Comparison of Antimicrobial Resistance in Patients with Obstructive Pyelonephritis Associated with Ureteral Stones and Uncomplicated Pyelonephritis

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Abstract

Background

This study aimed to investigate the clinical outcomes and antibiotic susceptibilities of causative microorganisms in patients with obstructive pyelonephritis associated with ureteral stones (OPU).

Methods

This retrospective cohort study included female patients diagnosed with community-acquired acute pyelonephritis (APN) at a tertiary care hospital from 2008 to 2017. Cases of APN associated with obstruction of the upper urinary tract due to the presence of ureteral stones and cases of APN without complications were compared. Propensity score matching was used to adjust for heterogeneity within each group.

Results

Of the 588 female patients with community-acquired APN, 107 patients were diagnosed with OPU and 481 patients were diagnosed with uncomplicated APN. Propensity score matching revealed that Enterobacteriaceae strains isolated from OPU cases were more resistant to fluoroquinolones (51.9% vs. 16.0%, $p < 0.001$). Extended-spectrum β-lactamase was detected in 22.2% and 21.0% of the Enterobacteriaceae strains isolated from OPU cases and uncomplicated APN cases, respectively ($p = 1.000$). The treatment failure rate was similar in the OPU and uncomplicated APN groups (16.0% vs. 21.0%, $p = 0.545$).

Conclusions

Antibiotic treatment for patients with OPU may be empirically selected in accordance with the treatment protocol for general pyelonephritis. Clinicians should exercise caution before prescribing fluoroquinolones for the treatment of OPU.

Background

Urinary tract infections (UTIs) are one of the most common bacterial infections. Approximately 40–50% of women experience UTIs at least once in their lifetime [1–3]. Acute pyelonephritis (APN) is a type of UTI that manifests as pain during urination, fever, chills, flank pain, nausea, and vomiting. The number of hospital admissions for APN is five times higher in women than in men [4].

Urinary tract obstruction is important in the pathophysiology of APN. The management of APN resulting from urinary tract obstruction consists of elimination of the obstructive lesions and antibiotic treatment for the infection itself. APN in patients with urinary tract obstruction should be managed medically in the same way as pyelonephritis in patients without urinary tract obstruction, and surgical therapy should be directed toward eliminating the obstruction and preserving renal function [5–8].

In APN resulting from urinary tract obstruction, the types of causative bacteria and their antibiotic susceptibility vary depending on the disease severity, geographical region, cause of urinary tract obstruction, and patient history of healthcare-associated infections (HCAIs) or community-acquired infections, and evidence is currently insufficient to make other antibiotic recommendations for such patients [1].

The purpose of our study was to investigate the antimicrobial resistance pattern in isolates from patients with obstructive pyelonephritis associated with ureteral stones (OPU) and compare it with that in isolates from patients with uncomplicated APN, in order to guide recommendations with respect to empiric antibiotic regimens.

Materials And Methods

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. This study included the patient cohort of our previous study [9]. In the present study, we reviewed the medical records of adult female patients who were diagnosed with APN (N10), other UTIs (N39), or calculus of the kidney and ureter (N20) based on the International Classification of Diseases (ICD)-9. The study protocol was approved by the institutional review board of Gachon University Gil Medical Center.

Definitions

In this study, APN was defined as fever (temperature ≥ 38.0 °C) with at least one of the symptoms of urgency, frequency, dysuria, suprapubic tenderness, or flank pain, and a positive dipstick test result for leukocyte esterase, nitrate, or > 5–9 white blood cells observed on a high-power microscopy field. We included patients who underwent an abdominopelvic computed tomography (APCT) 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.

The criteria for OPU were obstruction of the upper urinary tract due to urinary stones and a diagnosis of APN. Patients with infectious staghorn calculi of the kidney were excluded.

The primary outcome in this study was treatment failure, which was defined as clinical failure or recurrence of UTI within 1 year. The clinical outcomes were assessed after 7 days of treatment, at the time of discharge, and at the completion of antibiotic treatment. Clinical treatment failure was defined as a recurrence of signs and symptoms during the follow-up after clinical improvement. The secondary endpoint was overall in-hospital mortality and prolonged hospitalization (≥ 10 days).

Microbiological data

Urine and blood cultures were processed at the time of admission. Etiologic agents were determined as present when organisms at ≥ 10^5 colony-forming units/mL were identified in urine cultures and/or when urinary pathogens were isolated from blood cultures. Antibiotic susceptibility tests were performed using a semi-automated system (VITEK II; bioMérieux, Hazelwood, MO, USA). Extended-spectrum β-lactamase (ESBL)-

producing isolates were confirmed as Enterobacteriaceae detected by an ESBL test using a semi-automated system according to the Clinical and Laboratory Standards Institute guidelines.

Statistical methods

Categorical variables are presented as number of cases and percentages, and continuous variables are presented as means and standard deviations or medians and interquartile ranges. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, and continuous variables were compared using Student's t-test or the Mann–Whitney *U* test. Patients were censored at the time of death or at loss to follow-up. The time-to-recurrence and cumulative recurrence rates were analyzed using reverse Kaplan–Meier curves. We performed propensity score matching at a 1:1 ratio to minimize the risk of bias for exposure. Propensity scores were estimated based on the logistic regression method including the following variables: age, bedridden status, menopause, HCAI, acute kidney injury, and bacteremia. A *p*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22.0 for Windows (IBM, Armonk, NY, USA) and R software version 3.4.3 (The R Foundation, 2017).

Results

During the study period, a total of 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 had simple ureter stones without UTI symptoms and signs, and were excluded from the analysis. Among the 825 patients with community-acquired APN, 588 (71%) underwent an APCT examination within 48 h of admission. Of the 588 patients with community-acquired APN who were finally enrolled, 107 patients were diagnosed with OPU and 481 patients were diagnosed with uncomplicated APN (Figure 1).

Table 1 summarizes the characteristics of the patients included in this study. HCAI cases were more common in the OPU group than in the uncomplicated APN group (15.9% vs. 2.7%, $p < 0.001$). *Escherichia coli* was the most common pathogen in both groups (61.7% vs. 65.5%, $p = 0.502$), and *Proteus* species were identified as the causative agent in 9.3% of OPU cases and 0.4% of uncomplicated APN cases ($p < 0.001$). *Pseudomonas aeruginosa* was reported in < 1% of cases in both groups. Drainage of the upper urinary tract through the placement of retrograde stents or via percutaneous nephrostomy was reported in 54% (58/107) of patients with OPU (25 patients underwent transurethral catheterization and 34 patients underwent percutaneous nephrostomy). For urinary stones, surgical procedures including extracorporeal shock wave lithotripsy and transurethral lithotripsy were reported in 79.2% of the patients. None of the patients underwent nephrectomy.

Non-matched data showed significantly more cases caused by antibiotic-resistant strains in the OPU group. After propensity score matching, Enterobacteriaceae strains isolated from OPU cases were more resistant to fluoroquinolones (51.9% vs. 16.0%, $p < 0.001$). ESBL was detected in 22.2% and 21.0% of the Enterobacteriaceae strains isolated from OPU cases and uncomplicated APN cases, respectively ($p = 1.000$) (Table 2). HCAI was more frequent in OPU patients with fluoroquinolone resistance than in those without fluoroquinolone resistance (Supplementary Table 1).

After matching the two groups, no statistically significant differences were observed among variables except for prolonged hospitalization. The treatment failure rate was similar in the OPU and uncomplicated APN groups

(odds ratio [OR] 0.72, 95% confidence interval [CI] 0.32–1.60, p = 0.545), 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 = 0.002). The overall in-hospital mortality rate was similar between groups (OR 0.74, 95% CI 0.16–3.41, p = 0.699) (Table 3).

Discussion

APN is a common infectious disease requiring antibiotics. The increasing prevalence of infectious diseases caused by antibiotic-resistant bacteria makes treatment of APN more difficult [7, 10-12]. The characteristics of patients with APN due to urinary tract obstruction have been highly varied, and the clinical standard for diagnosing APN has been unclear in previous studies. In this study, we aimed to establish the resistance patterns of uropathogenic strains isolated from patients with community-acquired OPU.

In this study, fluoroquinolone resistance in uropathogenic Enterobacteriaceae was found to be alarmingly high in OPU cases compared with that in uncomplicated pyelonephritis cases. In prior studies, the rate of fluoroquinolone resistance was higher in complicated UTIs than in uncomplicated UTIs [8, 13, 14]. However, the rate was uncertain in complicated UTIs due to urolithiasis [7, 8]. The reason for this inconsistency might be related to the heterogeneous causative diseases of complicated UTIs. Therefore, we excluded male patients, patients with functional uropathy such as urinary bladder dysfunction, and patients with known obstructive uropathy due to urogenital tumor or other anatomic abnormalities, which are common causes of urinary tract obstruction [15]. Moreover, we performed propensity score matching to reduce the possibility of selection bias.

In this study, fluoroquinolone resistance did not affect the prognosis regardless of the drug resistance of the pathogens. However, patients who received inappropriate empirical treatment in this study were eventually treated with appropriate antibiotics. Thus, appropriate definitive therapy should be emphasized. Further, it could be inappropriate or unsafe to use fluoroquinolones as the initial empirical treatment for patients with OPU showing critical conditions such as sepsis or septic shock. Further studies are needed in this regard.

Complicated UTIs are associated with more severe infectious diseases (such as cases involving septic shock) and high mortality due to obstruction [16-18]. Therefore, broad-spectrum antibiotics including carbapenems are commonly used in complicated UTI cases. In this study, intensive care unit stay, shock, and acute kidney injury were more common in the OPU group. Moreover, carbapenems were also more frequently used in the OPU group. However, no meaningful differences were observed in antibiotic susceptibility (except for fluoroquinolones), clinical outcomes, empirical antibiotics, or prognosis between the two groups. The similarity between the therapies administered in the two groups and the clinical outcomes in this study suggest that APN in patients with ureteral stones can be managed medically in the same way as pyelonephritis in patients without urologic abnormalities.

In complicated UTIs, correcting urologic abnormalities is an important treatment option, and several methods are available for the management of ureteral stones causing obstruction [6]. In this study, no standard protocol was used for relieving urinary tract obstruction, and the decision on whether drainage should be placed depended on the judgment of relevant physicians, including urologists. It is possible that the prompt relief of urinary tract obstruction might have prevented the worsening of the condition and led to better outcomes. However, early drainage was not related to treatment failure in this study (Supplementary Table 2). It is difficult

to determine how relief of urinary tract abnormalities can contribute to the treatment of OPU, although prompt relief of urinary tract obstruction is commonly necessary for a cure.

This study had several limitations. First, the study was limited by its retrospective design and the relatively small sample size of patients with OPU. The data were also limited because we were unable to evaluate prior antibiotic use based on the available data from electronic medical records covering our study period. Our goal, however, was to characterize antibiotic resistance patterns and compare them with antibiotic regimen recommendations. Second, relatively high antibiotic resistance was observed in both study groups. This is probably because the study was conducted in a tertiary university hospital. Therefore, the present results may exaggerate the antimicrobial resistance of organisms compared with results obtained in a primary care setting. Third, the relatively small number of included patients did not provide enough study power to demonstrate non-inferiority. Despite the low power of the study, obstructive pyelonephritis was consistently a risk factor for UTI caused by drug-resistant species in prior studies [7, 8, 13, 14]. Our study could be a pilot study evaluating the clinical impact of antimicrobial resistance in OPU.

In summary, the results of this study suggest that antibiotics for patients with APN related to urinary tract obstruction by ureteral stones may be empirically selected in accordance with the treatment protocol for general pyelonephritis. The selection may need to be based on the treatment protocol for severe UTIs accompanied by sepsis or healthcare-associated UTIs as opposed to community-associated UTIs [13, 19-21]. Fluoroquinolones should be used cautiously for OPU because of emerging resistance.

List Of Abbreviations

UTI, urinary tract infection; HCAI, healthcare-associated infection; ICD, International Classification of Diseases; APN, acute pyelonephritis; APCT, abdominopelvic computed tomography; OPU, obstructive pyelonephritis associated with ureteral stones; ESBL, extended-spectrum β-lactamase; PCN, percutaneous nephrostomy; ESWL, extracorporeal shock wave lithotripsy; TUL, transurethral lithotripsy

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Gachon University Gil Medical Center (approval no. 2016090). As this was a retrospective study, informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

JO: project development and manuscript writing. SJA: project development, data analysis, and manuscript writing. JW, JH, JSE, WC, and YKC: data collection and management. YRJ: project development, supervision, and manuscript editing. All authors reviewed the results and approved the final version of the manuscript.

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Tables

Table 1. Demographic characteristics of study population

	Obstructive pyelonephritis (N=107)	Non-obstructive pyelonephritis (N=481)	*P* value
Age ≥ 60	53 (49.5)	153 (31.8)	0.001
Comorbidity			
Malignancy	8 (7.5)	22 (4.6)	0.225
COPD	1 (0.9)	1 (0.2)	0.243
DM	25 (23.4)	122 (25.4)	0.713
CNS condition	11 (10.3)	30 (6.2)	0.144
Liver cirrhosis	1 (0.9)	5 (1.0)	0.922
Bed-ridden status	14 (13.1)	9 (1.9)	<0.001
Menopause	80 (74.8)	236 (49.1)	<0.001
Previous UTI	18 (16.8)	109 (22.7)	0.197
Recurrent UTI	7 (6.5)	39 (8.1)	0.693
HCAI	17 (15.9)	13 (2.7)	<0.001
Fever ≥ 72 hours	43 (40.6)	150 (31.2)	0.068
Acute kidney injury	37 (34.6)	56 (11.6)	<0.001
Bacteremia	48 (44.9)	151 (31.4)	0.009
Care in ICU	29 (27.1)	26 (5.4)	<0.001
MAP < 65 mmHg	22 (20.6)	20 (4.2)	<0.001
Etiology of APN			
E. coli	66 (61.7)	315 (65.5)	0.502
Klebsiella pneumoniae	7 (6.5)	30 (6.2)	0.829
Proteus spp.	10 (9.3)	2 (0.4)	<0.001
Enterobacter spp.	1 (0.9)	3 (0.6)	0.723
Citrobacter spp.	1 (0.9)	1 (0.2)	0.243
Pseudomonas aeruginosa	1 (0.9)	2 (0.4)	0.496
Staphylococcus aureus	0	2 (0.4)	0.504
Enterococcal spp.	8 (7.5)	17 (3.5)	0.068
Streptococcal spp.	0	4 (0.8)	0.344
Culture negativity	19 (17.8)	112 (23.3)	0.248

Note. The data represent the no. (%) of patients, unless otherwise specified.
CNS=cerebrovascular, COPD=chronic obstructive pulmonary disease, DM=diabetes mellitus, HCAI=health care associated infection, ICU=intensive care unit, UTI=urinary tract infection, MAP=mean arterial pressure, APN=acute pyelonephritis

Table 2. Comparison between non-matched data and matched data of antimicrobial susceptibilities of Enterobacteriaceae isolates between APN groups

	Number (%) of isolates non-susceptible to antimicrobial agents in Enterobacteriaceae group					
	Non-matched		*P* value	Propensity score matched		*P* value
	Obstructive pyelonephritis (N=81)	Non-obstructive pyelonephritis (N=345)		Obstructive pyelonephritis (N=81)	Non-obstructive pyelonephritis (N=81)	
Cefotaxime	23 (28.4)	50 (14.5)	0.005	23 (28.4)	19 (23.5)	0.591
Cefepime	17 (21.0)	43 (12.5)	0.052	17 (21.0)	17 (21.0)	1.000
Ceftazidime	23 (28.4)	49 (14.2)	0.005	23 (28.4)	17 (21.0)	0.362
FQs	42 (51.9)	70 (20.3)	<0.001	42 (51.9)	13 (16.0)	<0.001
Ampicillin	55 (67.9)	227 (65.8)	0.795	55 (67.9)	54 (66.7)	1.000
Aztreonam	20 (24.7)	44 (12.8)	0.010	20 (24.7)	17 (21.0)	0.709
TMP-SMX	19 (23.5)	107 (31.0)	0.223	19 (23.5)	15 (18.5)	0.563
AGs	17 (21.0)	76 (22.0)	0.882	17 (21.0)	19 (23.5)	0.850
ESBL	18 (22.2)	44 (12.8)	0.036	18 (22.2)	17 (21.0)	1.000

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

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

Table 3. Comparison of clinical outcomes between APN groups.

	Non-matched		*P* value	Propensity score matched		*P* value
	Obstructive pyelonephritis (N=81)	Non-obstructive pyelonephritis (N=345)		Obstructive pyelonephritis (N=81)	Non-obstructive pyelonephritis (N=81)	
Initial antibiotic regimen						
ESCs	35 (43.2)	126 (36.5)	0.308	35 (43.2)	37 (45.7)	0.874
FQs	25 (30.9)	201 (58.3)	<0.001	25 (30.9)	30 (37.0)	0.507
Carbapenems	22 (27.2)	25 (7.2)	<0.001	22 (27.2)	13 (16.0)	0.126
Others	5 (6.2)	10 (2.9)	0.150	5 (6.2)	5 (6.2)	1.000
Appropriate antibiotics usage within 72 hours	66 (81.5)	294 (85.2)	0.397	66 (81.5)	68 (84.0)	0.836
Duration of antibiotics, median days (IQR)	18 (14-21)	15 (14-18)	0.016	18 (14-21)	15 (14-18)	0.603
Duration of proper antibiotics, median days (IQR)	17 (14-20)	14 (13-17)	0.233	17 (14-20)	15 (13-17)	0.218
Prolonged hospitalization (≥10 days)	50 (61.7)	88 (25.5)	<0.001	50 (61.7)	29 (35.8)	0.002
Overall in-hospital mortality	3 (3.7)	6 (1.7)	0.270	3 (3.7)	4 (4.9)	0.699
Treatment failure	13 (16.0)	91 (26.4)	0.780	13 (16.0)	17 (21.0)	1.000

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

Figures

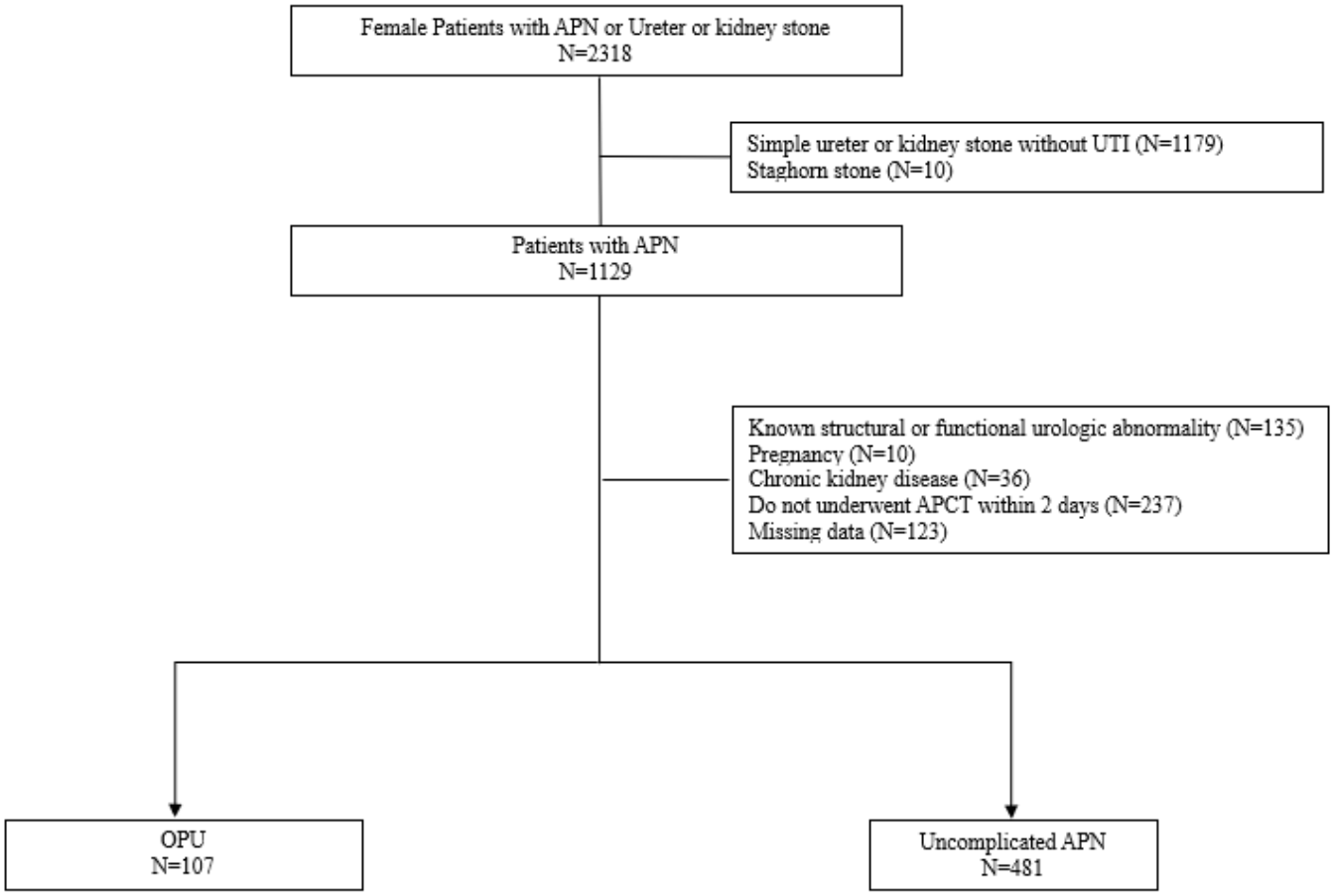

Figure 1

Study population Abbreviations: APN, acute pyelonephritis; UTI, urinary tract infection, OPU, obstructive pyelonephritis associated with ureteral stones

Supplementary Files

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