



# Single-dose amikacin plus 7 days of amoxicillin/clavulanate to treat acute cystitis caused by extended-spectrum beta-lactamase-producing *Escherichia coli*: A retrospective cohort study

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**Purpose:** Treatment options for urinary tract infection (UTI) caused by extended-spectrum beta-lactamase (ESBL)-producing organisms are limited other than carbapenem. Accordingly, clinicians should investigate alternative antimicrobial options for limited infection. This study was performed to assess the efficacy of single-dose amikacin and a 7-day oral regimen of amoxicillin/clavulanate for the treatment of acute cystitis caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*.

**Materials and Methods:** A single-dose amikacin and 7-day oral amoxicillin/clavulanate regimen was given to all patients with acute cystitis or recurrent cystitis between May 2016 and October 2018. We conducted a retrospective cohort study assessing the efficacy of this regimen for the treatment of UTI due to ESBL-producing organisms. Both clinical and laboratory efficacy were assessed a minimum of 7 days and a maximum of 14 days after the completion of treatment.

**Results:** A total of 47 patients were enrolled in this study. *E. coli* and *K. pneumoniae* were isolated in 44 patients (93.6%) and 3 patients (6.4%), respectively. Of the 47 enrolled, 39 patients (83.0%) showed sterile culture results on follow-up. Thirty-seven patients (78.7%) showed improvement of symptoms. Of 8 patients who showed bacterial persistence, 4 patients showed ESBL-producing *E. coli*, whereas 4 patients showed non-ESBL *E. coli* on follow-up cultures. During follow-up, 12 patients experienced the recurrence of acute cystitis with a median recurrence period of 2.5 months.

**Conclusions:** The combination of amoxicillin/clavulanate and amikacin may be an alternative to carbapenem treatment in patients with acute cystitis caused by ESBL-producing Enterobacteriaceae.

**Keywords:** Amikacin; Amoxi-clavulanate; Cystitis; *Escherichia coli*

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## INTRODUCTION

The incidence of lower urinary tract infections (UTIs) due to extended-spectrum beta-lactamase (ESBL)-producing

Enterobacteriaceae is increasing worldwide. These infections are not restricted to nosocomial infections but are also now frequently observed in the community setting [1]. More importantly, two-thirds of UTIs caused by ESBL-producing En-

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terobacteriaceae are reported to recur with ESBL-producing Enterobacteriaceae [2].

The treatment options for ESBL-producing strains are extremely limited owing to their extensive drug resistance. Although carbapenem has been considered as the treatment of choice for ESBL-producing lower UTIs [3,4], daily parenteral administration of this drug is not suitable and is inconvenient in an outpatient setting. Most of all, carbapenem is considered to be the last resort for severe infection with ESBL-producing strains; as such, the use of carbapenem should be restricted to cases of severe infection.

Thus, it is essential to investigate alternative noncarbapenem treatment options with effective oral antimicrobial agents. In previous studies, amikacin was shown to be highly effective for treating ESBL-producing *E. coli* in South Korea [5,6]. The rate of resistance to amikacin was extremely low, whereas resistance to gentamicin and tobramycin was high, with rates of over 20% [5,6]. Many *in vitro* studies have demonstrated the bactericidal activity of amoxicillin-clavulanate against ESBL-producing strains; however, few clinical studies are available to validate these results in clinical practice [7-9]. Thus, we conducted this study to assess the efficacy of a regimen of single-dose amikacin and 7 days of oral amoxicillin/clavulanate as an alternative treatment for acute cystitis caused by ESBL-producing *E. coli* and *K. pneumoniae*. This observational cohort study was possible because from 2016 to 2018 all patients with acute cystitis were given a single dose of amikacin and 7 days of amoxicillin/clavulanate empirically in our single center until culture results were reported.

## MATERIALS AND METHODS

### 1. Study design and patients

This retrospective observational study was conducted between May 2016 and October 2018 at Korea University Guro Hospital, which is a tertiary referral teaching hospital. All female patients who were suspected of having lower UTIs on the basis of their symptoms and urine analysis were prescribed a single dose of amikacin (250 mg) and 7 days of amoxicillin/clavulanate (500 mg/125 mg) empirically irrespective of culture results, which were usually reported 7 days after. Among these patients, we retrospectively recruited those with ESBL-producing Enterobacteriaceae.

Eligibility criteria for inclusion in this study were: (1) adults (age >18 years); (2) presenting with at least one of the typical symptoms of dysuria, frequency, urgency, or suprapubic pain; (3) pyuria (>5 white blood cells per high-power field on microscopic examination of centrifuged urine); (4) having culture-proven ESBL-producing *E. coli* or *K. pneu-*

*moniae* in the urine ( $\geq 10^5$  colony-forming units/mL) before initial treatment; and (5) receiving a single dose of amikacin intramuscularly and 7 days of oral amoxicillin/clavulanate.

The exclusion criteria were as follows: (1) patients with pyelonephritis (having fever or flank pain); (2) patients requiring hospitalization owing to limited mobility; (3) patients who had predisposing factors for UTIs such as anatomical abnormality (cystocele, diverticulum, fistula, prior urinary tract surgery, bladder or renal calculi, and vesicoureteral reflux), neurogenic bladder, or the presence of a urethral catheter; (4) immunocompromised state except for diabetes mellitus (DM); (5) history of allergy to aminoglycosides; (6) preexisting renal insufficiency; (7) pregnancy; and (8) patients with insufficient follow-up data.

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Korea University Guro Hospital (approval number: 2019GR0440). Informed consent was waived because of the retrospective nature of the study.

### 2. Data collection

We collected the patients' comprehensive medical history, including age, body mass index, underlying comorbidities (DM, malignancy, cerebrovascular accident, and neurogenic bladder), history of UTI episodes in the previous 12 months, and history of Foley catheterization or intermittent catheterization 1 month prior to the index UTI episode. Clinical symptoms and laboratory data (initial urinalysis, urine cultures, antimicrobial susceptibility profiles, and renal function) were assessed before and within 2 weeks after treatment to evaluate clinical and microbial efficacy.

### 3. Clinical and microbiological assessments

Urinary specimens were obtained by the midstream, clean-catch voided method. Antimicrobial susceptibility tests and species identification were conducted by means of a semi-automated system (VITEK; bioMérieux, Hazelwood, MO, USA). The presence of ESBL-producing species was confirmed by the synergy method or disc combinations. Results were interpreted according to the Clinical and Laboratory Standards Institute criteria [10].

Microbiological cure was defined as a sterile urine culture after amikacin and amoxicillin/clavulanate therapy. Clinical cure was defined as complete resolution of all presenting symptoms of UTI after amoxicillin/clavulanate therapy. Nephrotoxicity was defined as an increase in serum creatinine of  $\geq 0.5$  mg/dL [11].

## RESULTS

During the course of the study, a total of 114 patients were diagnosed with UTI caused by ESBL-producing *E. coli* or *K. pneumoniae*. Of the 114 patients, we excluded patients with pyelonephritis (n=14), anatomical abnormalities (n=5), neurogenic bladder (n=2), immunocompromised state (n=9), or preexisting renal insufficiency (n=3); patients requiring hospitalization (n=3); patients treated with other antibiotic agents (n=10); and patients with limited data on follow-up (n=21) to give a final cohort for analysis of 47 patients. The patients' clinical characteristics are summarized in Table 1. The mean age of the patients was 62.9±15.3 years. Of the 47 patients, 12.8% (6/47) had at least one risk factor for UTI, 44.7% (21/47) had a previous history of a UTI episode within 1 year, and 29.8% (14/47) had experienced recurrent UTI more than three times in the preceding year.

The initial urine culture study showed that *E. coli* and *K. pneumoniae* accounted for 93.6% (44/47) and 6.4% (3/47)

**Table 1.** Clinical characteristics of the patients (n=47)

Patient characteristic	Value
Age (y)	62.9±15.3
Body mass index (kg/m <sup>2</sup> )	23.3±3.1
DM	4 (8.5)
CVA	2 (4.3)
Postmenopausal	39 (83.0)
Previous history of UTIs within a year	21 (44.7)
History of recurrent UTI >3 times	14 (29.8)
Microorganisms, identified	
<i>Escherichia coli</i>	44 (93.6)
<i>Klebsiella pneumoniae</i>	3 (6.4)
Clinical and microbiological outcomes	
Improved symptoms	37 (78.7)
Bacterial eradication	39 (83.0)

Values are presented as mean±standard deviation or number (%). DM, diabetes mellitus; CVA, cerebrovascular accident; UTI, urinary tract infection.

of the pathogens isolated from the patients, respectively. The antibiotics susceptibility profile of ESBL-producing *E. coli* and *K. pneumoniae* is presented in Table 2. All strains were susceptible to amikacin and ertapenem. Twenty-nine patients (61.7%) showed susceptibility to amoxicillin/clavulanate and 14 patients (29.8%) showed intermediate susceptibility, respectively. The highest resistance rate was to ciprofloxacin (83.0%; Table 2).

Overall microbiological cure was observed in 39 patients (83.0%), and clinical cure was achieved in 37 patients (78.7%) within 2 weeks of treatment. Of 8 patients who showed bacterial persistence, 4 patients showed ESBL-producing *E. coli*, whereas 4 patients showed non-ESBL-producing *E. coli* in a subsequent urine culture after treatment (Fig. 1). Five of eight patients who showed bacterial persistence showed poor clinical improvement after treatment with single-dose amikacin and 7 days of oral amoxicillin/clavulanate. Those patients repeated treatment with single-dose amikacin and 7 days of oral amoxicillin/clavulanate and finally improved. Twelve patients showed recurrence during follow-up and 10 patients had recurrences caused by ESBL-producing *E. coli*. All 10 patients who recurred with ESBL-producing *E. coli* had previously been diagnosed with ESBL-producing *E. coli*. The median time to recurrence was 25 months (IQR, 20 to 38 months).

All the patients showed full compliance with treatment. None of the patients experienced significant nephrotoxicity. Regarding ototoxicity, no patients reported changes in hearing, tinnitus, vertigo, or headache. No other serious adverse events were reported.

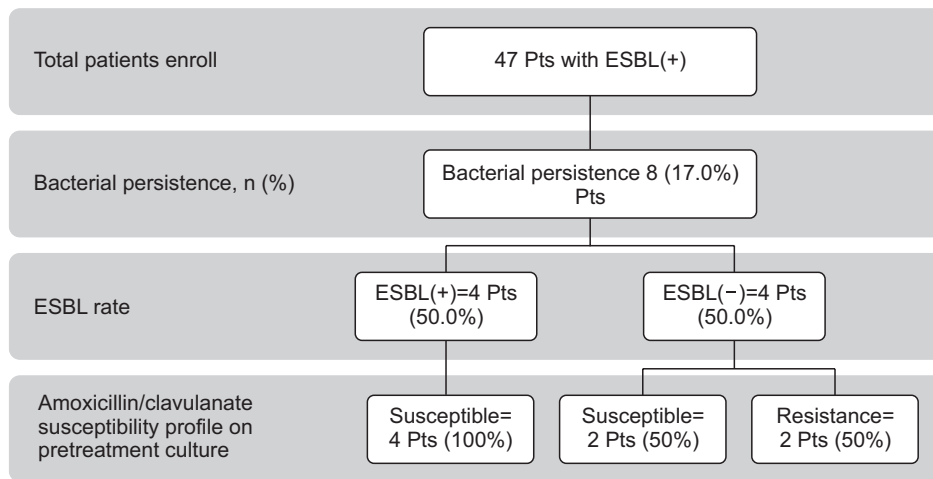
## DISCUSSION

Managing UTI caused by ESBL-producing Enterobacteriaceae showing multidrug resistance is a challenge, especially in the outpatient setting. Although the most effective treatment against ESBL-producing Enterobacteriaceae is the intrave-

**Table 2.** Antimicrobial susceptibility profile of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* before treatment and persistence of ESBL-producing species after treatment

Antibiotics	Pretreatment (n=47)			Post-treatment (n=8)		
	Susceptible	Intermediate	Resistance	Susceptible	Intermediate	Resistance
Amikacin	47 (100.0)	-	-	8 (100.0)	-	-
Amoxicillin/clavulanate	29 (61.7)	14 (29.8)	4 (8.5)	7 (87.5)	-	1 (12.5)
Cefoxitin	36 (76.6)	5 (10.6)	6 (12.8)	6 (75.0)	-	2 (25.0)
Ciprofloxacin	8 (17.0)	-	39 (83.0)	2 (25.0)	-	6 (75.0)
Ertapenem	47 (100.0)	-	-	8 (100.0)	-	-

Values are presented as number (%). ESBL, extended-spectrum beta-lactamase; -, not available.



**Fig. 1.** Schematic of the study results. Pts, points; ESBL, extended-spectrum beta-lactamase; ESBL(+), patients with acute cystitis caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*; ESBL(-), patients with acute cystitis caused by non-ESBL-producing organisms.

nous administration of carbapenems [12], outpatient parenteral antibiotic therapy results in patient inconvenience and raises issues of cost-effectiveness. Most of all, carbapenems should be saved for patients with severe infections to prevent the development of carbapenemase-producing organisms [13,14]. Therefore, a number of studies have attempted to identify alternatives to carbapenems [15-17]. Recently, once-daily amikacin monotherapy was shown to be efficacious for managing UTI caused by ESBL-producing Enterobacteriaceae [6,18]; however, concern remains over the inconvenience of daily visits to the hospital and of nephrotoxicity by aminoglycoside antibiotics. Therefore, it is essential to replace the intravenous antibiotic regimen with an oral antibiotic regimen, especially in patients with mild-to-moderate lower UTIs.

Previously, data from *in vitro* studies demonstrated that β-lactam/β-lactam inhibitor combinations (BLBLI) such as amoxicillin/clavulanate or piperacillin/tazobactam remain active against a considerable proportion of ESBL-producing Enterobacteriaceae [9,19]. Additionally, in a recent *in vitro* study, ESBL-producing *E. coli* showed high susceptibility to BLBLI treatment when BLBLI was used as a combination therapy with amikacin [20]. However, clinical data for the use of combination therapy of amikacin and amoxicillin/clavulanate for the treatment of lower UTI caused by ESBL-producing Enterobacteriaceae are scarce. To the best of our knowledge, the present study is the first to examine the clinical and microbiological outcomes of lower UTIs due to ESBL-producing *E. coli* and *K. pneumoniae* treated with amikacin and amoxicillin/clavulanate in an outpatient setting.

In this study, we found that the overall rates of microbiological cure and clinical cure were 83.0% and 78.7%, respectively, after treatment with single-dose amikacin and 7 days of oral amoxicillin/clavulanate. Previous studies of

alternatives to carbapenem, including daily amikacin and several oral antibiotic agents such as fluoroquinolones, fosfomycin, or nitrofurantoin, reported microbiological and clinical cure rates ranging from 68% to 91.7% and from 69% to 94.1%, respectively [18,21-24]. Those clinical studies, including other clinical studies involving outpatient therapy in acute cystitis caused by ESBL-producing Enterobacteriaceae, are summarized in Table 3. The current study results showed therapeutic efficacies consistent with previously reported efficacies of those alternative antibiotic agents. Additionally, recent Korean domestic retrospective studies reported excellent therapeutic effects of BLBLI and amikacin against bacteremia and UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae* [6,25]. These observations suggest that combination treatment including amikacin and amoxicillin/clavulanate could be an alternative to carbapenem treatment.

However, it is unclear whether the effect of treatment is due to amikacin or to amoxicillin/clavulanate. The antibiotics seem to have a synergic effect. Previous studies demonstrated antimicrobial synergy with a β-lactam and aminoglycoside combination treatment that allows for different mechanisms of bactericidal activity [26,27]. Additionally, a recent study showed that the combination of BLBLI with amikacin was the most effective regimen among other combinations including ceftazidime, cefotaxime, cefepime, and ciprofloxacin [20].

There is controversy regarding the efficacy of amoxicillin/clavulanate treatment in infections caused by ESBL-producing Enterobacteriaceae. Actually, many authors focused on other antibiotics including nitrofurantoin, fosfomycin, and pivmecillinam as alternative treatments for home-based therapy rather than amoxicillin/clavulanate [23,28-30]. Unfortunately, nitrofurantoin and pivmecillinam are not available in this country. Additionally, susceptibil-

**Table 3.** Clinical studies of outpatient therapy in patients with acute cystitis caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae

Author	Study type	Country	Antibiotic agent, daily dose, and duration of therapy	Number of patients (complicated cystitis/uncomplicated cystitis)	Microbiology cure rate (%)	Clinical cure rate (%)
Jansåker et al. [28]	Prospective	Sweden, Denmark	Pivmecillinam, 200 or 400 mg daily, 3–>10 days	39 (13/26)	79.0	84.0
Ipekci et al. [18]	Retrospective cohort	Turkey	Amikacin, 15 mg/kg once daily, 10 days	36 (0/36)	94.1	97.2
Bielen and Likic [22]	Retrospective	Croatia	Fosfomycin, 3 g every other day, 1–7 doses	42 (42/0)	50.0	71.4
Tumturk et al. [21]	Retrospective	Turkey	Fosfomycin, 3 g every other day, 2 doses	19 (0/19)	70.8	73.6
Tasbakan et al. [23]	Retrospective	Turkey	Nitrofurantoin, 50 mg 4 times daily, 14 days	45 (no record)	69.0	68.0

ity testing for fosfomycin is not available at our institution, which precludes us from conducting microbiological studies. Although the efficacy of amoxicillin/clavulanate for treating UTIs caused by ESBL-producing Enterobacteriaceae is controversial, a recent post hoc analysis study suggested that amoxicillin/clavulanate and piperacillin/tazobactam are not inferior to carbapenem in ESBL-producing *E. coli* bacteremia, and thus can be used as an alternative to carbapenem [17]. Also, amoxicillin/clavulanate maintained *in vitro* activity even at a high bacterial load with ESBL-producing *E. coli*, unlike piperacillin/tazobactam [9].

There were several limitations to this study. First, this was a single-center, retrospective study with a relatively small number of patients. However, this is the first clinical study to provide important data on the feasibility of combination treatment of amikacin and amoxicillin/clavulanate for treating lower UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae*. Second, there was no control group with which to compare the efficacy of the current antibiotic regimen with other antibiotic regimens. Further studies are needed to evaluate the efficacy, adverse events, and cost-effectiveness of single-dose amikacin and 7 days of oral amoxicillin/clavulanate compared with other antibiotic regimens.

## CONCLUSIONS

This is the first clinical study to show that single-dose amikacin and 7 days of oral amoxicillin/clavulanate were effective as an alternative treatment for acute cystitis caused by ESBL-producing *E. coli* and *K. pneumoniae*. Furthermore, the current antibiotic regimen minimizes amikacin administration, which eliminates the concern regarding nephrotoxicity. In addition, it provides economic savings by allowing patients to be treated with a single hospital visit. However, it

will be necessary to conduct further randomized controlled studies to determine the effectiveness of single-dose amikacin plus 7 days of oral amoxicillin/clavulanate treatment in patients with acute cystitis caused by ESBL-producing Enterobacteriaceae.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

## AUTHORS' CONTRIBUTIONS

Research conception and design: Mi Mi Oh and Sun Tae Ahn. Data acquisition: Sun Tae Ahn, Dong Hyun Lee, and Da Eun Han. Statistical analysis: Dong Hyun Lee and Da Eun Han. Data analysis and interpretation: Sun Tae Ahn, Jong Wook Kim, and Mi Mi Oh. Drafting of the manuscript: Sun Tae Ahn. Critical revision of the manuscript: all authors. Administrative, technical, or material support: Hong Seok Park and Du Geon Moon. Supervision: Mi Mi Oh. Approval of final manuscript: all authors.

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