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■ 원저 ■

Extended-spectrum β-lactamase 를 생산하는 *Enterobacteriaceae* 요로감염에서 카바페넴 이외의 항생제 사용 가능성에 대한 고찰

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Use of Non-carbapenem Antibiotics in Patients with Urinary Tract Infection Caused by Extended-spectrum Beta-lactamase-producing *Enterobacteriaceae*

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Background: Alternatives to carbapenem are increasingly needed to decrease the usage of carbapenem. We evaluated the possibility of using non-carbapenem antibiotics against urinary tract infections (UTI) caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE).

Methods: This retrospective study was performed at 2 university hospitals between October 2010 and December 2012. All diagnosed adult cases of ESBL-PE UTI were identified from the microbiological database. The subjects were divided into 3 groups based on the empirical antibiotic classes and susceptibility: carbapenem (C) group, susceptible non-carbapenem (SNC) group, and non-susceptible non-carbapenem (NSNC) group.

Results: A total of 84 patients were eligible for analysis. For empirical therapy, 41, 23, and 20 patients were included in the NSNC, SNC, and C empirical groups, respectively. During the empirical therapy, 7 patients (17.1%) in the NSNC group, 18 patients (78.3%) in the SNC group, and 19 patients (78.3%) in the C group experienced clinical improvement. No significant difference was observed between the SNC and C empirical groups (P=0.192). Severe sepsis or shock was the predictor of empirical SNC treatment failure (P=0.048). There was a tendency to use carbapenem as a definite therapy in cases of NSNC. In contrast, empirical SNC was maintained as a definite therapy.

Conclusion: SNC could be considered as an alternative to carbapenems for treating ESBL-PE UTI. This strategy might decrease the usage of carbapenem without clinical deterioration. However, it should be noted that SNC therapy may fail in the case of severe sepsis or shock.

Keywords: Carbapenem, Extended-spectrum beta-lactamase, Urinary tract infection

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Introduction

The incidence of infections caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) has steadily increased worldwide [1]. Since carbapenems are regarded as the first-line therapy for ESBL-PE infections, their use has also increased. However, the increasing prevalence of carbapenem-resistant Gram-negative bacteria has become an emerging problem [2]. Frequent exposure to carbapenems may result in the development of carbapenem resistance [3]. Therefore, there is a need for alternatives to carbapenems.

In recent years, several studies have evaluated the potential of non-carbapenem antibiotics as an alternative treatment for ESBL-PE infections [4-10]. Previous studies have demonstrated that non-carbapenem alternatives could be used in limited situations. However, more definitive data are needed for their use for ESBL-PE infections. In addition, most previous studies have targeted bacteremia cases from various origins instead of organ-specific infections. One observational study reported that beta-lactam/beta-lactamase inhibitors were comparable to carbapenems for the treatment of ESBL *Escherichia coli* bacteremia [4]. In contrast, another study reported that the inhibitors appeared to be inferior to carbapenems for the treatment of ESBL bacteremia [11]. These inconclusive findings might be due to different proportions of bacteremia source. Therefore, caution is needed when generalizing these results to each site of infection.

In practice, urinary tract infections (UTI) are one of common organ infections caused by ESBL-PE [12]. Although a few observational studies have evaluated alternatives to carbapenems for the treatment of ESBL-PE UTI, most studies have focused on lower uncomplicated UTI [13,14]. The purpose of this study was to evaluate the possibility of using non-carbapenem antibiotics for treatment of UTI caused by ESBL-PE.

Materials and Methods

1. Ethics statement

This study was approved by the Institutional Review Board of each hospital and performed in accordance with the Principles of the Declaration of Helsinki and Good Clinical Practice. This study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [15].

2. Study subjects

This retrospective study was conducted at 2 university hospitals from October 2010 to December 2012. All cases with a positive urine culture for ESBL-PE were identified in the microbiological database. Among the cases, adult patients (age ≥19 years) were eligible for the analysis if they met the following criteria: 1) UTI based on 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes (urinary tract infection, N390; acute pyelonephritis, N10.03); and 2) fever defined as a body temperature ≥38°C. The exclusion criteria were: 1) the presence of suspicious or confirmatory infectious foci other than UTI; 2) new development of other infection sites during treatment; 3) preexisting use of antibiotics; 4) concomitant use of more than 2 antibiotics; and 5) total duration of antibiotic therapy less than 72 hours.

3. Bacterial isolates and empirical antibiotic groups

Bacterial isolates were identified at the diagnostic laboratory of each hospital using a Vitek-2 system (bioMérieux, Inc., Durham, NC). Vitek-2 cards containing an ESBL test were used. Susceptibility to amikacin, ampicillin, ampicillin-sulbactam, aztreonam, cefepime, cefotaxime, cefotetan, ceftazidime, cephalothin, ciprofloxacin, ertapenem, gentamicin, imipenem, piperacillin-tazobactam, and trimethoprim-sulfamethoxazole was recorded. Empirical therapy was

defined as antibiotics initiated before definite treatment. Definite therapy was defined as antibiotics that were administrated after antimicrobial susceptibility data were available. Empirical antibiotic treatment was divided into 3 groups based on antibiotic classes and susceptibility based on the Clinical Laboratory Standard Institute (CLSI) breakpoints at the time of the study, as follows: carbapenem (C) group, susceptible non-carbapenem (SNC) group, and non-susceptible non-carbapenem (NSNC) group. The C group was treated with carbapenems such as imipenem, meropenem, or ertapenem. The SNC group included cases treated with one of the non-carbapenem antibiotics to which the isolates were noted as susceptible in vitro tests even in the presence of ESBL. The NSNC group was treated inappropriately with non-susceptible antibiotics. Intermediate susceptibility was regarded as non-susceptibility.

4. Clinical assessments

Patient medical records were reviewed to obtain clinical data on age, gender, comorbidities, Charlson comorbidity index (CCI), need for intensive care unit (ICU) care, uropathogens, susceptibility, antimicrobial agents, and duration of antibiotic therapy. Clinical severity (severe sepsis or shock) was assessed according to proposals from the European Association of Urology (EAU) and EAU Section of Infections in Urology (ESIU) [16]. The number of cases treated with carbapenems or susceptible to non-carbapenem antibiotics for empirical and definitive therapy was counted. Treatment success was defined as the resolution of fever and eradication of causative bacteria in urine culture. Otherwise, cases were defined as treatment failures. The total durations of antibiotic therapy and 28-day mortality were also calculated.

5. Statistical analysis

The clinical assessments were compared among the 3 antibiotic groups. Wilcoxon rank sum and t-tests were used to analyze continuous variables between pairs of groups. One-way analysis of variance (ANOVA) was used to compare continuous variables among the 3 groups. Chi-square and Fisher's exact tests were used for bivariate analyses. Variables with P-values < 0.10 in univariate analyses were included as candidate variables in multivariate analyses. Logistic regression with backward selection was used to select variables in the final model. All P-values were two-sided and accepted when $P < 0.05$. All analyses were performed using SPSS version 18.0 (SPSS Korea, Seoul, Korea).

Results

1. Process for selecting eligible patients

During the study period, a total of 153 adult cases were culture-positive for ESBL-PE. Of these 153 cases, 130 patients had UTI. However, 29 patients presented with infectious foci other than UTI, 13 developed other infectious illnesses during treatment, and 4 were treated with combination antibiotic therapy. Therefore, a total of 84 patients were eligible for this study (Fig. 1).

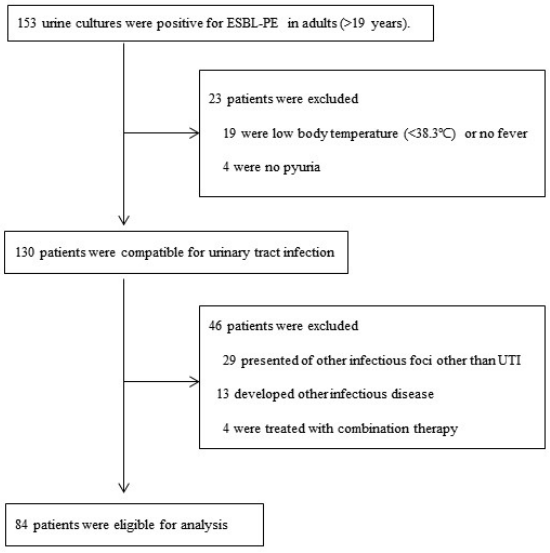

Fig. 1. Flow chart describing the process for patient selection.

2. Baseline characteristics and clinical outcomes

For empirical therapy, a third-generation cephalosporin (n=21, 25.0%) was used most frequently, followed by carbapenems (n=20, 23.8%), beta-lactam beta-lactamase inhibitors (n=20, 23.8%), fluoroquinolones (n=19, 22.6%), fourth-generation cephalosporins (n=2, 2.4%), and aminoglycosides (n=2, 2.4%). The beta-lactam beta-lactamase inhibitors were all piperacillin/tazobactam. There were 41, 23, and 20 patients in the NSNC, SNC, and C groups, respectively. The demographic and clinical characteristics of each group are summarized in Table 1. The majority of subjects were female, but the proportions of female subjects were similar among the 3 groups. The most frequently observed uropathogen was *E. coli*. The distributions of uropathogens were similar among the 3 groups. There were no significant differences in age, comorbidities, CCI, proportions of ICU admission, and severe sepsis or shock cases.

During empirical therapy, only 7 patients (17.1%) in the NSNC group experienced clinical improvement, which was significantly ($P<0.001$) lower than the rates of the SNC (78.3%) and C (95.0%) groups (Table 2). Interestingly, the clinical improvement rates were similar between the SNC and C groups (P=0.192). Regarding definite therapy, no cases were treated with non-susceptible antibiotics. The regimen for 34 patients (82.9%) who were treated with NSNC for empirical therapy was changed to carbapenems for definitive therapy. However, most patients in the SNC group were maintained on the empirical antibiotics as definitive therapy. The therapy for only 7 patients (30.4%) was changed to carbapenems. The 28-day mortal-

Table 1. Characteristics of patients with urinary tract infectionscaused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* based on empirical antibiotic groups

	NSNC group (n=41)	SNC group (n=23)	C group (n=20)	*P*-value
Age, mean±SD, years	69.5±12.0	70.9±17.3	73.8±14.0	0.544
Gender, female, n (%)	31 (75.6)	15 (65.2)	13 (65.0)	0.575
Comorbidity, n (%)				
Diabetes mellitus	7 (17.1)	4 (17.4)	5 (25.0)	0.739
Cerebrovascular accident	19 (46.3)	8 (34.8)	8 (40.0)	0.657
Dementia	2 (4.9)	1 (4.3)	2 (10.0)	0.679
Hemiplegia	5 (12.2)	3 (13.0)	0 (0)	0.250
Myocardial infarction	2 (4.9)	0 (0)	1 (5.0)	0.556
Congestive heart failure	1 (2.4)	3 (13.0)	0 (0)	0.083
Chronic obstructive lung disease	1 (2.4)	1 (4.3)	0 (0)	0.647
Chronic kidney disease	1 (2.4)	2 (8.7)	2 (10.0)	0.407
Liver cirrhosis	2 (4.9)	2 (8.7)	1 (5.0)	0.611
Malignancy	6 (14.6)	2 (8.7)	2 (10.0)	0.746
None	6 (14.6)	3 (13.0)	0 (0)	0.203
Charlson comorbidity index, median (interquartile range)	5.0 (4.0-7.0)	5.0 (3.0-6.0)	5.0 (4.25-5.0)	0.546
ICU admission, n (%)	17 (41.5)	10 (43.5)	11 (55.0)	0.596
Severe sepsis or shock, n (%)	14 (34.1)	5 (21.7)	5 (25.0)	0.528
Uropathogen, n (%)				0.691
Escherichia coli	29 (70.7)	18 (78.3)	14 (70.0)	
Klebsiella pneumoniae	8 (19.5)	2 (8.7)	4 (20.0)	
Proteus mirabilis	3 (7.3)	2 (8.7)	1 (5.0)	
Enterobacter cloacae	1 (2.4)	1 (4.3)	0 (0)	
Providencia	0 (0)	0 (0)	1 (5.0)	

Abbreviations: NSNC, non-susceptible non-carbapenem; SNC, susceptible non-carbapenem; C, carbapenem.

Table 2. Differences in clinical outcomes among empirical antibiotic groups

	NSNC group (n=41)	SNC group (n=23)	C group (n=20)	*P*-value
Clinical improvement, n (%)	7 (17.1)	18 (78.3)	19 (95.0)	<0.001
Selection of carbapenem for definite therapy, n (%)	34 (82.9)	7 (30.4)	18 (90.0)	<0.001
Selection of susceptible-non carbapenem for definite therapy, n (%)	7 (17.1)	16 (69.6)	2 (10.0)	<0.001
Total duration of antibiotic therapy, mean±SD	14.4±3.7	11.9±5.5	10.7±3.6	0.005
28-day mortality, n (%)	1 (2.4)	1 (4.3)	2 (10.0)	0.426

Abbreviations: NSNC, non-susceptible non-carbapenem; SNC, susceptible non-carbapenem; C, carbapenem.

Table 3. Factors associated with failure of empirical treatment for urinary tract infections caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae*

Variable	Success group (n=44)	Failure group (n=40)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, mean±SD, years	71.3±15.6	70.5±12.3	…	0.803	…	…
Gender, female, n (%)	29 (65.9)	30 (75.0)	1.27 (0.74-2.19)	0.363	…	…
Charlson comorbidity index, median (interquartile range)	5.0 (4.0-5.0)	5.0 (4.25-7.0)	…	0.048	1.31 (0.92-1.89)	0.139
ICU admission, n (%)	17 (38.6)	21 (52.5)	1.76 (0.74-4.18)	0.202	…	…
Severe sepsis or shock, n (%)	7 (15.9)	17 (42.5)	3.91 (1.41-10.87)	0.007	8.04 (1.50-43.06)	0.015
Uropathogen, n (%)						
Escherichia coli	30 (68.2)	31 (77.5)	1.61 (0.61-4.27)	0.339	…	…
Klebsiella pneumoniae	10 (22.7)	4 (10.0)	0.38 (0.11-1.32)	0.118	…	…
Proteus mirabilis	2 (4.5)	4 (10.0)	2.33 (0.40-13.49)	0.418	…	…
Enterobacter cloacae	1 (2.3)	1 (2.5)	1.10 (0.07-18.23)	1.000	…	…
Providencia	1 (2.3)	0 (0)	…	1.000	…	…
Empirical use, n (%)						
NSNC	7 (15.9)	34 (85.0)	29.95 (9.15-98.03)	<0.001	156.55 (14.06-1742.81)*	<0.001
SNC	18 (40.9)	5 (12.5)	0.21 (0.07-0.63)	0.004	6.38 (0.59-69.27)*	0.128
C	19 (43.2)	1 (2.5)	0.03 (0.01-0.27)	<0.001		

Ellipses indicate not available, *compared with carbapenem.
Abbreviations: NSNC, non-susceptible non-carbapenem; SNC, susceptible non-carbapenem; C, carbapenem.

ities did not differ significantly among the 3 groups. However, the total duration of antibiotic therapy was significantly longer in the NSNC group compared to that in the SNC and C groups (*P*=0.005).

3. Risk factors for empirical treatment failure

In multivariate analysis, severe sepsis or shock was independently associated with treatment failure after adjusting for other clinical factors in the NSNC group (odds ratio [OR], 8.04; 95% confidence interval [CI], 1.50-43.06; *P*=0.015) compared with the C group (OR, 156.55; 95% CI, 14.06-1742.81; *P*<0.001) (Table 3). The SNC group was not associated with increased treatment failure compared to the C group.

Discussion

There is limited clinical evidence regarding the use of non-carbapenem antibiotics for treatment of

ESBL-PE UTI. Several studies showed the possibility of using fosfomycin, pivmecillinam, fluoroquinolones, trimethoprim, and beta-lactam beta-lactamase inhibitors for the treatment of ESBL-PE UTI [13,17,18]. However, those reports focused mostly on cystitis. To the best of our knowledge, only one study focused on UTI to compare the use of cefmetazole to that of carbapenem, concluding that cefmetazole might be a useful alternative to carbapenem for the treatment of UTI caused by ESBL-PE [8].

As expected, the NSNC therapy was less effective than the carbapenem therapy in this study. Interestingly, the SNC therapy had a statistically similar clinical improvement rate. The only factor associated with treatment failure was severe sepsis or shock. This finding suggests that, if susceptible *in vitro*, antibiotics including beta-lactam beta-lactamase inhibitors, fluoroquinolones, fourth-generation cephalosporins, and aminoglycosides, could be considered as alternatives to carbapenems for the treatment of mild to moderate ESBL-PE UTI.

In this study, most patients who were treated with NSNC as empirical therapy were changed to carbapenems for definitive therapy. However, most patients in the SNC treatment group continued to use the same antibiotic as a definitive therapy. The total duration of antibiotic therapy was significantly longer in the NSNC group compared to that in the SNC group. Because the empirical NSNC therapy frequently resulted in initial treatment failure, clinicians might choose carbapenems as a definite therapy after confirming ESBL-PE. In contrast, clinicians maintained the empirical SNC antibiotics for definite therapy, which might be due to clinical improvement during the empirical period. In this way, the empirical use of SNC antibiotics based on the resistance patterns in the community or hospital could naturally reduce carbapenem usage.

This study had several limitations. First, we were not able to assess the efficacy of each SNC antibiotic agent due to the small sample size. Because of strict inclusion criteria, we could not collect enough data. In addition, this study lacked data regarding the true laboratory-determined minimum inhibitory concentrations (MIC) of each antibiotic agent. Finally, due to the retrospective nature of this study, unmeasured confounders might have influenced the results. Nevertheless, this small study revealed that SNC antibiotics could be used in mild to moderate cases of febrile ESBL-PE acute pyelonephritis.

Although carbapenems are the drug of choice for treatment of ESBL-PE UTI, SNC antibiotics could be alternatives. However, SNC antibiotics may fail in case of severe sepsis or shock. Prospective randomized control study is merited to confirm the efficacy of susceptible non-carbapenem antibiotics in cases of mild to moderate UTI.

Summary

ESBL을 생성하는 균주에 의한 요로 감염에서 카바페넴 계열 이외의 항생제를 사용할 수 있는지를 후향적으로 평가한 연구이다. 만약 in vitro 결과에서 감수성이 있다면 사용이 가능하다는 결과이나 환자의 중증도가 높다면 실패할 수 있음을 강조하였다. 이번 연구 결과를 바탕으로 전향적 연구를 기대해 본다.

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