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Comparison of antimicrobial resistance in patients with obstructive pyelonephritis associated with ureteral stones and uncomplicated pyelonephritis

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Abstract

This study aimed to investigate the clinical outcomes of causative microorganisms in obstructive pyelonephritis associated with ureteral stones (OPU) and their antibiotic susceptibilities. This retrospective cohort study included female patients diagnosed with community-acquired acute pyelonephritis (APN) at a tertiary-care hospital between 2008 and 2017. A comparison of APN cases associated with the obstruction of the upper urinary tract by ureteral stones and APN cases without complications was performed. Propensity score (PS) matching was used to adjust the heterogeneity within each group. Of the 588 female patients with community-acquired APN, 107 were diagnosed with OPU and 481 with uncomplicated APN. After PS matching, Enterobacteriaceae strains isolated from OPU cases were more resistant to fluoroquinolones (51.9% vs 16.0%, $P < .001$). Extended-spectrum β-lactamase was detected in 22.2% and 21.0% of the Enterobacteriaceae strains isolated from OPU and uncomplicated APN cases, respectively ($P = 1.000$). The treatment failure rate was similar in OPU and uncomplicated APN groups (16.0% vs 21.0%, $P = .545$). Patients with OPU may be empirically treated with antibiotics in accordance with the treatment protocol for general pyelonephritis. Clinicians should exercise caution in prescribing fluoroquinolones for treating OPU.

Abbreviations: APN = acute pyelonephritis, CFU = colony-forming units, CI = confidential interval, ESBL = extended-spectrum β-lactamase, HCAI = healthcare-associated infections, ICD = International Classification of Diseases, OPU = obstructive pyelonephritis associated with ureteral stones, PCN = percutaneous nephrostomy, PS = propensity score, UTI = urinary tract infection.

Keywords: acute pyelonephritis, empirical antimicrobial therapy, enterobacteriales, ureterolithiasis

1. Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections, and approximately 40% to 50% of women experience UTIs at least once in their lifetime.[1–3] Acute pyelonephritis (APN) or upper UTIs are kidney infections manifesting as pain during urination, fever, chills, flank pain, nausea, and vomiting. The number of hospital admissions due to APN is 5 times higher for females than for males.[4]

Urinary tract obstruction is essential in the pathophysiology of pyelonephritis. For APN resulting from urinary tract obstruction, prompt management of the urinary tract obstruction is needed in addition to the antibiotic treatment for the infection itself. An individualized approach should be made based on the causative organism.[5]

According to literature, pyelonephritis in patients with and without urinary tract obstruction should be medically managed in the same way.[6–8] However, the disease severity, region, cause of urinary tract obstruction, and patient history of healthcare-associated infections (HCAI) or community-acquired infections determine the types of causative bacteria and their antibiotic susceptibility. No comparative clinical research has been conducted to determine the empirical selection of antibiotics for patients with pyelonephritis related to urinary tract obstruction.[1] There is insufficient evidence to make antibiotic recommendations for such patients, and susceptibility knowledge from recently obtained clinically relevant culture studies is needed.

This study aimed to investigate the antimicrobial resistance pattern in patients with obstructive pyelonephritis associated

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(OPU) with ureteral stones, compare these with uncomplicated APN, and guide recommendations for empiric antibiotic regimens based on these data.

2. Patients and methods

2.1. Study design and patients

This retrospective cohort study was conducted at Gachon University Gil Medical Center, a 1400-bed tertiary-care referral hospital in Incheon, South Korea, between January 2008 and December 2017. This study includes the patient cohort of our previous study.[9] Medical records for adult female patients (aged ≥18 years) diagnosed with APN (N10), other UTIs (N39), or calculus of the kidney and ureter (N20) based on the International Classification of Diseases (ICD)-9 and ICD-10 were collected. The institutional review board of Gachon University Gil Medical Center approved the study protocol (approval no. 2016090).

2.2. Definitions

APN was defined as fever of a temperature ≥38.0°C with at least one of the following symptoms; urgency, frequency, dysuria, supra-pubic tenderness, or flank pain, and a positive dipstick test result for leukocyte esterase or nitrate, or >5 to 9 white blood cells observed on a high-power microscopy field.[10] We included patients who underwent an abdomino-pelvic computed tomography examination within 48 h of admission. Patients with chronic kidney disease, pregnancy, hemodialysis or peritoneal dialysis, a history of kidney transplantation, known urogenital structural abnormalities, or insufficient data were excluded. Community-acquired infections were classified as healthcare-associated if any of the following healthcare-associated risk factors were present:

1. hospitalization for >48 hours, residence in a nursing home or long-term care facility during the preceding 90 days;
2. intravenous therapy administration, specialized home care, or invasive procedures during the preceding 30 days;
3. hemodialysis during the preceding 30 days.

The criteria for OPU were patients who revealed urinary stone obstruction of the upper urinary tract and were diagnosed with APN. Patients with infectious staghorn calculi of the kidney were excluded.

In this study, the primary outcome was treatment failure, defined as clinical failure or the recurrence of UTI within a year. Clinical failure included worsened or persistent symptoms during antibiotic therapy and the recurrence of symptoms after the initial clinical cure during follow-up. Clinical treatment success was defined as the resolution of patients' signs and symptoms within 7 days or sign and symptom non-recurrence during the antimicrobial treatment. The secondary endpoint was overall in-hospital mortality and prolonged hospitalization. Prolonged hospitalization was defined as the length of hospital stay longer than 10 days.

2.3. Microbiological data

Urine and blood cultures were processed at the time of admission. Etiologic agents were determined when organisms at $\geq 10^5$ colony-forming units (CFU)/mL were identified in urine cultures or urinary pathogens were isolated from blood cultures. Antibiotic susceptibility patterns to antimicrobial agents were determined using a semi-automated system (VITEK II, bioMe'rieux; Hazelwood, MO). Extended-spectrum β-lactamase (ESBL) producing isolates were Enterobacteriaceae proved present by an ESBL test in either the semi-automated system or a double disk diffusion test.

2.4. Statistical methods

Categorical variables were compared using the chi-squared test or Fisher exact test, whereas continuous variables were compared using the Mann–Whitney *U* test. Univariate and multivariate logistic regression analyses were performed using the backward selection method. Patients were eliminated from the study at the time of death or loss to follow-up. The time-to-recurrence and cumulative recurrence rates were analyzed using reverse Kaplan–Meier curves. Associated factors of recurrence were analyzed using the Cox proportional-hazards model. Matched propensity score (PS) modeling of 1:1 was used to reduce the risk of bias for exposure. PSs were calculated based on the logistic regression method, including the following variates: age, bed-ridden status, menopause, HCAI, acute kidney injury, and bacteremia. Statistical significance was set at $P < .05$. Statistical analyses were performed using SPSS version 22.0 for Windows (IBM; Armonk, NY) and R software version 3.4.3 (The R Project for Statistical Computing, Vienna, Austria).

3. Results

During the study period, 2318 female patients with ICD-9 codes for APN (N10), other UTIs (N39), or calculus of the kidney and ureter (N20) were screened. Of these, 1179 (48%) patients who had simple ureter stones without UTI symptoms and signs were excluded. Among the 825 patients with community-acquired APN, 588 (71%) underwent an abdomino-pelvic computed tomography examination within 48 hours of admission. A hundred and seven patients were diagnosed with OPU, and 481 were diagnosed with uncomplicated APN (Fig. 1).

Table 1 summarizes the characteristics of the patients included in this study. HCAIs were the more common acquisition site in the OPU group (15.9% vs 2.7%, $P < .001$). *Escherichia coli* (*E coli*) was the most common pathogen in both groups (61.7% vs 65.5%, $P = .502$), and *Proteus* species were determined as the causative agent in 9.3% of OPU cases and 0.4% of cases with uncomplicated APN ($P < .001$). *Pseudomonas aeruginosa* was reported in <1% of cases in both groups. The upper urinary tract was drained through the insertion of retrograde stents or via percutaneous nephrostomy in 54% (58/107) of patients with OPU: 25 patients received a transurethral catheter, and 34 received percutaneous nephrostomy. For urinary calculus, surgical procedures including extracorporeal shock wave lithotripsy and transurethral lithotripsy were performed in 79.2% of patients. No patient underwent nephrectomy.

Non-matched data revealed significant cases of antibiotic-resistant strains in the OPU group. After PS matching, Enterobacteriaceae strains isolated from OPU cases were more resistant to fluoroquinolones (51.9% vs 16.0%, $P < .001$). ESBL was detected in 22.2% and 21.0% of the Enterobacteriaceae strains isolated from cases with OPU and uncomplicated APN, respectively ($P = 1.000$) (Table 2). HCAI was more frequent in OPU patients with fluoroquinolone resistance than those without fluoroquinolone resistance (Table S1, Supplemental Digital Content 1, http://links.lww.com/MD/H176).

No significant differences were observed among variables except prolonged hospitalization after matching the two groups. The treatment failure rate was similar in the OPU and uncomplicated APN groups (OR: 0.72, 95% CI: 0.32–1.60, $P = .545$), and prolonged hospitalization was more common in the OPU group than in the uncomplicated APN group (OR: 2.742, 95% CI: 1.14–5.17, $P = .002$). The overall in-hospital mortality rate was similar in the groups (OR: 0.74, 95% CI: 0.16–3.41, $P = .699$) (Table 3). The risk factors for ESBL isolates in both groups were recurrent UTI, HCAI, and admission

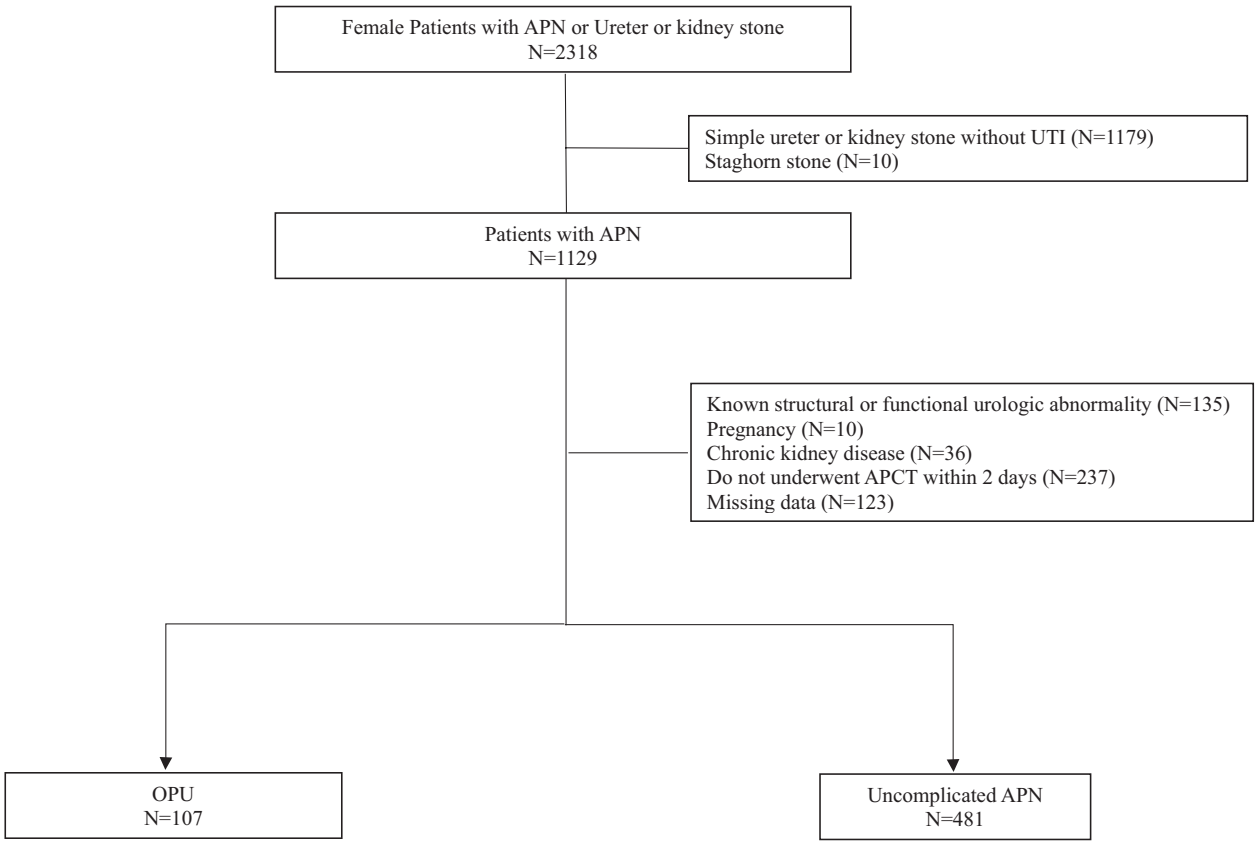

Figure 1. Study population. Abbreviations: APN = acute pyelonephritis, OPU = obstructive pyelonephritis associated with ureteral stones, UTI = urinary tract infection.

in ICU (Table S2, Supplemental Digital Content 2, http://links.lww.com/MD/H177).

4. Discussion

UTIs are a common indication for empirically prescribed antibiotics. The increasing prevalence of infections caused by antibiotic-resistant bacteria makes empirical treatment of these infections challenging.[7,11–13] The characteristics of patients with complicated UTIs vary, and the clinical standard for complicated UTIs has been unclear in previous studies. In this study, we aimed to establish the resistance patterns of uropathogenic strains isolated from cases of community-acquired OPU.

This study reveals that fluoroquinolone resistance in uropathogenic Enterobacteriaceae was alarmingly high, especially in patients with OPU compared to uncomplicated pyelonephritis. In prior studies, the rates of fluoroquinolone resistance were higher in complicated UTIs than in uncomplicated UTIs[8,14,15]; however, it is uncertain in UTIs complicated by urolithiasis.[7,8] This inconsistency might be the heterogeneous nature of the causative organisms in complicated UTIs. The most common causes of complicated UTIs include prostatic hypertrophy, neurogenic bladder, and urinary calculus.[16] Therefore, we excluded male patients and female patients with functional obstructive uropathy other than OPU. In this study, fluoroquinolone resistance did not affect prognosis. However, the patients who received inappropriate empirical treatment were treated using appropriate antibiotics thereafter. Thus, appropriate therapy should be emphasized. Consequently, fluoroquinolones as initial empirical treatment could be inappropriate or unsafe for patients with OPU who have severe and problematic conditions such as septic shock or progressive multi-organ failure.

According to literature complicated UTIs are associated with severe infectious diseases such as septic shock, and high mortality due to obstruction.[17–19] Therefore, broad-spectrum antibiotics such as carbapenems are commonly used in complicated UTIs. In this study, in intensive care unit stay, shock, and acute kidney injuries were more common in the OPU group, and carbapenems were used in this group frequently. However, there were no significant differences in antibiotic susceptibilities except fluoroquinolones, clinical outcomes, empirical antibiotics, or prognosis between both groups. The similarity between therapies administered in both groups and the clinical outcomes suggest that pyelonephritis in patients with ureteral stones can be medically managed the same way as pyelonephritis in patients without urologic abnormalities. The choice of empirical antibiotics in patients with complicated UTI should be individualized. With the unavailability of advanced antibiotics such as cefiderocol, plazomicin, or parental fosfomycin, a broad-spectrum antimicrobial regimen including carbapenem may be needed for the empiric therapy of patients with complicated acute UTIs critically ill or with a worsening prognosis on current therapy.

In complicated UTIs, correcting urologic abnormalities is an important treatment outcome, and there are several methods for managing OPU.[6] In this study, there was no rule concerning urinary tract obstruction relief, and the choice of drainage depended on the judgment of the physicians. The prompt relief of urinary tract obstruction might have prevented worsening of the condition and led to better outcomes. However, the patients' conditions varied, and management could hardly be standardized. It is challenging to determine how the management of urinary tract abnormalities can contribute to treating OPU, although prompt relief of urinary tract obstruction is necessary for a cure.

This study had several limitations. First, it was retrospective, and the sample size of patients with OPU was relatively

Table 1

Demographic characteristics of study population.

	Obstructive pyelonephritis (N = 107)	Non-obstructive pyelonephritis (N = 481)	*P* value
Age ≥60 yr	53 (49.5)	153 (31.8)	.001
Comorbidity			
Malignancy	8 (7.5)	22 (4.6)	.225
COPD	1 (0.9)	1 (0.2)	.243
DM	25 (23.4)	122 (25.4)	.713
CNS condition	11 (10.3)	30 (6.2)	.144
Liver cirrhosis	1 (0.9)	5 (1.0)	.922
Bed-ridden status	14 (13.1)	9 (1.9)	<.001
Menopause	80 (74.8)	236 (49.1)	<.001
Previous UTI	18 (16.8)	109 (22.7)	.197
Recurrent UTI	7 (6.5)	39 (8.1)	.693
HCAI	17 (15.9)	13 (2.7)	<.001
Fever ≥72 h	43 (40.6)	150 (31.2)	.068
Acute kidney injury	37 (34.6)	56 (11.6)	<.001
Bacteremia	48 (44.9)	151 (31.4)	.009
Care in ICU	29 (27.1)	26 (5.4)	<.001
MAP <65 mm Hg	22 (20.6)	20 (4.2)	<.001
Etiology of APN			
Escherichia coli	66 (61.7)	315 (65.5)	.502
Klebsiella pneumoniae	7 (6.5)	30 (6.2)	.829
Proteus spp.	10 (9.3)	2 (0.4)	<.001
Enterobacter spp.	1 (0.9)	3 (0.6)	.723
Citrobacter spp.	1 (0.9)	1 (0.2)	.243
Pseudomonas aeruginosa	1 (0.9)	2 (0.4)	.496
Staphylococcus aureus	0	2 (0.4)	.504
Enterococcal spp.	8 (7.5)	17 (3.5)	.068
Streptococcal spp.	0	4 (0.8)	.344
Culture negativity	19 (17.8)	112 (23.3)	.248

The data represent the no. (%) of patients, unless otherwise specified.

APN = acute pyelonephritis, CNS = cerebrovascular, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HCAI = health care associated infection, ICU = intensive care unit, MAP = mean arterial pressure, UTI = urinary tract infection.

Table 2

Comparison between non-matched data and matched data of antimicrobial susceptibilities of Enterobacteriaceae isolates between acute pyelonephritis groups.

	Number (%) of isolates non-susceptible to antimicrobial agents in Enterobacteriaceae group					
	Non-matched			Propensity score matched		
	Obstructive pyelonephritis (N = 81)	Non-obstructive pyelonephritis (N = 345)	*P* value	Obstructive pyelonephritis (N = 81)	Non-obstructive pyelonephritis (N = 81)	*P* value
Cefotaxime	23 (28.4)	50 (14.5)	.005	23 (28.4)	19 (23.5)	.591
Cefepime	17 (21.0)	43 (12.5)	.052	17 (21.0)	17 (21.0)	1.000
Ceftazidime	23 (28.4)	49 (14.2)	.005	23 (28.4)	17 (21.0)	.362
FQs	42 (51.9)	70 (20.3)	<.001	42 (51.9)	13 (16.0)	<.001
Ampicillin	55 (67.9)	227 (65.8)	.795	55 (67.9)	54 (66.7)	1.000
Aztreonam	20 (24.7)	44 (12.8)	.010	20 (24.7)	17 (21.0)	.709
TMP-SMX	19 (23.5)	107 (31.0)	.223	19 (23.5)	15 (18.5)	.563
AGs	17 (21.0)	76 (22.0)	.882	17 (21.0)	19 (23.5)	.850
ESBL	18 (22.2)	44 (12.8)	.036	18 (22.2)	17 (21.0)	1.000

The data represent the no. (%) of isolates non-susceptible to antimicrobial agents in group.

AG = aminoglycoside, ESBL = extended spectrum β-lactamase, FQs = fluoroquinolones, TMP-SMX = trimethoprim-sulfamethoxazole.

small. The data were also limited due to our inability to evaluate prior antibiotic use based on the available electronic medical record data. Our aim, however, was to characterize antibiotic resistance patterns and compare them with antibiotic regimen recommendations. Second, there was relatively high antibiotic resistance in both study groups. This is probably due to conducting the research in a tertiary university hospital. Therefore, the results may exaggerate the antimicrobial resistance of organisms more than that of a primary healthcare setting. Third, the relatively small sample size did not demonstrate the non-inferiority of this study. Despite this, obstructive pyelonephritis was consistently a risk factor for UTIs caused by drug-resistant species in previous studies.[7,8,14,15] Our study was a pilot study evaluating the clinical impact of antimicrobial resistance in OPU. Fourth, although many laboratories define a threshold of 10^5 CFU/mL of urine, this threshold causes many infections to escape. There was a significant number of females with symptoms and pyuria consistent with a UTI but colony counts <10^5 CFU/mL in voided urine.[20,21]

In summary, the results of this study suggest that antibiotics for patients with OPU may be empirically selected in accordance with the general treatment protocol for pyelonephritis. Selection may be based on the treatment protocol

Table 3

Comparison of clinical outcomes between acute pyelonephritis groups.

	Non-matched			Propensity score matched		
	Obstructive pyelonephritis (N = 81)	Non-obstructive pyelonephritis (N = 345)	*P* value	Obstructive pyelonephritis (N = 81)	Non-obstructive pyelonephritis (N = 81)	*P* value
Initial antibiotic regimen						
ESCs	35 (43.2)	126 (36.5)	.308	35 (43.2)	37 (45.7)	.874
FQs	25 (30.9)	201 (58.3)	<.001	25 (30.9)	30 (37.0)	.507
Carbapenems	22 (27.2)	25 (7.2)	<.001	22 (27.2)	13 (16.0)	.126
Others	5 (6.2)	10 (2.9)	.150	5 (6.2)	5 (6.2)	1.000
Appropriate antibiotics usage within 72 h	66 (81.5)	294 (85.2)	.397	66 (81.5)	68 (84.0)	.836
Duration of antibiotics, median days (IQR)	18 (14-21)	15 (14-18)	.016	18 (14-21)	15 (14-18)	.603
Duration of proper antibiotics, median days (IQR)	17 (14-20)	14 (13-17)	.233	17 (14-20)	15 (13-17)	.218
Prolonged hospitalization (≥10 d)	50 (61.7)	88 (25.5)	<.001	50 (61.7)	29 (35.8)	.002
Overall in-hospital mortality	3 (3.7)	6 (1.7)	.270	3 (3.7)	4 (4.9)	.699
Treatment failure	13 (16.0)	91 (26.4)	.780	13 (16.0)	17 (21.0)	1.000

The data represent the no. (%) of patients, unless otherwise specified.

ESCs = extended spectrum cephalosporins, FQs = fluoroquinolones, IQR = interquartile range.

for severe UTIs accompanied by sepsis or healthcare-associated as opposed to community-associated UTIs.[14,22–24] Fluoroquinolones should be used cautiously in OPU due to emerging resistance.

Author contributions

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