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.[9] 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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≥105 colony-forming units (CFU)/mL were identified in urine. Etiologic agents were determined when organisms at urine and blood cultures were processed at the time of admission. Prolonged hospitalization was defined as the length of hospital stay longer than 10 days.

2.3. Microbiological data

Urinary and blood cultures were processed at the time of admission. Etiologic agents were determined when organisms at ≥105 colony-forming units (CFU)/mL were identified in urine. Etiologic agents were determined when organisms at urine and blood cultures were processed at the time of admission. Prolonged hospitalization was defined as the length of hospital stay longer than 10 days.

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 covariates: 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 APN, 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 two 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...
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.\(^\text{[7,11–13]}\) 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\(^\text{[8,14,15]}\); however, it is uncertain in UTIs complicated by urolithiasis.\(^\text{[7,8]}\) 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.\(^\text{[16]}\) 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.\(^\text{[17–19]}\) 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 ceftazidime, 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.\(^\text{[6]}\) 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...
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.\cite{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.\cite{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 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                       | 29 (23.4)                          | 122 (25.4)                             | .713      |
| CNS condition            | 11 (10.3)                          | 30 (6.2)                               | .144      |
| Liver cirrhosis          | 1 (0.9)                            | 5 (1.0)                                | .322      |
| Bed-ridden status        | 14 (13.1)                          | 9 (1.9)                                | <.001     |
| Menopause                | 80 (74.8)                          | 236 (40.1)                             | <.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 (34.8)                          | 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.

|                          | Non-matched | Propensity score matched |
|--------------------------|-------------|--------------------------|
|                         | Obstructive | Non-obstructive          | $P$ value | Obstructive | Non-obstructive | $P$ value |
|                         | pyelonephritis (N = 81) | pyelonephritis (N = 345) |           | pyelonephritis (N = 81) | pyelonephritis (N = 81) |           |
| Cefotaxime               | 23 (28.4)   | 50 (14.5)                | .005      | 23 (28.4)   | 19 (23.5)       | .501      |
| Cefotimidine             | 17 (21.0)   | 43 (12.5)                | .052      | 17 (21.0)   | 17 (21.0)       | 1.000     |
| Cefazidime               | 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     |
| Achromobacter             | 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.
for severe UTIs accompanied by sepsis or healthcare-associated as opposed to community-associated UTIs. Fluoroquinolones should be used cautiously in OPU due to emerging resistance.

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Table 3
Comparison of clinical outcomes between acute pyelonephritis groups.

|                      | Non-matched | Propensity score matched |
|----------------------|-------------|--------------------------|
|                      | Obstructive | Obstructive | Non-obstructive | Non-obstructive |
|                      | pyelonephritis (N = 81) | pyelonephritis (N = 345) | pyelonephritis (N = 81) | pyelonephritis (N = 81) |
| P value               | .308        | .001                    | .150              | .397              |
| Duration of antibiotics, median days (IQR) | 18 (14-21) | 17 (14-20) | .016              | 15 (14-18) | .603 |
| Duration of proper antibiotics, median days (IQR) | 17 (14-20) | 14 (13-17) | .233              | 17 (14-20) | .218 |
| Duration within 72 h | 50 (61.7)   | 88 (25.5)               | <.001             | 50 (61.7)         | .002 |
| Overall in-hospital mortality | 3 (3.7)  | 6 (1.7)                   | .270              | 3 (3.7)           | .699 |
| Treatment failure     | 13 (16.0)   | 91 (26.4)               | .780              | 13 (16.0)         | 1.000 |

The data represent the no. (%) of patients, unless otherwise specified.
ESCs = extended spectrum cephalosporins, FOs = fluoroquinolones, IQR = interquartile range.