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Original Article

Does urinary tract infection caused by extended-spectrum β-lactamase-producing *Escherichia coli* show same antibiotic resistance when it recurs?☆

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ABSTRACT

This study was performed to evaluate what percentage of urinary tract infections (UTIs) caused by extended spectrum β-lactamase (ESBL)-producing strains recurs with ESBL-producing strains during follow up and to assess the risk factors for recurrence with ESBL-producing *Escherichia coli* strains on subsequent first recurrence episode. We enrolled female patients with UTIs caused by ESBL-producing *E. coli* between May 2012 and December 2015, who were longitudinally followed up for at least 24 months. Among the 206 patients with ESBL positive UTI, 180 completed the study. 60 (60/180, 33.3%) of patient with first episode of UTI caused by ESBL-producing *E. coli* experienced recurrent UTIs during follow up. Of 60 patients, 43 (43/60, 71.7%) recurred with ESBL-producing *E. coli* on the first UTI recurrence episode. On multivariate analysis, the time to recurrence and history of cephalosporin usage in the last 6 months were identified as risk factors for recurrence with ESBL-producing *E. coli* per se (odds ratio [OR] = 0.9, 95% confidence interval [CI] 0.8–1.0, p = 0.030 and OR = 27.0, 95% CI 2.4–299.8, p = 0.007, respectively). These findings show that high proportion of patient with UTI caused by ESBL-producing *E. coli* recurs with ESBL-producing *E. coli* on subsequent recurrence episode. While result of antibiotic susceptibility cannot be identified on the visit day empirical treatment should be referred to the antecedent antibiotic resistance profile in patients whose previous UTIs were due to ESBL-producing strains.

1. Introduction

Urinary tract infections (UTIs) are a prevalent disease in females with more than half affected in their lifetime [1,2]. Majority of UTIs in healthy women are uncomplicated cystitis, and the most common pathogen is *Escherichia coli (E. coli)*, accounting for 70–83% of community-acquired infections in Korea [3,4]. Therefore, empirical antibiotic regimens rely on the surveillance data of antibiotic resistance, particularly that of *E. coli*. Despite empirical antibiotic regimens showing highly successful treatment rates [5], recurrent cystitis in women is a common phenomenon, and previous studies have estimated its prevalence at 20–44% during the first year [6,7].

Additionally, acute cystitis caused by extended spectrum β-lactamase (ESBL)-producing *E. coli* that are commonly resistant to conventional empirical antibiotics has gradually increased up to 24.6% in Korea [8,9]. The standard treatment regimen for the management of ESBL-producing *E. coli* is parenteral administration of antibiotics such as carbapenem; thus, patients frequently required hospitalization even if they are mildly symptomatic and ambulatory [10,11]. In this setting, the choice of the appropriate empirical therapeutic regimen for women with recurrent cystitis who were previously infected with isolated ESBL-producing *E. coli* may be challenging because we do not know the antibiotic resistance profile on the visit day [12].

This study was performed to evaluate what percentage of UTIs caused by ESBL-producing strains recurs with ESBL-producing strains during follow up and to assess the risk factors for recurrence with ESBL-producing *E. coli* strains on subsequent first recurrence episode. Also antibiotic profiles were compared between the first episode of UTI caused by ESBL-producing UTI and

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the follow recurrence episodes so that empirical antibiotic could be referred to antecedent UTI caused by ESBL-producing *E. coli*.

2. Materials and methods

2.1. Patients

We included female patients aged ≥18 years with acute cystitis caused by ESBL-producing *E. coli*. Patients who had predisposing factors of UTIs, such as anatomical abnormality (cystocele, diverticulum, fistula, prior urinary tract surgery, bladder or renal calculi, and vesicoureteral reflux) and immunocompromised state except for diabetes mellitus (DM), were excluded. We also excluded the patients who loss the follow up during observation period or whose clinical data was insufficient to determine the primary study aim.

2.2. Study design

A longitudinal observational study was conducted between May 2012 and December 2017 with the approval from the Institutional Review Board of the authors' institute. We enrolled patients who met the criteria between May 2012 and December 2015 and longitudinally followed up each of them for 24 months after an index episode of cystitis caused by ESBL-producing *E. coli*. A comprehensive medical history was obtained, including age, body mass index (BMI), underlying comorbidities (DM, malignancy, cerebrovascular accident, neurogenic bladder), number of UTI episodes in the previous 12 months, exposure to cephalosporin or fluoroquinolone in the previous 6 months, and history of Foley catheterization or intermittent catheterization 1 month prior to inclusion. A UTI episode during the follow-up period was defined as clinically significant bacteriuria (at least 10^4 cfu/ml for symptomatic patients and at least 10^5 cfu/ml for asymptomatic patients). UTI recurrence was defined as an episode occurring at least 1 month after the index episode.

2.3. Clinical assessment

All patients showed a sterile urine culture after the completion of therapy for their initial episode. Then, we investigated the recurrence rate during a 24-month observational period, and if recurrence was observed, the time to recur were calculated.

We investigated what percentage of UTIs caused by ESBL-producing strains recurs with ESBL-producing strains during follow up by means of a semi-automated system (VITEK, bio-Me'rieux, Hazelwood, MO, USA) and to assess the risk factors for recurrence with ESBL-producing *E. coli* strains on subsequent first recurrence episode. Also antibiotic profiles were compared between the first episode of UTI caused by ESBL-producing *E. coli* and the follow recurrence episodes.

2.4. Statistical analysis

Continuous data including age and BMI were analyzed using Student's t-test, and the results were presented as the mean ± standard deviation (SD). Categorical variables including clinical features and recurrence rates were expressed as numbers and percentages. Categorical variables were examined using the Pearson chi-square test where appropriate (expected frequency, >5), and Fisher's exact test was used otherwise. Multivariate logistic regression was used to evaluate the risk factors for recurrence (odds ratio [OR]; 95% confidence interval [CI]). All analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). *P*-values of <0.05 were considered significant.

3. Results

Among the 206 patients who were initially enrolled 180 patients with acute cystitis caused by ESBL-producing *E. coli* completed a 24-month follow-up. Demographics and baseline characteristics are summarized in Table 1.

During the 24-month follow-up, 60 of the 180 (33.3%) women had recurred UTIs; altogether, 113 UTI episodes were diagnosed. Thirty-three (18.3%) had only 1 recurrence, 15 (8.3%) had 2, 6 (3.3%) had 3, 2 (1.1%) had 4, 2 (1.1%) had 5, and 2 (1.1%) had 7. All recurrences were identified as symptomatic UTIs.

Among those patients who experienced UTI recurrence, 43 of 60 patients (71.7%) had recurrences caused by ESBL-producing *E. coli* [ESBL (+) group] and 17 (28.3%) had recurrences caused by non-ESBL-producing organisms [ESBL (−) group]. The isolated non-ESBL-producing organisms identified as follows; *E. coli* (8/17), *Enterococcus faecalis* (3/17), *Pseudomonas aeruginosa* (2/17), *Enterococcus faecium* (1/17), *Klebsiella pneumoniae* (1/17), *Citrobacter freundii* (1/17) and *Staphylococcus epidermidis* (1/17).

For their second UTI recurrence episodes, 15 (68.2%) of 43 patients once again had recurrence UTIs caused by ESBL-producing *E. coli*. The flow chart of subsequent episode of UTIs and recurrence rate of UTIs caused by ESBL-producing *E. coli* is presented in Fig. 1.

The mean time to recurrence at initial recurrent episode of UTIs was 5.8 (range 1–24) months. The time to recurrence was shorter in the ESBL (+) group than the ESBL (−) group (3.2 ± 3.6 months vs. 9.8 ± 12.4 months, P < 0.003). The history of Foley catheterization and cephalosporin use was only observed in the ESBL (+) group. No significant differences were observed in other parameters, such as age, underlying comorbidities, and previous history of fluoroquinolone use (Table 2). After the multivariate analysis, the time to recurrence and history of cephalosporin use in the previous 6 months were independently associated with cystitis whose recurrence was caused by ESBL-producing *E. coli* (OR = 0.9, 95% CI 0.8–1.0, p = 0.030 and OR = 27.0, 95% CI 2.4–299.8, p = 0.007, respectively).

The results of antibiotics susceptibility profile of ESBL-producing *E. coli* in index and subsequent UTI episodes are presented in Table 3. Ertapenem showed 100% susceptibility in both episodes of UTIs caused by ESBL-producing *E. coli*. Amikacin also

Table 1
Demographics and baseline characteristics of patients.

	Total N = 180
Age (years), mean ± SD	63.0 ± 13.4
Body mass index (kg/m^2), mean ± SD	23.7 ± 4.3
DM, number (%)	26 (14.4)
CVA, number (%)	11 (6.1)
Malignancy, number (%)	7 (3.9)
Neurogenic bladder, number (%)	12 (6.7)
Previous history of UTIs, number (%)	84 (46.7)
Urinary retention, number (%)	1 (0.6)
Number of episode of UTIs in the previous 12 months	0.9 ± 1.6
History of Foley catheterization, number (%)	16 (8.9)
History of intermittent catheterization, number (%)	4 (2.2)
History of cephalosporin usage, number (%)	38 (21.1)
History of fluoroquinolone usage, number (%)	25 (13.9)
Initial antibiotic use	
Amikacin + amoxicillin/clavulanate	77 (42.8)
Amikacin + fosfomycin	28 (15.6)
Fosfomycin	34 (18.9)
Ertapenem	25 (13.9)
Cefoxitin	9 (5.0)
Quinolone	7 (3.9)

DM diabetes, mellitus; CVA, cerebrovascular accident; UTI, urinary tract infection; SD, standard deviation.

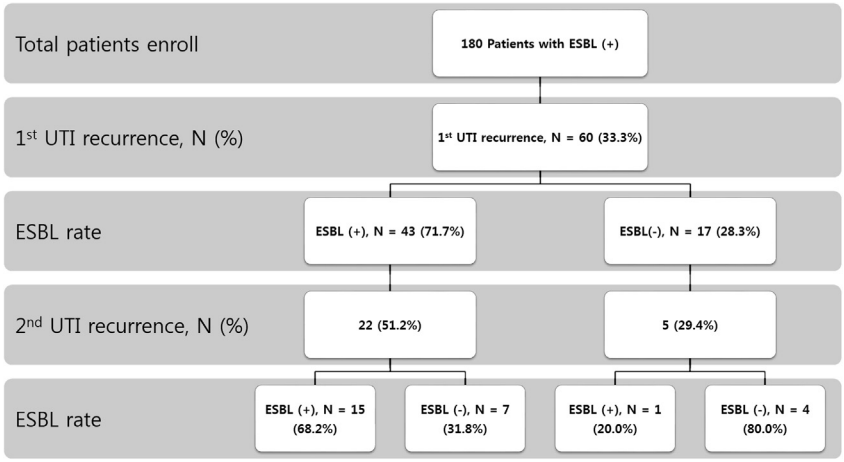

Fig. 1. Schematic diagram of the results of the study. ESBL, extended spectrum b-lactamase; ESBL (+), patients with recurrent cystitis caused by ESBL-producing *E. coli;* ESBL (−), patients with recurrent cystitis caused by non-ESBL-producing organisms.

Table 2
Comparison of clinical and microbiological factors between UTI recurrence with ESBL-producing *E. coli* and those with non-ESBL-producing organisms.

Variable	ESBL (+) recurrence, N = 43	ESBL (−) recurrence, N = 17	*P*-values
Age	65.9 ± 10.9	61.2 ± 13.9	0.172
Body mass index	25.9 ± 5.0	23.6 ± 5.1	0.131
Number of episode of UTIs in the previous 12 months	1.6 ± 2.4	1.5 ± 1.6	0.906
Cumulative time to recurrence (months)	**3.2 ± 3.6**	**9.8 ± 12.4**	**0.003**
DM	9 (20.9%)	4 (23.5%)	0.860
CVA	9 (20.9%)	3 (17.6%)	0.774
Malignancy	4 (9.3%)	2 (11.8%)	0.774
Neurogenic bladder	9 (20.9%)	1 (5.9%)	0.159
History of Foley catheterization, number (%)	**11 (25.6%)**	**0 (0.0%)**	**0.021**
Previous history of UTIs	28 (68.3%)	8 (53.3%)	0.301
History of cephalosporin usage	**21 (48.8%)**	**1 (5.9%)**	**0.002**
History of fluoroquinolone usage	19 (44.2%)	4 (23.5%)	0.138

Abbreviations as in Table 1. Variables that results statistically significant at 5% level of significance were represented in bolds.

Table 3
Antimicrobial susceptibility profile of ESBL-producing *E. coli* in index and subsequent UTI episodes, and non ESBL-producing organisms in subsequent UTI episodes.

Antibiotics	Index UTI episode			Subsequent UTI episode			*P*	non ESBL-producing organisms		
	Susceptible	Intermediate	Resistance	Susceptible	Intermediate	Resistance		Susceptible	Intermediate	Resistance
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)
Amikacin	176 (97.8)	1 (0.6)	3 (1.7)	42 (97.7)	1 (2.3)	–	0.381[a]	12 (100.0)	–	–
Amoxicillin/clavulanate	93 (51.7)	65 (36.1)	22 (12.2)	21 (48.8)	16 (37.2)	6 (14.0)	<0.001	9 (81.8)	–	2 (18.2)
Cefoxitin	130 (72.2)	21 (11.7)	29 (16.1)	32 (74.4)	4 (9.3)	7 (16.3)	0.041[a]	9 (90.0)		1 (10.0)
Ciprofloxacin	40 (22.2)	2 (1.1)	138 (76.7)	5 (11.6)	1 (2.3)	37 (86.0)	0.009[a]	9 (52.9)	–	8 (47.1)
Ertapenem	180 (100.0)	–	–	43 (100.0)	–	–	–	10 (100.0)	–	–

Statistical analysis performed using chi-square test.
[a] Likelihood ratio test.

showed a high susceptibility profile of over 90% in initial UTI episodes and maintained its high susceptibility in subsequent UTI episodes with ESBL-producing *E. coli.* By contrast, ciprofloxacin and amoxicillin/clavulanate show high resistance rates (77.8% and 48.3%, respectively) at index UTI episodes, and both antibiotics had a significantly decreased susceptibility at recurrent UTI episodes. Additionally, the antibiotics susceptibility profiles of ESBL (−) group were summarized in Table 3.

4. Discussion

UTIs caused by ESBL-producing *E. coli* have become a serious health concern worldwide due to their multidrug resistance with seriously limited therapeutic options [13,14]. Although several studies reported the risk factors for development of ESBL-producing *E. coli,* few follow-up or long-term studies on women with uncomplicated recurrent UTIs have been published [7,15,16]. Previous studies provide important information about the characteristics of recurrent infections by comparing different populations with the same disease. However, previous studies provide little information about recurrent UTIs caused by multidrug-resistant organisms, such as ESBL-producing *E. coli*.

In the present study, we have analyzed the ultimate fate of UTI caused by ESBL-producing *E. coli* by assessing the recurrence rates of UTIs with ESBL-producing *E. coli* on subsequent recurrence episodes. Moreover, we also analyzed changes in antibiotic susceptibility through longitudinal long-term follow-up of the same population. In this context, our study is important because it has

the potential to guide clinical therapeutic options for recurrent cystitis before confirming the culture results in patients who were previously diagnosed with UTIs caused by ESBL-producing *E. coli*.

In the present study, 33% patients with UTIs caused by ESBL-producing *E. coli* had at least one recurrent UTI episode during follow-up. The recurrence rate of UTIs in our study appears to be lower than the 49.2–70% as estimated in previous longitudinal studies by Ikaheimo R. et al. and Kenneth L. et al. [7,15]. This can be attributed to the fact that one study included UTI incidence within 2 weeks, which was excluded in our study as initial bacterial persistence (failure to eradicate the infection) [7]. In another study, the treatment and sterile urine culture after index UTI episodes were not clearly mentioned [15]. Furthermore, both studies include incidence of asymptomatic bacteriuria. Therefore, the actual recurrence rates of UTIs in those studies could be highly likely overestimated. In contrast, although this study is limited to ESBL-producing *E. coli,* we enrolled patients with a strict inclusion criteria and confirmed sterile urine after the treatment of index UTIs; thus, this provides information on the recurrence rate of UTIs more accurately.

The most interesting finding of this study was that approximately 70% of patients had UTI recurrences caused by identical ESBL-producing *E. coli* during follow-up (Fig. 1). A similar phenomenon was observed at the second recurrent UTI episodes. In our knowledge, this was the first findings that patients with UTIs caused by ESBL-producing *E. coli* had high prevalence of ESBL-producing *E. coli* in their subsequent UTI episodes. Additionally, we identified that short-term interval to recurrence and cephalosporin use in the previous 6 months found to be an independent risk factor for recurrent infection by ESBL-producing *E. coli.* Thus, we should consider ESBL-producing *E. coli* as the pathogens when patients with a history of acute cystitis caused by the same microorganism with short intervals and previous history of cephalosporin usage.

Many studies have demonstrated that previous cephalosporin exposure is a major independent risk factor for the development of infection by ESBL-producing *E. coli* [17–19]. Surprisingly previous cephalosporin use is also the risk factor for recurrence of UTI with ESBL-producing *E. coli* during follow up in patients with andecent UTI caused by ESBL-producing *E. coli*. Etienne et al. have demonstrated that relative fecal abundance of ESBL-producing *E. coli* was 13-fold higher in women who were exposed to antibiotics and consequently linked to the occurrence of UTIs caused by ESBL-producing *E. coli* [20]. The classic theory of ascending reinfection is well reflected in our results, considering the virulence factors of *E. coli* to enable it to ascend the urethral mucosa and subsequently colonize and infect the urinary tract [21]. Recent studies have demonstrated that the source of ESBL-producing *E. coli*, which caused the UTIs, was each the host's indigenous *E. coli* [22]. Additionally, patients who had UTIs caused by ESBL-producing *E. coli* were found to have prolonged fecal carriage of ESBL-producing *E. coli* for over 3 years after UTI treatment [23]. Another factor that made our patients more vulnerable to the virulence factor of *E. coli* is that most of them were postmenopausal. The resulting estrogen loss at menopause is hostile to *Lactobacilli*, resulting in decreased numbers. Consequently, vaginal pH increases, and an increased propensity for colonization with *E. coli* was observed [24]. However, another theory, instead of repeated ascending infections, was raised. Recently, uropathogenic *E. coli* has been reported to invade the urothelium, potentially accumulating bacteria in the cells forming quiescent intracellular bacterial reservoirs (QIRS). QIRS is presumed to provide continuing bacterial survival and recurrent UTIs [25–27]. This model for persistent uropathogenic *E. coli* in the urinary bladder results in recurrent UTIs with the same organism as before, and consequently ESBL-producing *E. coli* continue to recur in high distribution as findings in this study. In this setting, short recurrence interval was notably identified as a risk factor. In this study, 27 out of 43 (62.8%) patients with recurrent UTIs caused by ESBL-producing *E. coli* recurred within 2 months.

Another remarkable point of this study is the comparison result of antibiotic susceptibility profiles of ESBL-producing *E. coli* between index and subsequent UTI episodes caused by ESBL-producing *E. coli*. Both amikacin and ertapenem had a high susceptibility profile of >90%, which were not significantly different in subsequent UTI episodes. Thus, considering that the resistance threshold of the antimicrobial agent for the empirical treatment of cystitis in the current guidelines is less than 20% [28,29], amikacin and ertapenem should be appropriately used as empirical antibiotics for patients with recurrent cystitis caused by ESBL-producing *E. coli.* Although the current gold standard treatment for ESBL-producing *E. coli* is intravenous administration of carbapenem, we should consider its cost-effectiveness and patient compliance. As amikacin shows similar sensitivity to ertapenem, it can be an alternative empirical antibiotic therapy in patients who allegedly have UTIs caused by ESBL-producing *E. coli*.

A limitation of this study was that it was conducted in a single center with relative small number of cases. Although representing the epidemiology of a regional community through our study is challenging, its result is sufficient to identify the longitudinal course of recurrent UTIs caused by ESBL-producing *E. coli* because we enrolled patients with clear-cut criteria and conducted the study in a prospective maneuver. Another limitation was that during the observational period we treated the patients with recurrent UTIs using various antibiotic regimens and duration, and irregular follow-up schedule for each patient could be a weakness point of our study design. However, we advised patients to visit promptly when they developed UTI symptoms and to follow up at least twice annually even if they were asymptomatic. Moreover, we identified sterile urine culture after the treatment of subsequent UTI episodes. Patients who were not compatible with above the criteria excluded in this study.

Despite these limitation, the present study is the first study to report the ultimate outcome of recurrent cystitis caused by ESBL-producing *E. coli* through longitudinal follow up. We believe that our study would provide important information for choosing empirical antibiotics in patients with recurrent cystitis who recurred from UTI caused by ESBL-producing *E. coli.*

5. Conclusion

Over two thirds of the initial UTIs caused by ESBL-producing *E. coli* had ESBL positive *E. coli* on subsequent recurrence episode of UTIs. Previous exposure to cephalosporin within 6 months and short interval to recurrence were the risk factors for recurrence with ESBL-producing *E. coli* after its first attack in our cohort. Thus, we should keep in mind that patient with history of UTI caused by ESBL-producing *E. coli* will have ESBL positive *E. coli* as causative pathogen in subsequent recurrent episodes if they recurred in short intervals and had a history of cephalosporin use. So in when patients with history of previous UTI caused by ESBL-producing *E. coli* empirical antibiotics should be referred to antecedent UTI caused by ESBL-producing *E. coli*.

Conflicts of interest

The authors have nothing to disclose.

Author contribution

Sun Tae Ahn: The conception and design of the study, analysis and interpretation of data, drafting the article.

Sang Woo Kim, Jong Wook Kim: Acquisition of data and helped to draft the manuscript.

Hong Seok Park, Du Geon Moon: Revising the article critically for important intellectual content.

Mi Mi Oh: The conception and design of the study, revising it critically for important intellectual content, final approval of the version to be submitted.

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