)	0.619
Hypertension	0.85 (0.35–2.10)	0.728	–	–
Cardiac disease (CHF, MI)	1.40 (0.30–6.42)	0.669	–	–
CKD stage (group A vs. group B)	2.56 (0.99–6.63)	0.054	2.86 (1.06–7.73)	0.039
Hyperlipidemia	1.80 (0.38–8.43)	0.456	–	–
Other malignancy	0.99 (0.22–4.50)	0.996	–	–
BMI (kg/m <sup>2</sup> )	0.93 (0.86–1.01)	0.102	0.80 (0.34–1.85)	0.595
Indications for ureteral stenting				
Urethral stricture	0.76 (0.27–2.12)	0.602	–	–
Nephrolithiasis	0.55 (0.15–2.06)	0.377	–	–
Obstruction due to malignancy	–	–	–	–
Dependent functional capacity	6.82 (1.91–24.3)	0.003	17.2 (1.85–159)	0.012
Indwelling urethral catheter use	4.36 (1.44–13.2)	0.009	5.75 (0.89–37.2)	0.067
GFR (mL/min/1.73 m <sup>2</sup> )	0.99 (0.97–1.00)	0.055	0.98 (0.96–0.99)	0.008
Ureteral stent duration (days)	1.01 (1.00–1.03)	0.045	1.01 (1.00–1.02)	0.049
The number of previous replacements of ureteral stents	0.98 (0.90–1.06)	0.599	–	–
ESBL-producing bacteria	1.10 (0.36–3.39)	0.872	–	–

CKD stage by using calculated eGFR. Group A including CKD stage 1, 2, and 3. Group B including CKD stage 4, and 5. BMI, body mass index; CKD, chronic kidney disease; CHF, congestive heart failure; GFR, glomerular filtration rate; ESBL, extended-spectrum beta-lactamase; MI, myocardial infarction, OR, odds ratio; CI, confidence interval.

most frequently isolated from urine, followed by *S. epidermidis* and *S. aureus* (13). Altunal *et al.* reported similar results (35). In addition, previous systematic reviews have reported that *Staphylococcus*, *E. coli*, *Klebsiella* species, *P. aeruginosa*, *Enterococcus*, and *Candida* species were the microorganisms most commonly identified in urine or ureteral stents (16,17).

Lara-Isla *et al.* reported that in patients with ureteral stents, the most frequently isolated microorganism was *E. coli* (25.7%), followed by *Enterococcus* (22.9%). Other microorganisms such as *Klebsiella* (9%), *Pseudomonas* (9%), and *Candida* species (11%) were also frequently isolated, which is in concordance with the results of our study (9). In addition, they demonstrated that regarding the origin

of the infection, *E. coli* was found in 50% of bacteriuria in community-acquired infections, while *E. coli* and *Enterococcus* were found in 22.6% of hospital-acquired infections, implying a higher incidence rate of *Enterococcus* in healthcare-associated infections.

In this study, DM and impaired renal function (in particular, CKD stage 4 and 5) were associated with the occurrence of bacteriuria. Similarly, Kehinde *et al.* suggested that the incidence of bacteriuria in patients with systemic diseases, including DM, chronic renal failure, and diabetic nephropathy, was significantly higher than that in patients without such diseases (12). Akay *et al.* reported that the incidence of bacteriuria increased 10-fold in patients with DM or CKD (34).

This finding may have been due to DM, chronic renal failure, diabetic nephropathy, and pregnancy that induce immunosuppression, thereby promoting urinary infection (34). Additionally, these diseases may be responsible for weakening the natural defensive mechanisms of the bladder hence increasing the incidence of bacteriuria (36). DM and CKD predispose individuals to infections occurring in other parts of the body. Therefore, the maintenance of ureteral stents in these patients is expected to lead to an increase in the occurrence of bacteriuria.

Additionally, we found that the female sex was significantly associated with a higher incidence of bacteriuria in patients with ureteral stents than the male sex. In previous studies, several researchers reported similar results in patients with ureteral stents (11,12), while other reports showed that sex was not associated with the incidence of bacteriuria (25,34). The reasons for this difference are not clear. However, a possible explanation could be the anatomically closer location of the urethral orifices with the genital tract in the females.

Moreover, the longer duration of ureteral stenting was significantly associated with bacteriuria occurrence. Several previous studies showed results similar to our study's (7,11,12). Additionally, Paick *et al.* (31) reported that bacterial colonization began two weeks after stenting. However, Lifshitz *et al.* did not find any relationship between stent duration and incidence of bacteriuria (25). They examined 65 patients, a small population compared with our study's relatively larger population (307 patients). Additionally, recent literature reviews demonstrated that a longer duration of ureteral stenting was an associated risk factor for the occurrence of bacteriuria, although the included studies presented multiple methodological biases (16,17).

Additionally, in our study, the number of previous replacements of ureteral stents did not show a significant association with the development of bacteriuria.

In addition to specific microbiological characteristics, high rates of resistance to antibiotics should be considered when managing UTI in patients with ureteral stents. The antimicrobial resistance of bacteria causing UTI has been recently increasing worldwide, which is thought to be a result of the widespread and indiscriminate use of antibiotics (8). Among them, the increased incidence of ESBL-producing bacteria that present resistance to most antibiotics, except the carbapenem group, is a major concern, with an increased length of stay and economic consequences, as proper antibiotic treatment is challenging (9). Several studies have demonstrated that 27.8% of ESBL-producing bacteria have been identified in patients with healthcare-associated UTIs, including those with ureteral stents (10).

However, few reports have described the resistance patterns and related factors of bacteria isolated from patients with ureteral stents. Kehinde *et al.* described the susceptibility patterns of isolated bacteria in patients with ureteral stents, which showed that in this population a larger proportion of bacteria was generally more resistant to antibiotics than bacteria cultured from the urine of general hospital patients (12). In another study, Altunal *et al.* reported that there were 58% ESBL, 67% trimethoprim/sulfamethoxazole, 58% ciprofloxacin, and 58% ceftriaxone resistance among 12 *E. coli* strains in patients with ureteral stents (35). Lara-Isla *et al.* reported that *Klebsiella* showed a higher resistance pattern among isolated bacteria: 66.7% were ESBL-producing *Klebsiella* in patients with ureteral stents, while 11.1% were ESBL-producing *E. coli* (9).

Similar to previous studies, in our study, ESBL-producing bacteria were found in 52 (27.8%) of the isolated bacteria. ESBL-producing bacteria were identified in 43 of 60 patients (71.7%) with *E. coli* and 9 of 13 (69.2%) patients with *K. pneumoniae*. In addition, the incidence of ESBL-producing bacteria in urine cultures was associated with old age and a longer duration of ureteral stenting using multivariate logistic analysis. The high incidence of ESBL-producing bacteria may be due to ureteral stent insertion being performed in the hospital environment, which is vulnerable to nosocomial infection, with ureteral stent retention in place working as contributing factor resulting in complicated UTIs.

Additionally, we aimed to determine the risk factors for the development of symptomatic UTI, including underlying

comorbidities, duration of treatment, and the number of previous ureteral stent replacements.

Only a few studies have been conducted to assess the development of symptomatic UTI and related factors in patients with retained ureteral stents (14,15). Moreover, some previous studies did not differentiate bacterial colonization from true UTI with clinical symptoms. Recently, two literature reviews have tried to clarify the risk factors for UTI in patients with ureteral stents; however, they could not come to clear conclusions due to discrepancies in methodology and a low level of evidence of the included studies (16,17).

Kehinde *et al.* reported an incidence of symptomatic UTI of 6.4% (32). In their study, patients with symptomatic UTI received appropriate antibiotic treatment. Among the 16 patients with symptomatic UTI, four had no systemic disease, while 12 had systemic diseases, such as chronic renal failure, diabetic nephropathy, and DM. Out of the 16 patients with symptomatic UTI, 7 (43.8%) showed recovery from UTI with antimicrobial therapy. However, nine had septicemia, necessitating removal of ureteral stents. In another study, Altunal *et al.* reported that 11 (18%) of 60 patients developed symptomatic UTI (35). They demonstrated that a longer duration of ureteral stent placement, presence of DM, and chronic renal failure were significantly associated with the development of symptomatic UTI. Another study reported that about 15% of patients developed symptomatic UTI, which was higher than that reported in a similar study (37).

In our study, the incidence of symptomatic UTI was 22 (7.2%) among all patients. Out of the 22 patients, 15 had their ureteral stents replaced with new ones and were subsequently administered antibiotics based on the susceptibility test results from urine cultures. After using antibiotics and replacement of ureteral stents, the symptoms associated with UTI resolved, and bacteriuria was not found in urine. The remaining seven patients with symptomatic UTI were treated with appropriate antibiotics, with the ureteral stents left in place. However, in seven patients in whom the same ureteral stent was retained, UTI recurred, and the mean time to symptom recurrence was 10 days. After replacement of ureteral stents, the UTI symptoms were relieved.

Similar to our results, Altunal *et al.* reported that of the 11 patients with symptomatic UTI, six had their ureteral stent replaced and were treated with antibiotics. However, the remaining five were treated with appropriate antibiotics, with ureteral stents left in place. UTI relapsed in all five

patients (35).

This finding may have been due to the low effectiveness of antibiotics in bacterial colonization of ureteral stents due to biofilm formation on the surface of the material. Based on this result, we recommend that ureteral stents should be replaced in patients with symptomatic UTI, who require persistent indwelling ureteral stents, after appropriate antibiotic treatment.

In our study, the incidence of symptomatic UTI was associated with dependent functional capacity, impaired renal function, and a longer duration of ureteral stenting. Regarding these findings, it may be thought that dependent functional capacity and longer duration of ureteral stenting were more associated with the development of symptomatic UTI when compared to baseline patient characteristics including age, sex, and presence of DM, although these patient characteristics might also affect the development of UTI to some extent.

Additionally, renal function may be considered as the capacity to produce and excrete urine, in which microorganisms flow into the outer environment. Therefore, severely impaired renal function (in particular CKD state 4 and 5) may result in both concentrated bacteria and subsequent development of symptomatic UTI which is consistent with our results. In previous literature reviews (16,17), CKD appeared to be associated with an increased colonization rate of ureteral stents without any clear evidence of an increase in the development of UTI, although the methodological quality of the included studies was inadequate to derive any clear conclusions. It is known that fewer virulence factors are required for infection in patients with ureteral stents than in those with good function of the urinary tract. Additionally, impaired renal function are known to be potential risk factors for UTI due to the immunosuppression associated with these conditions (36).

A longer duration of ureteral stenting increased the incidence of symptomatic UTI and bacteriuria, which was associated with biofilm formation on the surface of ureteral stents. Our study showed that the number of previous replacements of ureteral stents was not associated with the development of symptomatic UTI, as in bacteriuria. This finding may imply that periodic replacement of ureteral stents in patients who require persistent indwelling ureteral stents would be important to prevent UTI. Additionally, although patients retaining ureteral stents have bacteriuria, not symptomatic UTI, with factors associated with UTI, replacement of ureteral stents with shorter duration should

be considered.

Our study was not without limitations and had a potentially limited observational design and small sample size. The study was performed at a single center. However, it included a group of patients commonly managed in urology; therefore, the results may be applied to similar centers. We could not evaluate the incidence of ureteral stent colonization because microbiological tests were not performed for ureteral stents. Colonization of ureteral stents may be a factor associated with bacteriuria. However, colonization of ureteral stents does not necessarily coincide with UTI development. We plan to perform microbiological testing for ureteral stents and assess the incidence of ureteral stent colonization and its association with other factors.

Additionally, it is known that indwelling catheters and female sex are risk factors for bacteriuria and UTI. Therefore, these factors may be potential confounding factors, although analysis of this study was adjusted for variables, including these factors. We have also focused on other factors affecting bacteriuria and symptomatic UTIs, such as longer duration of ureteral stenting. Moreover, since we did not perform microbiological tests for urine samples on a weekly or monthly basis, we could not assess the incidence of bacteriuria and symptomatic UTI with time.

## Conclusions

Infections related to ureteral stents showed a specific microorganism profile and resistance pattern compared to community-acquired UTIs. Additionally, we identified the factors associated with the occurrence of bacteriuria, ESBL-producing bacteria, and symptomatic UTI in patients with retained ureteral stents.

In our study, the possible short duration of ureteral stent placement and periodic replacement in patients with prolonged use of ureteral stents prevented the occurrence of bacteriuria, ESBL-producing bacteria, and symptomatic UTI. Considering the microbiological profile and factors associated with bacteriuria and symptomatic UTIs may be associated with better outcomes in patients with retained ureteral stents.

## Acknowledgments

The authors thank the entire staff of the Department of Urology, Sanggye Paik Hospital, Inje University College

of Medicine. Our Abstract has been published in <https://onlinelibrary.wiley.com/doi/10.1111/iju.15019>.

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-331/rc>

*Data Sharing Statement:* Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-331/dss>

*Peer Review File:* Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-331/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-331/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of Sanggye Paik Hospital, Inje University (committee reference number: 2018-11-011), and informed consent was obtained from each patient after careful explanation of the scope of the study.

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**Cite this article as:** Kim JY, Yeo JK, Park MG, Sung LH, Cho DY, Yu JH. Determination of microbiological characteristics and risk factors associated with bacteriuria and symptomatic urinary tract infection in patients with retained ureteral stents: an observational study. *Transl Androl Urol* 2023;12(1):19-32. doi: 10.21037/tau-22-331