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Prevalence and Risk Factors for Extended Spectrum Beta-Lactamase-Producing Uropathogens in Patients with Urinary Tract Infection

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Purpose: The aim of this study was to determine the prevalence and risk factors of extended spectrum beta-lactamase (ESBL)-producing microorganisms in urinary tract infection.

Materials and Methods: A total of 2,312 patients older than 25 years and diagnosed from January 2007 to December 2009 as having urinary tract infection were studied. The prevalence of ESBL-producing microorganisms including *Escherichia coli* and the antimicrobial susceptibility of *E. coli* were examined. Univariate analyses were performed with gender, age, inpatient status, previous hospitalization, recent history of urinary catheterization, recent exposure to specific antibiotics, and past history of urogenital organ operation as risk factors for the emergence of ESBL-producing microorganisms. Then, multivariate analysis was performed with all significant variables.

Results: In outpatient urinary tract infection, the antimicrobial susceptibility of *E. coli* to each of the third-generation cephalosporins, cefotaxime, ceftazidime, and ceftriaxone, was 87.6%, 93.4%, and 87.7%, respectively, and the prevalence of ESBL-producing *E. coli* was 12.1%. In inpatient urinary tract infection, the susceptibility of *E. coli* was 78%, 84.5%, and 76.9%, respectively, and the prevalence was 23.1%.

Conclusions: The overall prevalence of ESBL-producing microorganism was 12.6% and the risk appeared to be increased in cases with a previous hospitalization, a recent history of urinary catheterization, inpatient status, cefaclor medication, cefminox administration, and female gender.

Key Words: *Beta-lactamases; Cephalosporins; Prevalence; Risk factors*

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INTRODUCTION

Since their development in the 1960s, fluoroquinolones have been frequently prescribed for infectious disease. Together with trimethoprim-sulfamethoxazole (TMP-SMZ), fluoroquinolones are included among the antibiotics recommended by the Infectious Disease Society of America (IDSA) for urinary tract infection [1]. Despite this, resistance to TMP-SMZ and fluoroquinolones has been reported in urinary tract infection worldwide [2-5]. Ampicillin has been frequently used for urinary tract infection as an alternative drug owing to its activity against gram-negative microorganisms. Nonetheless, as acquired resistance to beta-lactam class antibiotics was reported [6], cephalosporins stable to beta-lactamase were developed, and thus the choice of antibiotics for urinary tract infection was widened [7,8]. However, after the report of extended spectrum beta-lactamase (ESBL)-producing organisms in 1983 in Germany, anxiety over the emergence of bacteria resistant to cephalosporins has been growing more and more [9].

According to the beta-lactamase classification by Bush et al, ESBL belongs to group 2be and is an enzyme that inactivates extended spectrum beta-lactam antibiotics such as cefotaxime, ceftazidime, and aztreonam [10]. The preva-

lence of ESBL-producing bacteria is gradually on the rise [11].

Therefore, we investigated the current situation of resistance of *Escherichia coli* to antibiotics and the prevalence of ESBL-producing bacteria in patients treated for urinary tract infection at our hospital as outpatients and as inpatients. In addition, by examining the past history of antibiotic administration, the past history of catheterization, and the past history of urological treatments and assessing their effects on the emergence of ESBL-producing bacteria, we made efforts to establish measures to prevent the emergence of resistant bacteria.

MATERIALS AND METHODS

1. The subjects and the methods

The clinical characteristics of 2,312 patients older than 25 years and diagnosed from January 2007 to December 2009 as having urinary tract infection were assessed by examining the patients' medical records.

Patients diagnosed as having urinary tract infection in the outpatient clinic or emergency room or patients diagnosed within 48 hours after hospitalization were classified as having outpatient urinary tract infection (O-UTI), and patients diagnosed during the hospitalization period were classified as having inpatient urinary tract infection (I-UTI).

The diagnosis of urinary tract infection was based on the standard of the Centers for Disease Control and Prevention (CDC) of detection of 10^5 bacterial colonies/ml by urine culture with more than one of the following symptoms or signs: fever higher than 38°C, tenderness in the suprapubic area, painful urination, urgency, and frequency.

The automatic identification and sensitivity Microscan system (Baxter Diagnostics Inc, USA) was used to identify the bacteria, and the minimal inhibitory concentration (MIC) was measured by the micro broth dilution method. At that time, ampicillin/clavudaric acid, cefazolin, cefotaxime, ceftazidime, ceftriaxone, cefotetan, cefuroxime, ciprofloxacin, imipenem, and trimethoprim/sulfamethoxazole were used as antibiotics.

I-UTI, previous hospitalization, female gender, old age, previous antimicrobial medication, Foley catheterization, and urogenital organ operation were considered as risk factors for the appearance of ESBL-producing bacteria.

Past history of hospitalization was defined as cases hospitalized for more than 1 day before the time of the diagnosis of urinary tract infection. Past history of use of antibiotics was defined as cases administered at least one antibiotic for more than one day before the time of the diagnosis of urinary tract infection. At that time, 10 antibiotics including quinolones, beta lactams, and cephalosporins that are known to be effective against gram-negative microorganisms were examined. We defined a past history of Foley catheterization as cases with catheterization for more than 3 days before the diagnosis of urinary tract infection [12].

2. Statistics

SPSS® version 12.0 (SPSS Inc. Chicago, IL, USA) was used, and $p < 0.05$ was considered to be statistically significant.

Factors suspected to be risk factors for the emergence of ESBL-producing bacteria were analyzed by univariate analysis, Kruskal Wallis test, and chi-square test. Afterward, a multivariate analysis was performed with all significant variables, and the odds ratio was calculated with a confidence interval of 95%.

RESULTS

1. Epidemiology of ESBL-producing bacteria in UTI

Among the total 2,312 patients with urinary tract infection, 291 patients (13.02% of the total) were infected with ESBL-producing bacteria. The incidence of ESBL-producing *E. coli* was shown to be 14.5%; it was 12.1% in O-UTI (122/1010) and 23.1% in I-UTI (64/277), and thus the risk of development of ESBL-producing *E. coli* was 2 times higher in I-UTI (Table 1).

2. Antimicrobial susceptibility

In O-UTI and I-UTI, susceptibility to ciprofloxacin, one of the fluoroquinolones, was 68.1% and 57.8%, respectively, and was lower than that to cephalosporins. Among the cephalosporins, susceptibility to cefotetan, one of the second-generation cephalosporins, was the highest. However, lower susceptibility to cefuroxime, one of the second-generation cephalosporins, than to other third-generation cephalosporins was shown. Among the third-generation cephalosporins, susceptibility of *E. coli* was highest to ceftazidime. Susceptibility to ceftazidime in O-UTI and

TABLE 1. Comparison of antimicrobial susceptibilities between O-UTI and I-UTI

Antimicrobial susceptibility of *Escherichia coli*				
	O-UTI n (%)	I-UTI n (%)	OR	95% CI[a]
A/C	667 (66.0)	151 (54.5)	1.63	1.24-2.13
CZ	769 (76.1)	192 (69.3)	1.41	1.05-1.89
CTX	885 (87.6)	216 (78.0)	1.99	1.42-2.81
CT	994 (98.4)	258 (93.1)	4.57	2.32-9.02
CTZ	943 (93.4)	234 (84.5)	2.59	1.71-3.89
CFT	887 (87.8)	213 (76.9)	2.05	1.49-2.89
CFX	848 (84.0)	192 (69.3)	2.32	1.71-3.15
CF	688 (68.1)	160 (57.8)	1.56	1.19-2.05
IP	1,003 (99.3)	271 (97.8)	3.17	1.05-9.51
T/S	619 (61.3)	141 (50.9)	1.53	1.17-1.99
ESBL	122 (12.1)	64 (23.1)	2.19	1.56-3.07

O-UTI: outpatient urinary tract infection, I-UTI: inpatient urinary tract infection, OR: odds ratio, CI: confidence interval, A/C: ampicillin/clavulanate, CZ: cefazolin, CTX: cefotaxime, CT: cefotetan, CTZ: ceftazidime, CFT: ceftriaxone, CFX: cefuroxime, CF: ciprofloxacin, IP: imipenem, T/S: trimethoprim/sulfamethoxazole, ESBL: extended spectrum beta-lactamase, [a]: $p < 0.01$ except for imipenem ($p=0.047$)

I-UTI was 93.4% and 84.5%, respectively. Generally, susceptibility of *E. coli* to antibiotics was lower in I-UTI than in O-UTI (Table 1). On the other hand, the susceptibility of ESBL-producing *E. coli* to all antibiotics, except imipenem and cefotetan, was lower than 50% (Table 2).

3. Risk factors and odds ratios

Table 3 shows the results of the univariate analysis of risk factors that may exert effects on the emergence of ESBL-producing bacteria. I-UTI, previous hospitalization, female gender, past history of Foley catheterization, and past history of exposure to specific antibiotics were revealed as statistically significant variables. Among antibiotics, only the second-generation cephalosporin drug cefaclor in oral form and the second-generation cephalosporin cefminox in injection form were statistically significant.

Table 4 shows the relative risks in association with the emergence of ESBL-producing bacteria analyzed by multivariate analysis performed with all significant variables in the univariate analysis. Previous hospitalization and past history of catheterization were associated with relative risks for the emergence of ESBL-producing bacteria of 2.5 and 2.4, respectively, followed by (in order) I-UTI, cefaclor medication, cefminox administration, and female gender.

TABLE 2. Antibiotic susceptibility patterns of ESBL-producing *E. coli*

Antibiotic susceptibility (%)	
Ampicillin/Clavulanate	3.8
Cefazolin	1.3
Cefotetan	95.9
Cefotaxim	3.8
Ceftazidime	42.3
Ceftriaxone	3.8
Ciprofloxacin	28.2
Imipenem	98.7
TMP/SMX	42.3

ESBL: extended spectrum beta-lactamase, TMP/SMX: trimethoprim/sulfamethoxazole

TABLE 3. Patient characteristics and epidemiological and clinical variables associated with ESBL-producing pathogens (univariate analysis)

	ESBL (n=291)	Non-ESBL (n=2,021)	p-value
Mean age±SD (years)[a]	65.82±12.74	64.74±14.15	0.183
Inpatient origin (%)[b]	46.73	31.89	<0.001
Previous hospitalization (%)[b]	21.31	8.11	<0.001
Sex (female%)[b]	78.69	70.46	0.004
Operation history of the urinary tract (%)[b]	6.87	10.47	0.055
Foley catheterization (%)[b]	12.71	6.64	<0.001
Previous medication (%)[b]			
CFC	12.02	8.43	0.043
CDN	0	0.64	0.166
CFX	2.02	15.16	0.561
CXV	14.43	10.85	0.045
CTXV	1.03	0.54	0.767
CPDX	6.19	5.95	0.875
CZXV	5.84	5.80	0.949
CTRV	12.03	9.96	0.296
FXV	5.50	7.88	0.161
CF	17.18	14.97	0.340
LVF	2.06	2.68	0.571
AUG	7.90	8.23	0.809

ESBL: extended spectrum beta-lactamase, SD: standard deviation, CFC: cefaclor, CDN: cefdinir, CFX: cefuroxime, CXV: cefminox, CTXV: cefotaxime, CPDX: cefpodoxime, CZXV: ceftazidime, CTRV: ceftriaxone, FXV: flomoxef, CF: ciprofloxacin, LVF: levofloxacin, AUG: ampicillin/clavulanate, [a]: by Kruskal Wallis test, [b]: by chi-square test

DISCUSSION

The development of antibiotics has contributed greatly to reducing mortality caused by infection; nonetheless, as the use of antibiotics becomes generalized, the vicious circle of the development of new antibiotics and the emergence of resistant bacteria cannot be severed. In fact, according to an epidemiological study conducted by the National Nosocomial Infections Surveillance (NNIS), the resistance rate of most bacteria to antibiotics has increased [13].

Comparison of two studies conducted on ambulatory patients well explains the increasing resistance of *E. coli* to TMP-SMZ and ciprofloxacin in America [4,5]. In the report of the European Antimicrobial Resistance Surveillance System (EARSS), similarly, in most European countries, the prevalence of *E. coli* resistant to fluoroquinolones, the third-generation cephalosporins, and aminoglycosides is on the increase every year [3].

In Korea, according to the study reported by Ryu et al, a trend for a reduction in sensitivity of *E. coli* to the third-generation cephalosporins and fluoroquinolones was observed, and *E. coli* resistance to antibiotics was greater in I-UTI [14]. An increase in resistance to antibiotics in O-UTI has been shown already in other Korean studies [15-17].

We investigated the antimicrobial susceptibilities of *E. coli* in I-UTI compared with O-UTI. Because of the possi-

TABLE 4. Multivariate analysis of relative risks associated with ESBL-producing pathogens

Risk factors	OR	95% CI	p-value
Inpatient origin	1.71	1.308-2.235	<0.001
Previous hospitalization	2.49	1.762-3.505	<0.001
Sex (female)	1.44	1.062-1.951	0.019
Foley catheterization	2.38	1.593-3.567	<0.001
CFC	1.68	1.126-2.510	0.011
CXV	1.54	1.068-2.210	0.021

ESBL: extended spectrum beta-lactamase, OR: odds ratio, CI: confidence interval, CFC: cefaclor, CXV: cefminox

bility of contamination from a nosocomial component, we used the term 'outpatient' instead of 'community-acquired.' The sensitivity of *E. coli* to cephalosporins and fluoroquinolones was lower in I-UTI. In contrast, the emergence of ESBL-producing bacteria was observed to be higher in I-UTI (Table 1). In O-UTI, sensitivity of *E. coli* to the third-generation cephalosporins did not show a great difference from the studies reported in 2008 by Lee [17]; nonetheless, in comparison with other previous studies, slightly reduced patterns were observed [15,16]. In comparison with Europe, concerning the second-generation cephalosporin drug cefuroxime, sensitivity was comparable to that in a multinational study conducted by Naber et al [18]. Nonetheless, in comparison with the 2008 EARSS report, the sensitivity of *E. coli* to the entire class of third-generation cephalosporins was observed to be lower, excluding Bulgaria (29%) and Turkey (42%) [3].

The current situation of resistance to antibiotics has reached a serious point In urinary tract infection, and presently, multidrug-resistant bacteria including ESBL-producing bacteria can be readily encountered in clinics. Antibiotics that can be used for the treatment of multidrug-resistant bacteria including ESBL-producing bacteria In urinary tract infection are limited [19]. In our study, similarly, excluding imipenem and cefotetan, antibiotics with sensitivity higher than 50% to ESBL-producing *E. coli* were absent (Table 2). In addition, infection with ESBL-producing bacteria raises mortality, and it not only prolongs hospital stay but also increases relative treatment costs [20]. Therefore, it is very important to assess the risk factors for the emergence of multidrug-resistant bacteria, including ESBL-producing bacteria, and to provide means to prevent such resistance.

Recent studies showed that the emergence of ESBL-producing bacteria is more frequent in patients with a past history of hospitalization, a past history of exposure to antibiotics, a past history of catheterization, and a past history of urogenital surgery [21-23]. In the present univariate analysis, female gender, I-UTI, recent history of hospitalization, recent history of Foley catheterization, and recent exposure to specific antibiotics were observed to be associated with the emergence of ESBL-producing bacteria (Table 3). In the multivariate analysis, recent hospitalization was shown to be the greatest risk factor, followed by (in order) Foley catheterization, I-UTI, exposure to cefaclor, exposure to cefminox, and female gender (Table 4). Rodriguez-Bano et al reported in a case-control study conducted on 147 patients with O-UTI that the strongest risk factor for the emergence of ESBL-producing *E. coli* was a past history of hospitalization within the recent 1 year (odds ratio, 18.2; 95% confidence interval, 1.9 to 30.1) [24]. In our study, similarly, the probability of infection with ESBL-producing *E. coli* was higher in patients with a recent history of hospitalization than in patients without a history by approximately 2.5 times (Table 4). This suggests that blocking of infection within hospitals could reduce the prevalence of ESBL-producing bacteria and could lower the spread to communities. Thus, efforts to reduce the opportunities for inpatient infection with ESBL-producing bacteria should be considered very important. Siegel et al recommended that to block the spread of multidrug-resistant bacteria within hospitals, hospitals should restrict contact with patients infected with multidrug-resistant bacteria internally and provide detergents containing alcohol in the area and require their use [25]. In addition, they mentioned that hand hygiene education for medical staff and guardians should be required. Furthermore, Siegel et al emphasized the need to monitor the trend of multidrug-resistant bacteria by routine bacterial culture and also to establish organized report systems.

A past history of exposure to a specific antibiotic may be another risk factor for the emergence of ESBL-producing bacteria, and this topic is currently an active research area. Calbo et al reported the risk factors of exposure to the second-generation cephalosporins in oral form and the second-generation cephalosporin drug cefuroxime in injection form [21]. In our study, similarly, the second-generation cephalosporin drug cefaclor in oral form and the second-generation cephalosporin drug cefminox in injection form were shown to be risk factors. Among ESBL patients, the percentages of patients already exposed to these drugs were 12.2% and 14.4%, respectively. The percentage of patients already exposed to ciprofloxacin, one of the fluoroquinolones, was 17.2%; nonetheless, it was not associated with the emergence of ESBL-producing bacteria. Goossens et al explained the association of the level of use of antibiotics with bacteria acquiring resistance and emphasized the adequate use of antibiotics [26]. In fact, it has been reported that the appropriate use of antibiotics against gram-negative bacteria decreases the frequency of multidrug-resistant bacteria [25]. On the other hand, in clinics, prescription of antibiotics empirically for pyuria in asymptomatic bacteriuria patients or catheterized patients is seen occasionally, and the IDSA suggests the standard of prescription of antibiotics for such patients [27]. Therefore, to prevent the emergence of multidrug-resistant bacteria in urinary tract infection, efforts should be made to strictly observe the indications for the administration of antibiotics and to use antibiotics appropriately for a minimal period through culture for cases requiring antibiotics.

Foley catheterization is well known to be a risk factor for urinary tract infection. About 20% of urinary tract infection associated with Foley catheterization occurs due to unskilled sterilization techniques during the insertion of the catheter [28]. Infection may occur due to contamination of the collecting system through the lumen of the catheter [29]. Other cases have been reported to occur through the biofilm formed between catheter and the urethral mucosa [30]. Some reports emphasized that Foley catheterization may play an important role as a risk factor for the appearance of ESBL-producing bacteria [22]. In our study, similarly, the risk of emergence of ESBL-producing bacteria appeared to be approximately 2.4 times higher in patients

with Foley catheterization (Table 4). Therefore, unnecessary Foley catheterization should be avoided in patients with urinary tract infection to prevent the emergence of ESBL-producing bacteria. If unavoidable, Foley catheterization should be performed by use of sterile techniques, and a closed drainage system should be applied during the minimal indwelling period.

Female gender appeared to be a risk factor for the emergence of ESBL-producing bacteria, and the proportion of women was about 8% higher in the ESBL group than in the non-ESBL group, although some studies have shown no statistical difference in gender or a slightly higher incidence of ESBL-producing bacterial infection in men [21-24]. Because many studies had a relatively small scale and were conducted retrospectively in limited age groups, large, prospective clinical studies with all age groups will be required to minimize the selection bias.

A past history of urogenital surgery, regardless of the type of the surgery, had no association with ESBL-producing bacterial infection in this study. Therefore, further clinical studies are needed because the fraction of the ESBL group with a urogenital operative history was too low to avoid the error of false generalization.

CONCLUSIONS

The total prevalence of ESBL-producing microorganisms in urinary tract infection was approximately 13%. In O-UTI and I-UTI, the prevalence of ESBL-producing *E. coli* was 12.1% and 23.1%, respectively. The risk appeared to be increased in cases with I-UTI, previous hospitalization, a history of Foley catheterization, previous exposure to specific antibiotics, and female gender. Among the risk factors, a past history of hospitalization appeared to be the greatest risk factor.

Therefore, to prevent the spread of multidrug-resistant microorganisms, especially ESBL-producing species in urinary tract infection, medical institutions should make efforts to develop administrative and educational programs and to provide appropriate guidelines for the prescription of antibiotics as well as urinary catheterization and to follow these guidelines strictly.

Conflicts of Interest

The authors have nothing to disclose.

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