Original Article - Infection/Inflammation

Investig Clin Urol 2025;66:261-271.
https://doi.org/10.4111/icu.20250086
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
IC UROLOGY

Effect of long-term postoperative OM-89 administration on bacteriuria from suspected infectious stones

Seung-Ju Lee[1], Jemo Yoo[1], Hee Youn Kim[1], Jin Bong Choi[2], Dong Sup Lee[1]

[1]Department of Urology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, [2]Department of Urology, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon, Korea

Purpose: We aimed to evaluate the effect of long-term oral OM-89 therapy on the urinary microflora in patients with urolithiasis.

Materials and Methods: Patients underwent surgical removal of urinary stones followed by no OM-89 treatment for six months or daily OM-89 administration. Urine culture and urinary polymerase chain reaction (PCR) were performed at the baseline visit (V1) and at 2 months (V2) and 6 months (V3) after the operation.

Results: A total of 113 patients completed the study. The rate of urinary bacteria detection by urine culture at V3 did not differ between OM-89 treated and untreated groups (p>0.999); however, the PCR detection rate tended to be higher in OM-89 untreated group than in OM-89 treated group (p=0.052). *Escherichia coli* and *Enterococcus* spp. were the bacteria most commonly detected via both urine culture and PCR at all timepoints. Risk factors for the detection of bacteria by urine culture at V3 were positive culture at V1 (p=0.048) and female sex (p=0.048), whereas positive PCR at V3 was associated with female sex (p=0.023), positive PCR at V2 (p<0.001), and no OM-89 treatment (p=0.038). The use of OM-89 was associated with decreased rates of bacterial detection by PCR at V2 and a further decrease at V3.

Conclusions: Long-term immunization with OM-89 could further decrease the frequency of urinary bacterial colonization after surgical removal of urinary stones. OM-89 could be used as a complementary therapy if a retrieved stone is suspected to be related to infection.

Keywords: Bacteria; Immunization; Urolithiasis

INTRODUCTION

The mechanisms of carbapatite and struvite formation by urea-splitting microorganisms such as *Klebsiella pneumoniae*, *Proteus mirabilis*, and other species are already known [1]. However, a study of 1,191 patients revealed that nonurea-splitting microorganisms, such as *Escherichia coli* and *Enterococcus* spp., were found in approximately 40% of patients with struvite stones in the absence of identifiable urea-splitting microorganisms [2]. Although the key mechanism by which nonurea-splitting microorganisms create infectious stones is poorly understood, recent studies have shown that *E. coli* and *Enterococcus* spp. contribute to the development of urolithiasis through the creation of biofilms

Received: March 3, 2025 • **Revised:** March 23, 2025 • **Accepted:** March 25, 2025 • **Published online:** April 30, 2025
Corresponding Author: Dong Sup Lee https://orcid.org/0000-0003-0862-3205
Department of Urology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea
TEL: +82-31-881-8920, E-mail: bbangbbangi@naver.com

or reciprocal sharing of basic amino acids with urea-splitting bacteria [3-6].

According to guidelines for the treatment of infectious stones, acetohydroxamic acid, methionine, and ammonium chloride are recommended as preventive medicines [7]. Acetohydroxamic acid is a urease inhibitor that can be used in the presence of urea-splitting microorganisms [8]; however, it is not available in some areas [7]. Ammonium chloride and methionine are urinary acidity modifiers and thus can only be used in patients with alkaline urine. Therefore, the potential for the application of preventive methods is limited in different types of infectious stone cases.

Oral immunotherapy with OM-89 (Uro-Vaxom®) is widely used to prevent recurrent urinary tract infections [9]. OM-89 was originally thought to target *E. coli,* but a previous study suggested that OM-89 could also prevent infection by other species, including *K. pneumoniae*, *P. mirabilis*, and *Enterococcus* spp. [10]. Therefore, it would be of great interest to determine whether OM-89 affects the urinary microflora after surgical treatment for urolithiasis. Hence, we hypothesized that long-term use of oral OM-89 after surgical treatment for urolithiasis could decrease the detection rate of urinary microflora.

MATERIALS AND METHODS

1. Ethical approval

The present study was approved by the Institutional Review Board of St. Vincent's Hospital (approval number: VC-22MIDV0011, date of approval: April 21, 2022). Additionally, this project was registered at https://cris.nih.go.kr (registration number: KCT0007078, date of approval: March 11, 2022). This study was performed in accordance with the guidelines of the Declaration of Helsinki (2013) and did not include any studies with animals performed by any of the authors. Informed consent was obtained from all study participants.

2. Population and design

The present study was a prospective comparative cohort study performed at two university hospitals conducted from July 2022 to December 2023. Four surgeons with more than 10 years of experience in the field of urolithiasis managed the patients with renal stones in this work. Consecutive patients aged over 20 years who had renal stones with pyuria (white blood cell count >5/high-power field) and were scheduled for surgical removal of the stones were eligible.

Patients underwent surgical removal of urinary stones, followed by no OM-89 treatment for 6 months in the phase 0 study or daily OM-89 for 6 months after surgical removal of urinary stones in the phase 1 study. No patient who participated in the phase 0 study was eligible to participate in the phase 1 study.

The inclusion criteria were as follows: (1) afebrile outpatients with nephrolithiasis and (2) maximal stone diameter over 5 mm. The exclusion criteria were as follows: (1) patients with any clinical symptoms of urinary tract infection (e.g., fever, myalgia); (2) patients receiving ongoing cancer treatment with any chemotherapeutic agent that could increase urinary uric acid excretion; (3) patients who had been diagnosed with gout (uric acid leakage); (4) patients with hyperparathyroidism (phosphate leakage); (5) patients who were using immunosuppressants that could increase the risk of infection; (6) patients with abnormal urinary tracts, such as neobladder with intestinal substitution or ileal conduits; (7) patients with calyceal diverticular stones; and (8) patients with indwelling urinary catheters.

Urine culture; a urine polymerase chain reaction (PCR) test for *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *Enterococcus* spp.; and noncontrast urinary computed tomography (NCCT) were performed at the first visit (V1) and repeated at 2 months (V2) and 6 months (V3; final visit) after surgery for urolithiasis. Antibiotics were given for 7 days preoperatively according to the results of the urine culture susceptibility test. If the culture results were negative, prophylactic antibiotics (3rd-generation cephalosporins) were offered for 7 days preoperatively. Flexible ureteroscopy (retrograde intrarenal surgery [RIRS]) or percutaneous nephrolithotomy (PCNL) was used to remove the renal stones. After the surgical procedure, a double-J ureteral stent was routinely placed for 1 week. Admission for operation and the visit for the removal of ureteral stents were not counted as study visits. The visit to the outpatient office at 2 months after the operation was designated as the second visit (V2), and the visit 6 months after the operation was defined as the final visit (V3). Antibiotics were stopped just after the removal of the double-J ureteral catheter. In the OM-89 treated group, OM-89 was offered after the removal of the double-J ureteral catheter.

The drop-out criteria during follow-up were as follows: (1) patients who required further regimens of antibiotics beyond our protocol (e.g., those with pneumonia, urinary tract infection, admission for other surgeries, etc.); (2) patients who received immunosuppressive agents for any reason (e.g., rheumatologic or neurologic disease); (3) patients who experienced any adverse effects with OM-89; (4) patients who did not want to participate in the study follow-up; and (5) patients who were newly diagnosed with cancer or a life-threatening disease. During the 6-month follow-up, no oral medicines that affect urinary mineral metabolism, such as

https://doi.org/10.4111/icu.20250086

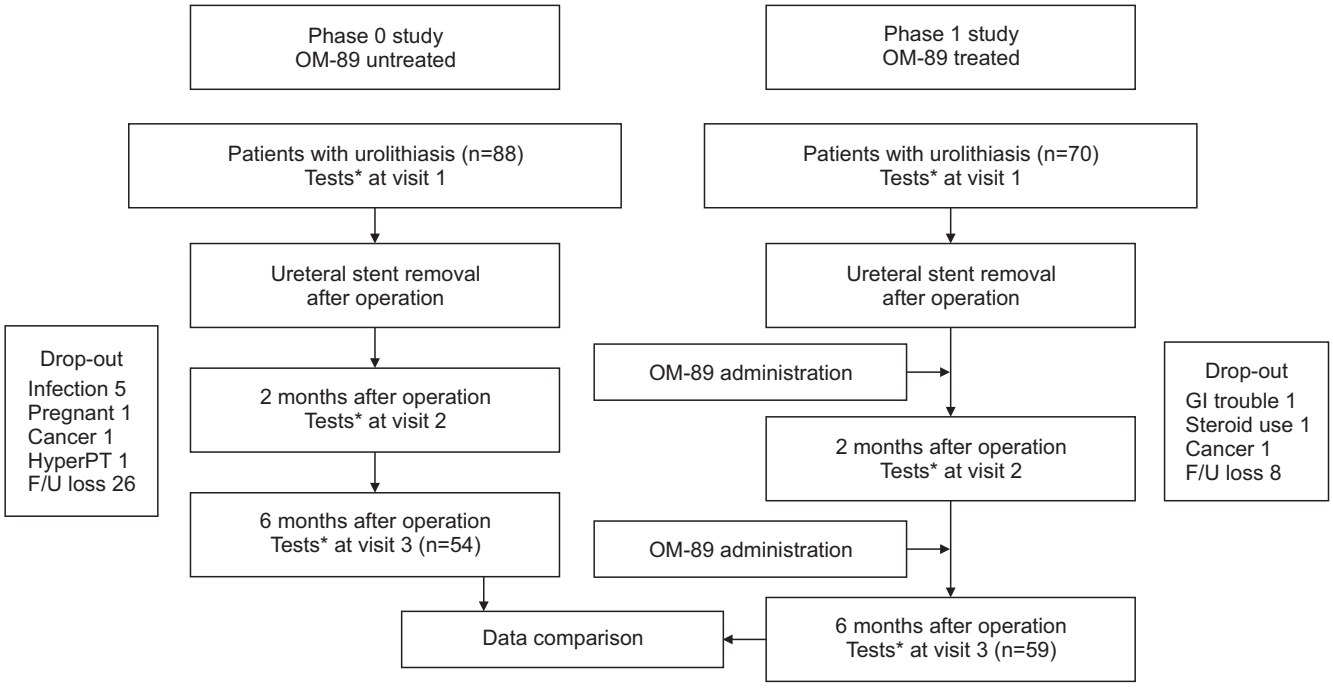

Fig. 1. Study design. Patients treated with or without OM-89 were compared by using nonenhanced urinary computed tomography, urine culture, and urinary polymerase chain reaction. HyperPT, hyperparathyroidism; F/U, follow-up; GI, gastrointestinal. *Tests include urine culture, urine polymerase chain reaction, and noncontrast urinary computed tomography.

citrate, bicarbonate, chlorothiazide, and methionine, were provided (Fig. 1).

3. Surgical procedures

In general, PCNL was selected for patients with a stone diameter greater than 2 cm [7]. PCNL was performed in the prone position by urologists who had at least 100 cases of experience. The PCNL tract was created using a 30 Fr and X-Force nephrostomy balloon dilator (Bard). After the outer sheath was in place, the procedure was continued by inserting a 24 Fr Universal Nephroscope (Richard Wolf). Stone fragmentation and suction removal of small fragments were performed using an ultrasound lithotriptor (Richard Wolf). A two-prong forceps was used to retrieve the larger fragments. During the procedure (usually at the end of the procedure), the sheath of the balloon dilator was removed carefully to allow monitoring for significant bleeding throughout the puncture site. If needed, a bipolar resectoscope (TURis 2.0, 30°) and sheath (26 Fr) was inserted into the sheath of the balloon dilator to control the bleeding of the PCNL tract lesion, while the sheath of the balloon dilator was slowly removed [11]. In contrast, RIRS was performed in the lithotomy position. Ureteroscopy (6/7.5 Fr; Richard Wolf) was performed to ensure ureter patency before RIRS. Before withdrawal of the ureteroscope, an Amplatz Superstiff Guide wire (Boston Scientific) was inserted via the ureteroscope. After removal of the ureteroscope, a 10 Fr (outer diameter 10 Fr, length 54 cm) dual lumen ureteral catheter (Dual Lumen; Boston Scientific) was introduced along the guidewire. Then, contrast material was administered although the dual lumen catheter for retrograde urography to assess the pelvicalyceal anatomy and stone location. After the removal of the dual lumen catheter, a ureteral access sheath (11–13 Fr; Boston Scientific) was introduced along the previously inserted guidewire under visualization of the C-arm [12]. Our preferred laser settings for the 120-Watt Holmium laser system (Lumenis Pulse™ 120H; Boston Scientific) with a 200 μm single-use fiber were as follows: for fragmentation and small particle removal, 1.0–1.2 J with 10–20 Hz; for dusting, 0.3–0.5 J with 50–60 Hz.

4. Measurements

Bacteria in a midstream urine sample were identified with the MicroScan identification system (Baxter Diagnostics Inc.), and the minimum inhibitory concentrations were measured via the broth microdilution method [13]. A positive urine culture was reported only when the bacterial growth was $\geq 10^4$ colony-forming unit (CFU)/mL [13]. In the present study, PCR detection of bacteria was also carried out, using 16S rRNA gene sequencing for *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *Enterococcus* spp. performed according to a company protocol (Seegene). Once midstream urine samples were

obtained from the patients, they were immediately stored in a -70°C freezer by the physicians and retrieved by the company that performed the PCR (Seegene). The method for 16S rRNA gene sequencing was similar to that described in a previous study [14].

NCCT is the preferred diagnostic tool for urolithiasis. In addition, many types of information provided by NCCT, including the distance from the skin to the stone, the infundibulopelvic angle, and the positions of the stones and calyces, can help surgeons make decisions regarding the optimal surgical approach. NCCT is also useful for evaluating the presence of residual stones after surgery [15]. The authors of a previous study demonstrated that neither ultrasound nor kidney, ureter, and bladder (KUB) X-ray could identify residual stones less than 2 mm in size. Therefore, we defined residual stones as stones of any size observed on NCCT at 2 months after the operation. 'Stone regrowth' was defined as the development of a new stone in a previously stone-free patient or an increase in the size of a residual stone six months after the operation.

5. Statistical analysis

IBM SPSS Statistics for Windows version 26.0 (IBM Corp.) was used to perform the statistical analysis. For a statistical power of 0.95, an α error of 0.05 and a medium effect size in a comparison between two independent groups, the minimum sample size required was 145 patients. The chi-square test was used to determine the difference in the frequency of two independent groups. If multiple factors were identified in the univariate analysis, we used a binomial regression test to perform binomial regression analysis (stepwise forward method). Student t-test was also applied if comparisons of continuous variables between groups were needed. Continuous variables are expressed as the mean±standard deviation, whereas binomial parameters are expressed as the cases/total number or frequency (%). For parameters with an ordinal pattern, the variables are expressed as the mean±standard deviation, and the Spearman test was subsequently applied to compare two groups. A p-value<0.05 was considered to indicate statistical significance.

RESULTS

Fifty-four (61.4%) of the 88 patients in OM-89 untreated group and 59 (84.3%) of the 70 patients in OM-89 treated group completed the follow-up. The baseline characteristics in both groups are presented in Table 1. Only 1 patient in OM-89 treated group reported drug-associated adverse effects (nausea and dyspepsia) throughout the present study (Fig. 1).

The frequency of positive urine culture at baseline was 26.5% (30/113), and the most common microorganism found in the baseline samples was *E. coli* (14.2%, 16/113). With respect to the PCR results, microorganisms were detected in 44.2% (50/113) of the patient urine samples at V1 (Table 2). Over half of the patients with positive urine cultures or PCR test results remained positive at the 6-month follow-up. From baseline to the final visit, the detection rates of *K. pneumoniae* and *P. mirabilis* were very low. Female sex and struvite stones were risk factors for both positive urine culture and positive urine PCR at V1, whereas pure calcium oxalate stones were associated with a lower likelihood of detection of microorganisms (Table 3). Among the 39 struvite stones, microorganisms were isolated by urine culture in 19 cases (48.7%), of which *E. coli* was detected in 11 cases (28.2%; 57.9% of positive urine cultures). With respect to urine PCR from patients with struvite stones, microorganisms were detected in 25 cases (64.1%), of which 15 cases (38.5%; 60.0% of positive cases of urine PCR) were *E. coli* (Supplementary Table 1).

At V3, the detection rates of microorganisms via urine culture did not differ between OM-89 treated and untreated groups; however, with respect to PCR detection, the rates tended to be higher in OM-89 untreated group than in OM-89 treated group (p=0.052) (Table 4). In the OM-89 treated group, the microorganism detection rates via not only urine culture but also urine PCR decreased at 2 months after the operation, and a further decrease in the detection rate at 6 months after the operation was observed (Table 4, Fig. 2). Regression analysis revealed that positive urine culture at V3 was correlated with positive culture at V1 (p=0.048) and female sex (p=0.048), whereas female sex (p=0.023), positive urine PCR at V2 (p<0.001), and no OM-89 treatment (p=0.038) were correlated with positive urine PCR at V3 (Table 4). PCNL was excluded as an explanatory variable for positive urine culture at V3 even though it had statistical significance in univariate analysis because PCNL was significantly related to positive culture at V1 (Supplementary Table 2). With respect to positive urine PCR at V3, OM-89 effectively reduced *E. coli* and *Enterococcus* spp. present at V2 (Supplementary Table 3, Fig. 2). In patients with struvite stones (n=39) in which *E. coli* composed the majority of microorganisms, the use of OM-89 tended to reduce the urine PCR detection rate of microorganisms, especially *E. coli* (Supplementary Table 4).

In terms of stone regrowth identified in NCCT, positive urine culture at V3, positive PCR test results at V3, uric acid levels, and documented residual stones at V2 were confirmed as risk factors in the univariate analysis (Table 5). Stone

https://doi.org/10.4111/icu.20250086

Table 1. Baseline characteristics (n=113)

Characteristic	Phase 0 (n=54)	Phase 1 (n=59)	p-value
Age (y)	57.22±12.10	59.07±10.22	0.382[a]
BMI (kg/m^2)	25.89±3.90	25.29±3.93	0.416[a]
Sex (male)	21 (38.9)	26 (44.1)	0.703[b]
Underlying condition			
Hypertension	28 (51.9)	31 (52.5)	>0.999[b]
Diabetes	14 (25.9)	13 (22.0)	0.664[b]
Dyslipidemia	12 (22.2)	13 (22.0)	>0.999[b]
Maximal stone size (mm)	15.82±10.53	14.38±9.32	0.443[a]
Hounsfield unit	827.62±313.21	884.03±355.39	0.379[a]
Stone complexity (Guy's score)	1.87±1.05	1.52±0.88	0.051[a]
Preoperative eGFR (mL/min/1.73 m^2)	87.30±30.54	82.69±21.34	0.361[a]
24-hour urine collection			
Urine volume (mL)	1,835.69±737.70	1,920.36±649.45	0.529[a]
Calcium (mg)	182.82±111.07	219.84±126.99	0.113[a]
Uric acid (mg)	559.90±236.69	565.15±211.99	0.904[a]
Citric acid (mg)	357.69±265.92	375.59±250.61	0.718[a]
Positive spot urinary nitrite	9 (16.7)	6 (10.2)	0.408[b]
Stone composition			
Pure calcium oxalate	22 (40.7)	28 (47.5)	0.446[b]
Carbapatite	18 (33.3)	22 (37.3)	0.693[b]
Struvite	15 (27.8)	24 (40.7)	0.163[b]
Uric acid	7 (13.0)	3 (5.1)	0.195[c]
Positive urine culture	16 (29.6)	14 (23.7)	0.527[b]
Escherichia coli	8 (14.8)	8 (13.6)	>0.999[b]
Klebsiella pneumoniae	0 (0.0)	2 (3.4)	0.497[c]
Proteus mirabilis	2 (3.7)	0 (0.0)	0.226[c]
Enterococcus spp.	3 (5.6)	2 (3.4)	0.669[c]
Others	3 (5.6)	2 (3.4)	0.669[c]
Positive urine PCR	26 (48.1)	24 (40.7)	0.453[b]
Escherichia coli	16 (29.6)	13 (22.0)	0.356[b]
Klebsiella pneumoniae	0 (0.0)	5 (8.5)	0.058[c]
Proteus mirabilis	5 (9.3)	0 (0.0)	0.023[c]
Enterococcus spp.	14 (25.9)	11 (18.6)	0.374[b]

Values are presented as mean±standard deviation or number (%).
Phase 0, OM-89 untreated group; Phase 1, OM-89 treated group; BMI, body mass index; eGFR, estimated glomerular filtration rate; PCR, polymerase chain reaction.
[a]:Based on Student t-test. [b]:Based on chi-square test. [c]:Based on Fisher exact test.

regrowth was negatively associated with long-term OM-89 administration, but the correlation did not reach statistical significance (*rs*=-0.145, p=0.133, by Spearman's correlation test). A binomial regression test revealed that positive urine PCR at V3 and residual stones at the second visit were associated with stone regrowth (Nagelkerke R^2=0.243; p=0.003 and 0.017, respectively), which means that infection-related stones could grow in the short term after the operation.

DISCUSSION

The major finding of the present study was that long-term use of OM-89 after surgery for urolithiasis decreased the rate of urinary microorganism detection at the 6-month follow-up. The anticipated result was significant only when considering microorganism detection with a urinary PCR test. Nevertheless, the fact that OM-89 treatment decreases the rate of urinary microorganism detection via PCR after surgery in patients with urolithiasis will be of great interest to endourological physicians. Although a cutoff value of

Table 2. Urinary microorganisms documented during the present study (n=113)

	V1	V2	V3
Pyuria	113 (100.0)	24 (21.2)	31 (27.4)
Any culture positive	30 (26.5)	18 (15.9)	18 (15.9)
Escherichia coli	16 (14.2)	10 (8.8)	10 (8.8)
Klebsiella pneumoniae	2 (1.8)	2 (1.8)	1 (0.9)
Proteus mirabilis	2 (1.8)	1 (0.9)	2 (1.8)
Enterococcus spp.	5 (4.4)	5 (4.4)	3 (2.7)
Other bacteria	5 (4.4)	2 (1.8)	2 (1.8)
Any PCR positive	50 (44.2)	34 (30.1)	28 (24.8)
Escherichia coli	29 (25.7)	23 (20.4)	18 (15.9)
Klebsiella pneumoniae	5 (4.4)	4 (3.5)	2 (1.8)
Proteus mirabilis	5 (4.4)	2 (1.8)	2 (1.8)
Enterococcus spp.	25 (22.1)	18 (15.9)	12 (10.6)

Values are presented as number (%).
Other bacteria include *Staphylococcus saprophyticus*, *Streptococcus agalactiae*, and *Morganella morganii*.
V1, before surgery; V2, 2 months after surgery; V3, 6 months after surgery; PCR, polymerase chain reaction.

$\geq 10^4$ CFU/mL for positive urine culture has been widely accepted as a diagnostic value, this criterion obviously neglects a certain proportion of occult bacteriuria ($<10^4$ CFU/mL). This could be important for patients with infectious stones because colonization of bacteria in the urinary tract may be associated with stone growth, as described in the introduction. In the present study, the detection of microorganisms at V3 revealed an increased rate of stone regrowth, and chronic use of OM-89 could reduce the detection rate in urine PCR at 6 months after the operation, although OM-89 was not demonstrated to have an independent role in decreasing stone regrowth.

A recent study revealed that previous interventions increased the risk for bacteriuria [16]. Therefore, physicians should be concerned by the presence of urinary bacteria even if bacteria cannot be cultured via traditional microdilution tests. Although PCR testing to detect bacteria is not always useful because of its cost, the lack of availability of susceptibility tests, and false-positive results (low specificity, as shown in Supplementary Table 5), PCR tests have high sensitivity, minimizing false-negative results [17]. For example, Haley et al. [18] reported that the proportion of positive PCR tests to negative cultures was 76% when infection-associated urinary biomarkers were used. Even though stone culture together with urine culture can slightly increase the sensitivity of the detection before surgery [19], the detection of microorganisms after surgery (during follow-up) should depend solely on urine sample analysis. Therefore, analyses performed after stone operation should use urine samples. In the present study, microorganism detection by urine PCR at V2 was associated with an increased probability of positive urine PCR at V3.

OM-89 (Uro-Vaxom®) has been widely used as an oral immunotherapy to prevent recurrent cystitis. Compared with placebo, 3 months of OM-89 treatment decreased the urinary tract infection rate within 6 months of follow-up by 20%, and compared with placebo, 3 months of OM-89 treatment plus 1 capsule booster for 10 days 9 months reduced the infection rate within 1 year of follow-up by 43% [20]. In accordance with previous studies, we considered 6 months to be an appropriate minimal follow-up period; however, we offered OM-89 for the entire follow-up period to maximize the drug effect. An important lesson from clinical studies is that OM-89 does not guarantee against the subsequent development of urinary tract infection, although it can reduce the risk of urinary tract infection. On the basis of previous studies [16,17,20] and the present study, we believe that OM-89 could be a useful complementary method to reduce the risk of bacterial acclimation in the urinary tract postoperatively. In the present study, the rate of microorganism detection by PCR at 6 months decreased significantly after daily OM-89 administration, which is highly relevant to endourologists because lowering the risk of bacteriuria, especially in patients with a history of urolithiasis, may reduce the incidence of complicated urinary tract infections and unnecessary exposure to antibiotics. Notably, in the present study, there were five cases of urinary tract infection after removal of the double-J ureteral catheter in patients who did not receive OM-89 treatment (excluded from the analysis because of their requirement for additional antibiotics), whereas there were no cases of urinary tract infection in patients who received OM-89 treatment (Fig. 1).

Stone regrowth may not have been a major issue in the present study because of the limited follow-up period. However, infection-related stones can grow rapidly [21]. Considering the possibility of infectious nephrolithiasis, surgeons should make great efforts to remove all clinically significant stones during the operation. Regardless of whether the surgery achieved stone-free status, further steps for preventing stone regrowth should be discussed, which leads us back to the role of urinary microorganisms. The effects of urinary microorganisms on stone formation remain unclear except in the case of traditional urea-splitting microorganisms (e.g., *P. mirabilis*), which are believed to cause struvite stones [1]. Recently, *E. coli* and *Enterococcus* spp. have emerged as leading microorganisms isolated from infectious stones in clinical studies [2,19]. Importantly, a recent study revealed that *E. coli* is an important factor in mixed struvite but not pure

https://doi.org/10.4111/icu.20250086

Table 3. Risk factors for the detection of microorganisms at the first visit (V1)

Detection by urine culture	Positive (n=30)	Negative (n=83)	p-value	Detection by urine PCR	Positive (n=50)	Negative (n=63)	p-value
Age (y)	59.77±11.42	57.61±11.06	0.367[a]	Age (y)	58.70±13.73	57.78±8.66	0.480[a]
BMI (kg/m^2)	26.00±4.40	25.43±3.74	0.491[a]	BMI (kg/m^2)	26.06±4.13	25.20±3.71	0.243[a]
Sex (female)	26/30	40/83	<0.001[b]	Sex (female)	40/50	26/63	<0.001[b]
DM	7/30	20/83	>0.999[b]	DM	12/50	15/63	>0.999[b]
HTN	15/30	44/83	0.833[b]	HTN	26/50	33/63	>0.999[b]
Dyslipidemia	7/30	18/83	>0.999[b]	Dyslipidemia	11/50	14/63	>0.999[b]
Maximal stone size (mm)	15.63±9.57	14.87±10.07	0.720[a]	Maximal stone size (mm)	15.30±9.87	14.90±10.01	0.831[a]
Hounsfield units	892.28±383.60	844.66±318.60	0.514[a]	Hounsfield units	878.06±345.30	840.53±329.61	0.561[a]
Stone complexity (Guy's score)	1.63±1.00	1.71±0.97	0.687[c]	Stone complexity (Guy's score)	1.68±0.98	1.69±0.98	>0.999[c]
Stone components				Stone components			
Pure calcium oxalate	6/30	44/81	0.001[b]	Pure calcium oxalate	17/50	33/61	0.038[b]
Carbapatite	14/30	26/81	0.184[b]	Carbapatite	22/50	18/61	0.164[b]
Struvite	19/30	20/81	<0.001[b]	Struvite	25/50	14/61	0.005[b]
Uric acid	3/30	7/81	>0.999[d]	Uric acid	5/50	5/61	0.752[b]

Values are presented as mean±standard deviation or number.
There were 2 missing values in the stone analysis.
V1, before surgery; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; PCR, polymerase chain reaction.
[a]:Based on Student t-test. [b]:Based on chi-square test. [c]:Based on Spearman test. [d]:Based on Fisher exact test.

Table 4. Risk factors for detection of microorganisms at the final visit (V3)

Detection by urine culture	Positive (n=18)	Negative (n=95)	p-value	Detection by urine PCR	Positive (n=28)	Negative (n=85)	p-value
Age (y)	62.83±14.23	57.31±10.32	0.131[a]	Age (y)	58.96±15.48	57.93±9.40	0.740[a]
BMI (kg/m^2)	25.13±4.15	25.67±3.88	0.597[a]	BMI (kg/m^2)	25.66±4.36	25.55±3.78	0.895[a]
Sex (male)	2/18	45/95	0.004[b]	Sex (male)	4/28	43/85	<0.001[b]
DM	3/18	24/95	0.556[d]	DM	5/28	22/85	0.454[b]
HTN	7/18	52/95	0.304[b]	HTN	13/28	46/85	0.519[b]
Dyslipidemia	3/18	22/95	0.759[d]	Dyslipidemia	5/28	20/85	0.609[b]
Maximal stone size (mm)	18.17±13.47	14.48±9.04	0.149[a]	Maximal stone size (mm)	17.71±13.79	14.20±8.14	0.210[a]
Hounsfield units	836.39±359.41	861.11±332.70	0.388[a]	Hounsfield units	757.43±323.57	890.72±334.77	0.069[a]
Stone complexity (Guy's score)	1.89±1.03	1.65±0.95	0.445[c]	Stone complexity (Guy's score)	1.93±1.09	1.61±0.93	0.141[c]
Microbiological results				Microbiological results			
Culture positive at V1	10/18	20/95	0.007[d]	PCR positive at V1	20/28	30/85	0.001[b]
Culture positive at V2	7/18	11/95	0.009[d]	PCR positive at V2	18/28	16/85	<0.001[b]
Stone components				Stone components			
Pure calcium oxalate	6/18	44/93	0.312[b]	Pure calcium oxalate	9/28	41/83	0.129[b]
Carbapatite	8/18	32/93	0.432[b]	Carbapatite	12/28	28/83	0.495[b]
Struvite	8/18	31/93	0.423[b]	Struvite	11/28	28/83	0.650[b]
Uric acid	2/18	8/93	0.664[d]	Uric acid	5/28	5/83	0.118[d]
Postoperative factors				Postoperative factors			
PCNL (not RIRS)	6/18	12/94	0.041[d]	PCNL (not RIRS)	7/28	11/84	0.148[b]
Residual stones	8/18	30/92	>0.999[b]	Residual stones	9/28	27/82	>0.999[b]
Use of OM-89	9/18	50/95	>0.999[b]	Use of OM-89	10/28	49/85	0.052[b]
Binomial regression test (Nagelkerke R^2=0.189)	B	SE	Exp(B)	Binomial regression test (Nagelkerke R^2=0.353)	B	SE	Exp(B)
Sex (male)	-1.591	0.806	0.204	0.048	Sex (male)	-1.410	0.622	0.244	0.023
Culture positive at V1	1.114	0.563	3.047	0.048	PCR positive at V2	1.916	0.529	6.793	<0.001
					Use of OM-89	-0.934	0.428	0.334	0.038

Values are presented as mean±standard deviation or number.
There were 2 missing values for stone analysis and 3 missing values for residual stones.
V3, 6 months after surgery; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; V1, before surgery; V2, 2 months after surgery; PCNL, percutaneous nephrolithotomy; RIRS, retrograde intrarenal surgery; B, unstandardized coefficients; SE, standard error; PCR, polymerase chain reaction.
[a]:Based on Student t-test. [b]:Based on chi-square test. [c]:Based on Spearman test. [d]:Based on Fisher exact test.

https://doi.org/10.4111/icu.20250086

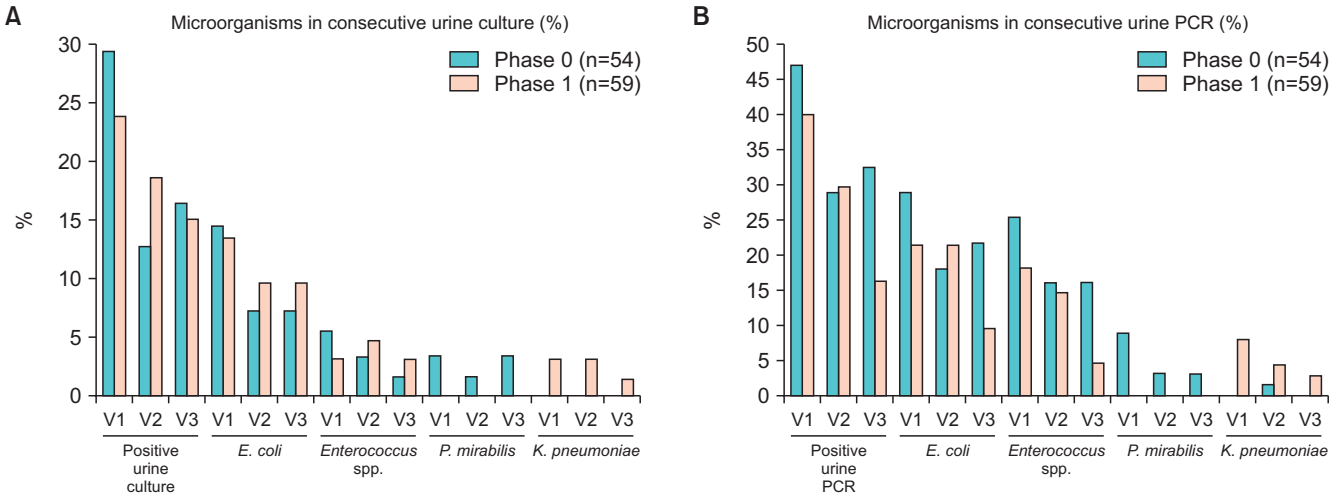

Fig. 2. The rates of microorganism detection via urine culture and urine polymerase chain reaction (PCR). Blue bars and orange bars indicate OM-89 untreated group (phase 0) and OM-89 treated group (phase 1), respectively. V1, before surgery; V2, 2 months after surgery; V3, 6 months after surgery; *E. coli*, *Escherichia coli*; *P. mirabilis*, *Proteus mirabilis*; *K. pneumoniae*, *Klebsiella pneumoniae*.

Table 5. Risk factors for stone regrowth at the final visit

Univariate test	No growth (n=96)		Regrowth (n=13)	p-value
Age (y)	25.84±3.94		24.34±3.79	0.200[a]
BMI (kg/m^2)	57.90±10.49		59.46±16.59	0.641[a]
Sex (female)	58 (60.4)		6 (46.2)	0.377[b]
DM	24 (25.0)		3 (23.1)	>0.999[c]
HTN	51 (53.1)		6 (46.2)	0.770[b]
Dyslipidemia	19 (19.8)		5 (38.5)	0.155[b]
Microbiological results				
Culture positive at V2	16 (16.7)		2 (15.4)	>0.999[c]
Culture positive at V3	12 (12.5)		6 (46.2)	0.007[c]
PCR positive at V2	28 (29.2)		6 (46.2)	0.220[c]
PCR positive at V3	20 (20.8)		8 (61.5)	0.004[c]
Stone components				
Pure calcium oxalate	44 (45.8)		4 (30.8)	0.181[c]
Carbapatite	36 (37.5)		4 (30.8)	0.381[b]
Struvite	36 (37.5)		3 (23.1)	0.765[c]
Uric acid	6 (6.3)		4 (30.8)	0.018[c]
Residual stones	27 (28.1)		8 (61.5)	0.025[c]
Use of OM-89	51 (53.1)		4 (30.8)	0.151[b]
Binomial regression test (Nagelkerke R^2=0.243)	B	SE	Exp(B)	
PCR positive at V3	1.959	0.662	7.090	0.003
Residual stones	1.589	0.664	4.897	0.017

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; V2, 2 months after surgery; V3, 6 months after surgery; PCR, polymerase chain reaction; B, unstandardized coefficients; SE, standard error.
[a]:Based on Student t-test. [b]:Based on chi-square test. [c]:Based on Fisher exact test.

struvite stones [22]. The likelihood of detecting microorganisms, including *E. coli* (at V1), is greater in struvite than in other stone types (Table 3, Supplementary Table 1), whereas the likelihood of detecting microorganisms is lower in pure calcium oxalate stone. Therefore, bacteriuria seems to be responsible for struvite formation. However, previously confirmed (treated) struvite was not identified as a risk factor for stone regrowth; rather bacteriuria detected by PCR and

residual stones were confirmed as risk factors for stone regrowth (Table 5). OM-89 is a bacterial extract prepared from 18 uropathogenic *E. coli* strains that targets urinary tract infections caused by *E. coli*. Nevertheless, a previous study showed its extended effects on other microorganisms [10]. In the present study, OM-89 suppressed the rate of detection of *E. coli* and *Enterococcus* spp. by PCR among cases in which they were present at the previous visit (Supplementary Table 3, Fig. 2). However, OM-89 treatment was not found to directly reduce stone regrowth, which might be due to the limited number of patients who were positive for microorganisms during the follow-up period and the fact that not all stones were infection-related stones. Nevertheless, considering the negative correlation between the use of OM-89 (phase 1) and stone regrowth (rs=−0.145, p=0.133), OM-89 might contribute to the prevention of stone regrowth by suppressing the urinary microflora. The discussion of the effects of OM-89 on stone recurrence rates could not be extended further here because OM-89 was only slightly negatively correlated with stone regrowth and was not statistically significant in this study, even though OM-89 tended to decrease the detection rate of microflora after stone treatment. Thus, further large-scale studies are needed to confirm the effect of OM-89 on stone regrowth.

The main limitation of the present study is that only eighteen patients exhibited positive cultures at the final visit. Securing many positive urine cultures in V3 is a practical challenge, as a very large number of patients need to be tested with culture and PCR and to be prescribed OM-89 (which requires a long study period or many institutions and high cost). Given that the present study had been conducted for one and a half years, we would have needed to conduct the present study over 6 years if we had enrolled only patients with positive urine cultures. Even though we tried to overcome this problem using urine PCR, potential selection/information bias may have occurred. Thus, further large-scale studies are needed to clarify the effect of OM-89 on infectious stones. In addition, the 6-month follow-up was relatively short for identifying stone regrowth for all types of stone compositions. However, infection-related stones can grow rapidly [21,23]. Among our cases in OM-89 untreated group, one case in which the baseline culture was negative but *E. coli* was detected via PCR showed rapid stone regrowth after PCNL (Supplementary Fig. 1). Furthermore, extending the follow-up duration may pose an ethical challenge because oral medicines that affect urinary mineral metabolism should not be provided during the study period. Therefore, further large studies are needed to investigate the role of OM-89 in stone regrowth in patients with infectious stones.

CONCLUSIONS

The long-term use of OM-89 decreased the rate of bacterial detection by urinary PCR after stone removal. Considering its preventive effect against the urinary microflora, physicians should consider prescribing OM-89 after surgical removal of urinary stones as a complementary drug if retrieved stones are suspected to be infection-related stones. Large-scale studies of the effects of OM-89 after the treatment of infectious stones are needed to confirm these findings.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

FUNDING

The present study was financially supported by Aju Pharm (Aju Pharm Co., Ltd., Seoul, Republic of Korea).

ACKNOWLEDGMENTS

We are particularly grateful to Woo Kyung Lee (Department of Urology, St. Vincent's Hospital) for assisting with sample collection and data processing.

AUTHORS' CONTRIBUTIONS

Research conception and design: Dong Sup Lee and Seung-Ju Lee. Data acquisition: Dong Sup Lee and Jemo Yoo. Statistical analysis: Dong Sup Lee and Hee Youn Kim. Data analysis and interpretation: Dong Sup Lee and Hee Youn Kim. Drafting of the manuscript: Dong Sup Lee and Jin Bong Choi. Critical revision of the manuscript: Dong Sup Lee and Hee Youn Kim. Obtaining funding: Dong Sup Lee and Jin Bong Choi. Administrative, technical, or material support: Dong Sup Lee and Seung-Ju Lee. Supervision: Dong Sup Lee and Seung-Ju Lee. Approval of the final manuscript: all authors.

DATA AVAILABILITY STATEMENT

The present study was registered at https://cris.nih.go.kr (registration number: KCT0007078, date of approval: March 11, 2022). The datasets generated during and/or analyzed during the current study are available from the correspond-

https://doi.org/10.4111/icu.20250086

ing author upon reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20250086.

REFERENCES

1. Espinosa-Ortiz EJ, Eisner BH, Lange D, Gerlach R. Current insights into the mechanisms and management of infection stones. Nat Rev Urol 2019;16:35-53.
2. Parkhomenko E, De Fazio A, Tran T, Thai J, Blum K, Gupta M. A multi-institutional study of struvite stones: patterns of infection and colonization. J Endourol 2017;31:533-7.
3. Barr-Beare E, Saxena V, Hilt EE, Thomas-White K, Schober M, Li B, et al. The interaction between Enterobacteriaceae and calcium oxalate deposits. PLoS One 2015;10:e0139575.
4. Amimanan P, Tavichakorntrakool R, Fong-Ngern K, Sribenjalux P, Lulitanond A, Prasongwatana V, et al. Elongation factor Tu on Escherichia coli isolated from urine of kidney stone patients promotes calcium oxalate crystal growth and aggregation. Sci Rep 2017;7:2953.
5. Ch'ng JH, Chong KKL, Lam LN, Wong JJ, Kline KA. Biofilm-associated infection by enterococci. Nat Rev Microbiol 2019;17:82-94.
6. Hunt BC, Brix V, Vath J, Guterman LB, Taddei SM, Deka N, et al. Metabolic interplay between Proteus mirabilis and Enterococcus faecalis facilitates polymicrobial biofilm formation and invasive disease. mBio 2024;15:e0216424.
7. Skolarikos A, Jung H, Neisius A, Petřík A, Kamphuis GM, Davis NF, et al. EAU guidelines on urolithiasis. European Association of Urology: 2025.
8. Williams JJ, Rodman JS, Peterson CM. A randomized double-blind study of acetohydroxamic acid in struvite nephrolithiasis. N Engl J Med 1984;311:760-4.
9. Brodie A, El-Taji O, Jour I, Foley C, Hanbury D. A retrospective study of immunotherapy treatment with Uro-Vaxom (OM-89®) for prophylaxis of recurrent urinary tract infections. Curr Urol 2020;14:130-4.
10. Huber M, Baier W, Serr A, Bessler WG. Immunogenicity of an E. coli extract after oral or intraperitoneal administration: induction of antibodies against pathogenic bacterial strains. Int J Immunopharmacol 2000;22:57-68.
11. Yoo JM, Kim HY, Lee DS. Application of bipolar cauterization during standard percutaneous nephrolithotomy. J Laparoendosc Adv Surg Tech A 2023;33:841-5.
12. Cho SY, Ryang SH, Lee DS. A presumptive role of lower ureteral angles in the difficulty of ureteral access sheath insertion during retrograde intrarenal surgery. Int Urol Nephrol 2020;52:1657-63.
13. Lee DS, Choe HS, Lee SJ, Bae WJ, Cho HJ, Yoon BI, et al. Antimicrobial susceptibility pattern and epidemiology of female urinary tract infections in South Korea, 2010-2011. Antimicrob Agents Chemother 2013;57:5384-93.
14. Cybulski Z, Schmidt K, Grabiec A, Talaga Z, Bociąg P, Wojciechowicz J, et al. Usability application of multiplex polymerase chain reaction in the diagnosis of microorganisms isolated from urine of patients treated in cancer hospital. Radiol Oncol 2013;47:296-303.
15. Danilovic A, Cavalanti A, Rocha BA, Traxer O, Torricelli FCM, Marchini GS, et al. Assessment of residual stone fragments after retrograde intrarenal surgery. J Endourol 2018;32:1108-13.
16. Calcagnile T, Sighinolfi MC, Rocco B, Assumma S, Di Bari S, Panio E, et al. Asymptomatic bacteriuria in candidates for active treatment of renal stones: results from an international multicentric study on more than 2600 patients. Urolithiasis 2022;51:16.
17. Clarridge JE 3rd. Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases. Clin Microbiol Rev 2004;17:840-62, table of contents.
18. Haley E, Luke N, Mathur M, Festa RA, Wang J, Jiang Y, et al. Comparison shows that multiplex polymerase chain reaction identifies infection-associated urinary biomarker-positive urinary tract infections that are missed by standard urine culture. Eur Urol Open Sci 2023;58:73-81.
19. Paonessa JE, Gnessin E, Bhojani N, Williams JC Jr, Lingeman JE. Preoperative bladder urine culture as a predictor of intraoperative stone culture results: clinical implications and relationship to stone composition. J Urol 2016;196:769-74.
20. Cruz F, Dambros M, Naber KG, Bauer HW, Cozma G. Recurrent urinary tract infections: Uro-Vaxom®, a new alternative. Eur Urol Suppl 2009;8:762-8.
21. Das P, Gupta G, Velu V, Awasthi R, Dua K, Malipeddi H. Formation of struvite urinary stones and approaches towards the inhibition: a review. Biomed Pharmacother 2017;96:361-70.
22. Nevo A, Shahait M, Shah A, Jackman S, Averch T. Defining a clinically significant struvite stone: a non-randomized retrospective study. Int Urol Nephrol 2019;51:585-91.
23. Jung HD, Lee JY, Kang DH, Ko K, Koh DH, Kwon O, et al.; Korean Society of Endourology and Robotics (KSER) Publication and Research Committees. Korean Society of Endourology and Robotics (KSER) recommendation on the diagnosis, treatment, and prevention of urolithiasis. Investig Clin Urol 2023;64:325-37.