Risk Factor Analysis of Ciprofloxacin-Resistant and Extended Spectrum Beta-Lactamases Pathogen-Induced Acute Bacterial Prostatitis in Korea

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The objectives of this study were to investigate risk factors and the incidence of ciprofloxacin resistance and extended-spectrum beta-lactamases (ESBL) in patients with acute bacterial prostatitis (ABP). We reviewed the medical records of 307 patients who were diagnosed with ABP between January 2006 and December 2015. The etiologic pathogens and risk factors for ciprofloxacin-resistant *E. coli* and ESBL-producing microbes, susceptibility to ciprofloxacin, and the incidence of ESBL in patients with ABP were described. History of prior urologic manipulation was an independent risk factor for ciprofloxacin-resistant ($P = 0.005$) and ESBL-producing microbes ($P = 0.005$). Advanced age (over 60 years) was an independent risk factor for ciprofloxacin-resistant microbes ($P = 0.022$). The ciprofloxacin susceptibility for *Escherichia coli* in groups without prior manipulation was documented 85.7%. For groups with prior manipulation, the susceptibility was 10.0%. Incidence of ESBL-producing microbes by pathogen was 3.8% for *E. coli* and 1.0% for *Klebsiella pneumonia* in the absence of manipulation group, and 20% and 33.3% in the presence of manipulation group, respectively. Initial treatment of ABP must consider patient's age and the possibility of prior manipulation to optimize patient treatment. With the high rate of resistance to fluoroquinolone, cephalosporins with amikacin, or carbapenems, or extended-spectrum penicillin with beta lactamase inhibitor should be considered as the preferred empirical ABP treatment in the patients with history of prior urologic manipulation.

Keywords: Acute Bacterial Prostatitis; Ciprofloxacin; Extended-spectrum Beta-lactamases; Risk Factors

INTRODUCTION

The prevalence of prostatitis is 8.2% (range 2.2%-9.7%) and the National Institutes of Health (NIH) classified prostatitis into four categories: acute bacterial, chronic bacterial, chronic prostatitis/chronic pelvic pain syndrome, and asymptomatic (1). Acute bacterial prostatitis (ABP) is a rare disease accounting for only 5% of prostatitis cases (2). However, ABP requires immediate treatment because it can lead to complications such as urosepsis (3). Inadequate antibiotic use leads to treatment failure and can increase mortality (4). In patients with ABP, fluoroquinolones are commonly used as first empirical antibiotics because of the broad action spectrum, good bioavailability, and high concentrations in the prostatic tissue (5).

Unfortunately, antibiotic resistance in urinary tract infections (UTIs) has increased globally (6). For example, the rate of ciprofloxacin resistance in the United States increased from 3% in 2000 to 17.1% in 2010 (6). In Korea, the use of fluoroquinolones has also been increasing, and consumption doubled during

2001-2012 (7). With these trends, the incidence of ciprofloxacin-resistant microbes increased from 15.2% in 2002 to 22.5% in 2012 in patients with community-onset acute pyelonephritis (8). Based on a recent study, fluoroquinolones were not recommended as a first empirical antibiotic for complicated UTIs in the Asia-Pacific region due to the high rates of quinolone resistance (> 20%) (9). In addition, the increasing extended-spectrum beta-lactamase (ESBL) producing microbes have become a major concern. Generally, ESBL-producing organisms are also resistant to quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole (10). In the 2010 Korean Antimicrobial Resistance Monitoring System report, the incidence of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in community-acquired infections was 9.5% and 12.8% and the incidence in hospital-acquired infections was 25% and 78.6%, respectively (11). Therefore, it is important to identify factors associated with antimicrobial resistance in order to choose an appropriate empiric antibiotic in patients with UTIs. Risk factors for ciprofloxacin resistance in *E. coli* have been reported in previous studies

and include advanced age, male gender, diabetes mellitus, urinary tract abnormalities, recurrent UTIs, previous therapy with quinolones, urinary catheterization, and presence of complicated UTIs (12-15).

In patients with UTIs, the treatment depends on the sensitivity of the microbes to the concentrations of the antibiotics in the urine rather than in the blood (16). This suggests that it is important to examine the clinical impact of antimicrobial resistance on treatment outcomes in UTIs. In this study, we describe the etiologic pathogens and risk factors for ciprofloxacin-resistant *E. coli* and ESBL-producing microbes, susceptibility to ciprofloxacin, and the incidence of ESBL in patients with ABP. The results of this study provide useful information for prescribing appropriate antibiotics and better ABP management, particularly for its association with increased incidence in patients that previously underwent urologic manipulation.

MATERIALS AND METHODS

Medical records of patients with ABP were retrospectively reviewed to determine risk factors for and the incidence of ciprofloxacin-resistant and ESBL in pathogens. We included patients who were diagnosed with acute prostatitis at the Kyung Hee University Hospital at Gangdong from January 2006 to December 2015. Acute prostatitis was diagnosed by a body temperature > 38°C, painful prostate on digital rectal examination, and leukocytes in urine sediments (17).

We investigated the known factors associated with ciprofloxacin-resistant *E. coli* or ESBL-producing microbes such as age greater than 60 years, history of prior urologic manipulation, hospital-acquired infection, history of operation in the preceding 180 days, diabetes mellitus, hypertension, antibiotic exposure during the preceding 90 days, history of UTI, prostate volume over 40 mL, and alpha-blocker medication. We classified patients into two groups based on patient records. Patients who had undergone prior urologic manipulation such as urethral catheterization, transrectal prostate biopsy, urodynamic study, or urethral dilation were defined as the manipulation group. Patients who did not experience urologic procedures were defined as the non-manipulation group. Standard blood biochemistry, urine examination by the dipstick method, and urinary sediment were performed for all patients. The identification and antimicrobial susceptibility of isolates were confirmed with the Vitek 2 system (bioMérieux, Marcy L'Ètoile, France) or disk diffusion susceptibility tests.

Data was analyzed using SPSS, version 18.0. Proportion comparisons for categorical variables were performed using χ^2 tests. *P* value and odds ratio were calculated for risk factors. A *P* value of < 0.05 was considered statistically significant. In addition, multivariate model analysis was performed to determine independent risk factors for ciprofloxacin resistance and ESBL-pro-

ducing microbes. The resistance to ciprofloxacin and ESBL-producing microbes were the dependent variables in binary logistic regression.

Ethics statement
The study was approved by the institutional review board of the Kyung Hee University Hospital at Gangdong (IRB No. KHNMC 2016-04-038-001). Informed consent was waived by the board.

RESULTS

ABP was diagnosed in 307 patients over the entire time period. Of those, 123/307 patients (40.1%) had positive urine cultures and their bacterial strains were identified, and 26/123 patients (21.1%) showed ciprofloxacin resistance. ESBL-producing microbes were found in 10 patients: 7 were associated with *E. coli* and 3 were associated with *K. pneumoniae* (Table 1). The distribution of ciprofloxacin-resistant and ESBL-producing microbes in relation with risk factors is shown in Table 2. In univariate analysis, age greater than 60 years (*P* = 0.001), history of prior urologic manipulation (*P* < 0.001), hospital acquired infection (*P* = 0.001), hypertension (*P* = 0.021), previous antibiotic use (*P* = 0.018), and prostate volume over 40 mL (*P* = 0.030) were found to be significant factors associated with ciprofloxacin resistance in *E. coli* infections. In multivariate analysis, age greater than 60 years (Odds ratio [OR], 7.31; confidence interval [CI], 1.326-40.279; *P* = 0.022) and history of prior urologic manipulation (OR, 7.65; CI, 1.824-32.065; *P* = 0.005) were associated with ciprofloxacin resistance in *E. coli* strains infections (Table 3). In addition, prior urologic manipulation (*P* < 0.001), history of recent operation (*P* = 0.030), and hypertension (*P* = 0.031) were risk factors for ESBL-producing microbes in univariate analysis. In multivariate analysis, presence of urologic manipulation (OR, 13.640; CI, 2.159-86.167; *P* = 0.005) was found to be associated with ESBL-producing microbes (Table 4).

The non-manipulation group consisted of 104/123 (84.6%) patients and the manipulation group consisted of 19/123 (15.4%) patients; 12 had urethral catheterization (63.2%), 5 (26.2%) had

Table 1. Urine culture results in patients with ABP (n = 123)

Microbial agents	All patients	Ciprofloxacin resistant microbes	ESBL-producing microbes
E. coli	80 (65.0)	18 (14.6)	7 (5.7)
E. faecalis	22 (17.9)	4 (3.3)	-
K. pneumoniae	11 (8.9)	4 (3.3)	3 (2.4)
P. aeruginosa	3 (2.5)	0 (0)	-
Others*	7 (5.7)*	0 (0)	-
Total	123 (100)	26 (21.1)	10 (8.1)

Values are presented as number of patients (%).
ABP = acute bacterial prostatitis, ESBL = extended-spectrum beta-lactamases.
Enterobacter, *S. marcescens*, *Citrobacter*, coagulase negative *Staphylococcus*, *S. agalactiae*, *P. mirabilis*.

Table 2. Antibiotic resistant and ESBL-producing microbes and risk factor associations (n = 123)

Risk factors	All patients	Ciprofloxacin		ESBL	
		Susceptible (n = 97)	Resistant (n = 26)	Negative (n = 113)	Positive (n = 10)
Age ≥ 60 yr	81 (65.9)	57 (70.4)	24 (29.6)	72 (88.9)	9 (11.1)
Prior urologic manipulation	19 (15.4)	7 (36.8)	12 (63.2)	13 (68.4)	6 (31.6)
Hospital acquired infection	9 (7.3)	3 (33.3)	6 (66.7)	7 (77.8)	2 (22.2)
Recent operation (≤ 6 mon)	7 (5.7)	4 (57.1)	3 (42.9)	5 (71.4)	2 (28.6)
Diabetes mellitus	30 (24.4)	20 (66.7)	10 (33.3)	26 (86.7)	4 (13.3)
Hypertension	47 (38.2)	32 (68.1)	15 (31.9)	40 (85.1)	7 (14.9)
History of antibiotic use (≤ 3 mon)	16 (13.0)	9 (56.3)	7 (43.8)	13 (81.2)	3 (18.8)
History of urinary tract infection	11 (8.9)	8 (72.7)	3 (27.3)	9 (81.8)	2 (18.2)
Prostate volume over 40 mL	44 (35.8)	30 (68.2)	14 (31.8)	38 (86.4)	6 (13.6)
Alpha-blocker medication	31 (25.2)	23 (74.2)	8 (25.8)	27 (87.1)	4 (12.9)

Values are presented as number of patients (%).
ESBL = extended-spectrum beta-lactamases.

Table 3. Univariate and multivariate analysis of ciprofloxacin-resistant microbes

Risk factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age ≥ 60 yr	8.42 (1.883-37.668)	0.001	7.31 (1.326-40.279)	0.022
Prior urologic manipulation	11.02 (3.709-32.746)	< 0.001	7.65 (1.824-32.065)	0.005
Hospital acquired infection	9.4 (2.167-40.782)	0.001	3.47 (0.626-19.214)	0.155
Recent operation (≤ 6 mon)	3.03 (0.634-14.504)	0.147	-	-
Diabetes mellitus	2.40 (0.949-6.103)	0.060	-	-
Hypertension	2.77 (1.142-6.716)	0.021	0.64 (0.196-2.082)	0.458
History of antibiotic use (≤ 3 mon)	3.60 (1.193-10.878)	0.018	1.10 (0.246-4.912)	0.900
History of urinary tract infection	1.45 (0.356-5.907)	0.602	-	-
Prostate volume over 40 mL	2.61 (1.077-6.301)	0.030	1.70 (0.566-5.100)	0.968
Alpha-blocker medication	1.43 (0.550-3.717)	0.462	-	-

OR = odds ratio, CI = confidence interval.

Table 4. Univariate and multivariate analysis of ESBL-producing microbes

Risk factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age ≥ 60 yr	5.13 (0.627-41.905)	0.093	-	-
Prior urologic manipulation	11.54 (2.871-46.366)	< 0.001	13.640 (2.159-86.167)	0.005
Hospital acquired infection	3.79 (0.673-21.2311)	0.108	-	-
Recent operation (≤ 6 mon)	5.90 (0.986-35.315)	0.030	2.415 (0.286-20.401)	0.418
Diabetes mellitus	2.23 (0.585-8.510)	0.230	-	-
Hypertension	4.26 (1.043-17.379)	0.031	1.544 (0.253-9.414)	0.637
History of antibiotic use (≤ 3 mon)	3.30 (0.757-14.349)	0.096	-	-
History of urinary tract infection	2.89 (0.532-15.696)	0.201	-	-
Prostate volume over 40 mL	2.882 (0.621-13.471)	0.105	-	-
Alpha-blocker medication	2.12 (0.558-8.085)	0.261	-	-

ESBL = extended-spectrum beta-lactamases, OR = odds ratio, CI = confidence interval.

transrectal prostate biopsy, 1 had urethral dilation (5.3%), and 1 had a urodynamic study (5.3%). Significant differences of microbial spectrum between two groups were observed. The most frequent microbe was *E. coli* (67.3% in the manipulation group vs. 52.6% in the non-manipulation group), followed by *E. faecalis* (19.2% vs. 10.5%), *K. pneumoniae* (4.8% vs. 31.6%), and *Pseudomonas aeruginosa* (2.9% vs. 0%). *K. pneumoniae* counted for a far higher proportion in the prior manipulation group than in the non-manipulation group. The antimicrobial susceptibility

profiles are displayed in Table 5. The incidence of *E. coli* that was susceptible to ciprofloxacin was 60/70 (85.7%) in the non-manipulation group and 1/10 (10.0%) in the manipulation group. Susceptibility to amikacin, imipenem, and piperacillin/tazobactam showed a high sensitivity in both groups. The antimicrobial susceptibilities of *E. coli* in the non-manipulation group compared to the manipulation groups were as follows: amikacin, 100% vs. 100%; ampicillin, 57.1% vs. 0%; 2nd generation cephalosporin, 100% vs. 80.0%; 3rd generation cephalosporin,

Table 5. Antibiotic susceptibility of pathogens isolated from patients with ABP (n = 123)

Antibiotics	E. coli		E. faecalis		K. pneumoniae		P. aeruginosa		Other pathogens	
	NM group (n = 70)	M group (n = 10)	NM group (n = 20)	M group (n = 2)	NM group (n = 5)	M group (n = 6)	NM group (n = 3)	M group (n = 0)	NM group (n = 6)	M group (n = 1)
Amikacin (%)	70 (100)	10 (100)	NT		4 (80.0)	5 (83.3)	3 (100)	0 (0)	6 (100)	1 (100)
Ampicillin (%)	40 (57.1)	0 (0)	19 (95.0)	2 (100)	0 (0)	0 (0)	1 (33.3)	0 (0)	2 (33.3)	1 (100)
Ciprofloxacin (%)	60 (85.7)	1 (10.0)	18 (90.0)	0 (0)	4 (80.0)	3 (50.0)	3 (100)	0 (0)	6 (100)	1 (100)
2nd generation cephalosporin (%)	70 (100)	8 (80.0)	NT		4 (80.0)	5 (83.3)	NT		4 (66.7)	1 (100)
3rd generation cephalosporin (%)	68 (97.1)	6 (60.0)	NT		4 (80.0)	4 (66.7)	3 (100)	0 (0)	6 (100)	1 (100)
Gentamicin (%)	60 (85.7)	7 (70.0)	NT		4 (80.0)	6 (100)	3 (100)	0 (0)	5 (83.3)	1 (100)
Imipenem (%)	70 (100)	10 (100)	NT		5 (100)	6 (100)	3 (100)	0 (0)	6 (100)	1 (100)
TMP/SMX (%)	55 (78.6)	5 (50.0)	NT		5 (100	6 (100)	1 (33.3)	0 (0)	6 (100)	1 (100)
Piperacillin/tazobactam (%)	65 (92.9)	10 (100)	NT		4 (80.0)	3 (50.0)	3 (100)	0 (0)	NT	
Vancomycin (%)	NT		20 (100)	2 (100)	NT		NT		NT	
ESBL positive (%)	3 (3.8)	4 (40)	-		1 (20)	2 (33.3)	-		-	

ABP = acute bacterial prostatitis, NM = non-manipulation, M = manipulation, NT = not tested, ESBL = extended-spectrum beta-lactamases.

97.1% vs. 60.0%; gentamicin 85.7% vs. 70.0%; imipenem, 100% vs. 100%; and TMP/SMX, 78.6% vs. 50.0%. ESBL-producing microbes were found in 10 patients (8.1%); 7 were *E. coli* (5.7%) and 3 were *K. pneumoniae* (2.4%). All ESBL-producing pathogens were resistant to quinolone.

DISCUSSION

ABP is a serious condition that can cause septicemia and urosepsis and is characterized by common symptoms including dysuria, lower urinary tract symptoms, urinary retention, fever, and malaise (18). In terms of microbiological characteristics, *E. coli* is the most prevalent pathogen occurring in 67% of cases, with *P. aeruginosa* in 13%, *Klebsiella* spp. in 6%, Gram-positive species in 5% and others in 9% (19). Several studies reported the different distribution of pathogen according to the prior manipulation. In the manipulation group, relatively fewer *E. coli* were detected. Regarding *Pseudomonas* spp. were counted for higher proportion in the manipulation group (20,21). In our study, relatively fewer *E. coli* was detected in the group with prior manipulation and *K. pneumoniae* was significantly higher in the manipulation group compared with the non-manipulation group.

Previous studies reported that the progression of chronic bacterial prostatitis and inflammatory chronic pelvic pain syndrome was 1.3% and 10.5% after ABP treatment (22). Therefore, appropriate therapeutic strategies for ABP are important for adequate treatment and prevention of progression to chronic infection. Fluoroquinolones are commonly used as first empirical antibiotics, however, recently, the increased use of fluoroquinolone has been associated with increased resistance (8). Additionally, to-date, only a limited number of studies have reported risk factors for ciprofloxacin-resistant *E. coli.* They concluded that advanced age, male gender, diabetes mellitus, urinary tract abnormalities, recurrent UTIs, previous therapy with quinolones, urinary catheterization, and presence of compli-

cated UTIs were risk factors for ciprofloxacin-resistance among uropathogens (12-15). However, our study showed different results compared with previous studies. This study showed that presence of prior urologic manipulation, age greater than 60 years, hospital-acquired infection, hypertension, history of prior use of antibiotics, and prostate size over 40 mL were found to be risk factors for the developing ciprofloxacin resistance in univariate analysis. Multivariate analysis indicated that age and history of prior manipulation were independent risk factors that contributed to ciprofloxacin resistance. In addition, prior urologic manipulation, history of recent operation, and hypertension were associated with ESBL-producing microbes in univariate analysis. In multivariate analysis, presence of urologic manipulation was found to be associated with ESBL-producing microbes.

It is well known that quinolone resistance impairs the capacity of *E. coli* to invade local tissue of the prostate and kidney (23,24). Some studies have reported that exposure to quinolone antibiotics results in the reduced production of certain factors that contribute to the virulence of bacteria (25). Indeed, quinolone resistant *E. coli* was less likely to produce invasive UTI such as pyelonephritis and prostatitis than is quinolone sensitive *E. coli*. They suggested that the physical disruption of mucosae and host factor alterations associated with urologic manipulation may increase invasiveness of quinolone resistant *E. coli*. Increased age may reflect the presence of age-related incontinence or other minor urologic abnormalities that are not considered to be structural abnormalities (26). Age-associated changes in immune function, exposure to nosocomial pathogens and an increasing number of comorbidities increased risk for developing infection (27).

This analysis confirmed a high rate of ciprofloxacin resistance in ABP. Overall, the susceptibility to ciprofloxacin of *E. coli* was 76.3%. This is similar to reported antibiotic resistance in previous study on patients with acute pyelonephritis (8). This warrants caution in selecting empiric treatment for ABP. In this

study, each group showed different results, and we found that 85.7% of susceptibility was identified in the non-manipulation group, whereas the manipulation group showed 10.0% susceptibility. In addition to fluoroquinolone resistant *E. coli*, we examined ESBL-producing microbes. As mentioned earlier, the incidence of ESBL-producing *E. coli* and *K. pneumoniae* in community-acquired infections was 9.5% and 12.8% and in hospital-acquired infections the incidence was 25% and 78.6%, respectively (11). In this study, the incidence of ESBL-producing *E. coli* was 2.9% in the non-manipulation group and 21.1% in the manipulation group, respectively. In regards to *K. pneumoniae*, the incidence was 1.0% in the non-manipulation group and 10.5% in the manipulation group. The ESBL frequency was low compared with the results of a previous study because it was conducted by tertiary care centers (11). All ESBL-producing microbes showed fluoroquinolone resistance by cotransferring of quinolone resistance and ESBL genes (28). For these patients, intravenous carbapenems are recommended as first antibiotic treatments (29).

Recent guideline for treatment of ABP recommended the administration of a quinolone or cephalosporins alone or in combination with an aminoglycoside (30). However, our results showed that fluoroquinolones as a first empirical antibiotic may have limited effects in patients with prior urologic manipulation. In addition, incidence of ESBL was significantly higher in the group with prior manipulation. With this regard, cephalosporins with amikacin, or carbapenems, or extended-spectrum penicillin with beta lactamase inhibitor should be considered as the preferred empirical ABP treatment in the patients with history of prior urologic manipulation.

There were some limitations to this study, which included the small sample size and retrospective nature. Therefore, we verified the diagnosis of ABP with the patient's final diagnosis in the medical records. In addition, patients with mild ABP cases with minimal fever may not have been included, which could have caused selection bias. Another limitation is that the data for previous antibiotic use before hospital visits might be underestimated, which could cause a higher culture negative rate. In this study, we found that only 16 patients had recorded use of antibiotics before hospital visit, and of these patients, 10 patients used fluoroquinolones. Therefore, the association between ciprofloxacin resistance and previous antibiotic use could be inaccurate. In order to overcome these limitations, a future prospective study with larger numbers of cases is necessary.

In conclusion, this study showed microbiological aspects of ABP in Korea. This may inform selection of appropriate empirical antibiotics. The results indicated that ABP with history of prior manipulation was associated with high resistance to fluoroquinolones and a high incidence of ESBL-producing bacteria. Therefore, initial treatments approaches for ABP should consider patients' age and whether the patient have undergone prior urologic manipulation.

AUTHOR CONTRIBUTION

Study conception and design: Lee Y, Yoo KH. Acquisition of data: Lee Y, Lee DG. Analysis and interpretation of data: Lee SH, Yoo KH. Drafting of manuscript: Lee Y, Yoo KH. Critical revision: Lee DG, Lee SH, Yoo KH. Final approval of manuscript and submission: all authors.

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