

Ceftazidime-avibactam activity against urinary carbapenem resistance *Escherichia coli* and *Klebsiella pneumoniae* isolates

Siavosh Salmanzadeh-Ahrabi^{1*}, Farzaneh Salehinejad², Masoud Sokhanvar-Mahani³

¹Women Research Center, Alzahra University, Tehran, Iran

²Department of Biotechnology, Faculty of Basic Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran

³Department of Microbiology and Microbial Biotechnology, Faculty of Life Sciences and Biotechnology, Shahid Beheshti University, Tehran, Iran

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ABSTRACT

Background and Objectives: Urinary tract infections (UTIs) are among the most prevalent bacterial infections in women, with *Escherichia coli* and *Klebsiella pneumoniae* as leading causative pathogens. The emergence of multidrug-resistant (MDR) and carbapenem-resistant strains poses a significant therapeutic challenge. Ceftazidime-avibactam (CZA) has shown activity against β -lactamase-producing Gram-negative bacteria; however, data on its activity against urinary carbapenem-resistant isolates remain limited. This study aimed to determine CZA activity against urinary carbapenem-resistant *E. coli* and *K. pneumoniae* isolates.

Materials and Methods: In this cross-sectional study, antimicrobial susceptibility testing was performed using the disk diffusion method according to CLSI guidelines. The tested antibiotics included carbapenems, third-generation cephalosporins, aminoglycosides, levofloxacin, fosfomycin, and CZA. Extended-spectrum β -lactamase (ESBL) production was assessed using the combined-disk method.

Results: A total of 76 previously collected urinary bacterial isolates, including 44 (57.9%) *E. coli* and 32 (42.1%) *K. pneumoniae* isolates were included in this study. Carbapenem resistance was detected in 25.0% (11/44) of *E. coli* and 28.1% (9/32) of *K. pneumoniae* isolates. ESBL production was observed in 36.4% and 37.5%, respectively. Overall, CZA susceptibility was 68.2% for *E. coli* and 68.7% for *K. pneumoniae*, decreasing to 27.3% and 22.2%, respectively, among carbapenem-resistant isolates. Overall, 25.0% of carbapenem-resistant isolates remained susceptible to CZA. Fosfomycin susceptibility was 81.8% and 46.9% among *E. coli* and *K. pneumoniae*, respectively.

Conclusion: CZA demonstrated substantial in vitro activity against urinary *E. coli* and *K. pneumoniae* isolates; however, its activity was markedly reduced among carbapenem-resistant strains. These findings highlight the importance of susceptibility-guided use of CZA and continued surveillance of antimicrobial resistance.

Keywords: Urinary tract infections; *Escherichia coli*; *Klebsiella pneumoniae*; Carbapenem resistance; Ceftazidime-avibactam

*Corresponding author: Siavosh Salmanzadeh-Ahrabi, Ph.D, Women Research Center, Alzahra University, Tehran, Iran. Tel: +98-21-88044040 Fax: +98-21-88035187 Email: s.salmanzadeh@alzahra.ac.ir

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, with women being particularly susceptible due to anatomical and physiological factors (1). *Escherichia coli* and *Klebsiella pneumoniae* are the primary pathogens responsible for UTIs, accounting for the majority of both community- and hospital-acquired cases (2). The rising prevalence of multidrug-resistant (MDR) strains, particularly carbapenem-resistant Enterobacteriaceae (CRE), has become a major clinical concern, severely limiting treatment options and contributing to increased morbidity, healthcare costs, and mortality (3). Carbapenems have long been considered the last line of defense against serious infections caused by MDR Gram-negative bacteria. However, the emergence and global spread of carbapenem-resistant *E. coli* and *K. pneumoniae* have significantly undermined their effectiveness (4). This alarming trend highlights the urgent need for novel therapeutic agents capable of overcoming these resistance mechanisms (5).

Ceftazidime-avibactam, a combination of a third-generation cephalosporin with a non- β -lactam β -lactamase inhibitor, has shown potent activity against a wide range of β -lactamase-producing Gram-negative bacteria (GNB), including carbapenem-resistant strains (6). Avibactam effectively inhibits class A, some class C, and selected class D β -lactamases, restoring the antibacterial activity of ceftazidime against otherwise resistant pathogens (7). Both clinical and in vitro studies have demonstrated promising efficacy of ceftazidime-avibactam in complicated UTIs, bloodstream infections, and hospital-acquired pneumonia caused by resistant GNB (8). Despite these encouraging findings, data specifically examining the activity of ceftazidime-avibactam against urinary carbapenem-resistant *E. coli* and *K. pneumoniae* isolates from women remain limited, especially within local populations (9). Understanding the in vitro susceptibility patterns of these pathogens is crucial for guiding empirical therapy and informing antimicrobial stewardship strategies (10). In this context, the present study aims to evaluate the in vitro activity of ceftazidime-avibactam against carbapenem-resistant *E. coli* and *K. pneumoniae* isolated from urine samples of women, providing essential insights into its potential as an effective therapeutic option for managing challenging UTIs.

MATERIALS AND METHODS

Sampling and bacterial isolation. This cross-sectional study was conducted from December 2024 to May 2025 using previously collected and archived urinary bacterial isolates. A total of 76 clinical isolates, including 44 (57.9%) *E. coli* and 32 (42.1%) *K. pneumoniae* isolates, recovered from urine specimens were included in the study. The archived isolates were retrieved and subjected to antimicrobial susceptibility testing and evaluation of ceftazidime-avibactam activity.

Antimicrobial susceptibility testing. Antimicrobial susceptibility testing was performed using the disk diffusion (Kirby–Bauer) method according to the Clinical and Laboratory Standards Institute (CLSI) M100, 34th edition guidelines (11). The antibiotics tested included cefazolin (CZ; 30 μ g), azithromycin (AZT; 15 μ g), gentamicin (GN; 10 μ g), tobramycin (TOB; 10 μ g), ceftazidime (CAZ; 30 μ g), ceftazidime-avibactam (CZA; 30/20 μ g), amikacin (AN; 30 μ g), levofloxacin (LEV; 5 μ g), trimethoprim-sulfamethoxazole (SXT; 1.25/23.75 μ g), aztreonam (ATM; 30 μ g), ampicillin (AMP; 10 μ g), and cefixime (CFM; 5 μ g). All antibiotic disks were obtained from Padtan Teb Co., except ceftazidime-avibactam, fosfomycin (FM; 200 μ g), and meropenem (MEN; 10 μ g), which were supplied by Mast Group Ltd. Mueller-Hinton agar plates were inoculated with standardized bacterial suspensions (0.5 McFarland standard), and disks were applied. Plates were incubated at $35 \pm 2^\circ\text{C}$ for 16-18 hours. Inhibition zones were measured in millimeters and interpreted as susceptible, intermediate, or resistant according to CLSI guidelines. All tests were performed in duplicate for accuracy and reproducibility. *E. coli* ATCC 25922 and *K. pneumoniae* strain ATCC 13883 were used as a quality control.

Detection of extended-spectrum β -lactamases (ESBLs). Extended-spectrum β -lactamase (ESBL) production was assessed using the combined-disk method. Briefly, ceftazidime (30 μ g) and cefotaxime (30 μ g) disks, alone and in combination with clavulanic acid (10 μ g), were placed on Mueller–Hinton agar inoculated with the test isolates. The plates were incubated at $35 \pm 2^\circ\text{C}$ for 16-18 h. An increase of ≥ 5 mm in the inhibition zone diameter for either ceftazidime or cefotaxime in combination with clavulanic acid, compared with the corresponding antibiotic

alone, was considered positive for ESBL production according to CLSI M100, 34th edition guidelines (12).

Statistical analysis. Descriptive statistics were used to summarize urine culture and antibiotic susceptibility testing of the microbial population. Categorical variables were presented as frequencies and percentages. A p-value less than 0.05 were considered statistically significant. All analyses were conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 44 (57.9%) *E. coli* and 32 (42.1%) *K. pneumoniae* isolates were included. Carbapenem resistance was detected in 25.0% of *E. coli* and 28.1% of *K. pneumoniae* isolates. High resistance rates were also observed to the tested cephalosporins, with cefazolin resistance recorded in 65.9% of *E. coli* and 59.4% of *K. pneumoniae* isolates, and cefixime resistance in 70.5% and 50.0%, respectively. Aminoglycosides, levofloxacin, and ceftazidime–avibactam showed comparatively higher in vitro activity against both species. Fosfomycin demonstrated high activity against *E. coli*, with 81.8% of isolates susceptible, whereas susceptibility was lower among *K. pneumoniae* isolates (46.9%) (Table 1).

Among the carbapenem-resistant isolates, CREC and CRKP exhibited high levels of resistance to most tested antibiotics, particularly ATM and AN in CREC, and CZ, ATM, and TOB in CRKP, with resistance rates ranging from 70% to 100%. In contrast, the carbapenem-sensitive isolates (CSEC and CSKP) remained largely susceptible, with susceptibility exceeding 60-90% for most agents, especially GN, LEV, and FM. Notably, LEV and GN retained moderate activity against CREC and CRKP, whereas β -lactam agents such as CZ, CAZ, and CFM showed limited effectiveness against these resistant strains (Table 2).

Among the isolates, 16 (36.4%) of *E. coli* and 12 (37.5%) of *K. pneumoniae* were identified as ESBL producers, and 23 *E. coli* and 18 *K. pneumoniae* isolates were classified as multidrug-resistant (MDR). Among the carbapenem-resistant isolates, 3 (27.3%) CREC and 2 (22.2%) CRKP isolates remained susceptible to CZA, corresponding to an overall CZA susceptibility rate of 25.0% (5/20). Fosfomycin sus-

ceptibility was observed in 6 (54.5%) CREC and 1 (11.1%) CRKP isolates. Among the MDR isolates, the most common resistance pattern involved a combination of β -lactams, aminoglycosides, and fluoroquinolones, accounting for 26.1% of MDR *E. coli* isolates and 33.3% of MDR *K. pneumoniae* isolates. Other frequent resistance patterns included combinations of β -lactams with aminoglycosides and folate pathway inhibitors, as well as aminoglycosides with folate pathway inhibitors and phosphonic acids, indicating resistance across multiple antimicrobial classes (Table 3).

DISCUSSION

UTI is among the most common bacterial infections in women and represents a substantial burden on outpatient healthcare services and antibiotic use worldwide. Anatomical and physiological factors contribute to the higher susceptibility of women to UTIs and recurrent infections (13, 14). In the present study, *E. coli* (n = 44) and *K. pneumoniae* (n = 32) were the most frequently recovered organisms, consistent with their established role as major uropathogens. Carbapenem resistance was detected in 25.0% of *E. coli* and 28.1% of *K. pneumoniae* isolates, indicating a considerable burden of antimicrobial resistance in the studied population. These findings are broadly consistent with previous Iranian and international reports (15-17). Differences in reported resistance rates may reflect variations in patient populations, antibiotic exposure, healthcare settings, and local epidemiological characteristics.

Resistance to the tested cephalosporins was prominent, with cefazolin resistance observed in 65.9% of *E. coli* and 59.4% of *K. pneumoniae*, while cefixime resistance reached 70.5% and 50.0%, respectively. ESBL production was identified in 36.4% of *E. coli* and 37.5% of *K. pneumoniae*. These findings indicate a substantial prevalence of ESBL-producing uropathogens and are consistent with reports from Iran and other regions (18-20). Askari et al. (2025) reported comparable ESBL prevalence among urinary isolates in Iranian hospitals (18). In contrast, Nasrollahian et al. (2025) reported a higher ESBL prevalence among UPEC isolates from children with vesicoureteral reflux, highlighting the potential influence of patient characteristics and clinical setting on resistance patterns (19). Sharahi et al. (2021) re-

Table 1. Antibiotic susceptibility profile of *E. coli* and *K. pneumoniae* isolates

Antimicrobial agents	Microbial isolates					
	<i>E. coli</i> (n; 44)			<i>K. pneumoniae</i> (n; 32)		
	S	I	R	S	I	R
CZ	20 (45.5%)	2 (4.5%)	22 (50.0%)	14 (43.7%)	0 (0.0%)	18 (56.3%)
MEN	33 (75.0%)	0 (0.0%)	11 (25.0%)	23 (71.8%)	0 (0.0%)	9 (28.1%)
AZT	26 (59.1%)	1 (2.3%)	17 (38.6%)	13 (40.6%)	0 (0.0%)	19 (59.4%)
GN	29 (65.9%)	0 (0.0%)	15 (34.1%)	20 (62.5%)	1 (3.1%)	11 (34.3%)
TOB	26 (59.1%)	0 (0.0%)	18 (40.9%)	20 (62.5%)	0 (0.0%)	12 (37.5%)
CAZ	14 (31.8%)	0 (2.3%)	29 (65.9%)	11 (34.4%)	2 (6.2%)	19 (59.4%)
CZA	30 (68.2%)	0 (0.0%)	14 (31.8%)	22 (68.7%)	0 (0.0%)	10 (31.3%)
AN	31 (70.5%)	2 (4.5%)	11 (25.0%)	21 (65.6%)	2 (6.2%)	9 (28.1%)
LEV	33 (75.0%)	2 (4.5%)	9 (20.5%)	24 (75.0%)	1 (3.1%)	7 (21.8%)
SXT	26 (59.1%)	0 (2.3%)	17 (38.6%)	19 (59.4%)	0 (0.0%)	13 (40.6%)
FM	36 (81.8%)	0 (0.0%)	8 (18.2%)	15 (46.8%)	0 (0.0%)	17 (53.1%)
ATM	32 (72.7%)	0 (0.0%)	12 (27.3%)	17 (53.1%)	0 (0.0%)	15 (46.8%)
AMP	22 (50.0%)	0 (2.3%)	21 (47.7%)	13 (40.6%)	0 (0.0%)	20 (62.5%)
CFM	10 (22.7%)	3 (6.8%)	31 (70.5%)	15 (46.8%)	1 (3.1%)	16 (50.0%)

Cefazolin (CZ), meropenem (MEN), azithromycin (AZT), gentamicin (GN), tobramycin (TOB), ceftazidime (CAZ), ceftazidime-avibactam (CZA), amikacin (AN), levofloxacin (LEV), trimethoprim-sulfamethoxazole (SXT), fosfomycin (FM), aztreonam (ATM;30 µg), ampicillin (AMP), and cefixime (CFM), sensitive (S), intermediate (I) and R (resistance).

Table 2. Antimicrobial Susceptibility Pattern of carbapenem-Resistant and -Sensitive Isolates

Antimicrobial agents	Microbial isolates [n (%)]							
	CREC (n=11)		CSEC (n=33)		CRKP (n=9)		CSKP (n=23)	
	S	R	S	R	S	R	S	R
CZ	2 (18.2%)	9 (81.8%)	20 (60.6%)	13 (39.4%)	0 (0.0%)	9 (100.0%)	14 (60.9%)	9 (39.1%)
AZT	0 (0.0%)	11 (100.0%)	27 (81.8%)	6 (18.2%)	0 (0.0%)	9 (100.0%)	13 (56.5%)	10 (43.5%)
GN	5 (45.5%)	6 (54.5%)	24 (72.7%)	9 (27.3%)	1 (11.1%)	8 (88.9%)	20 (87.0%)	3 (13.0%)
TOB	3 (27.3%)	8 (72.7%)	23 (69.7%)	10 (30.3%)	0 (0.0%)	9 (100.0%)	20 (87.0%)	3 (13.0%)
CAZ	1 (9.1%)	10 (90.9%)	14 (42.4%)	19 (57.6%)	2 (22.2%)	7 (77.8%)	11 (47.8%)	12 (52.2%)
CZA	3 (27.3%)	8 (72.7%)	27 (81.8%)	6 (18.2%)	2 (22.2%)	7 (77.8%)	20 (86.9%)	3 (13.0%)
AN	0 (0.0%)	11 (100.0%)	33 (100.0%)	0 (0.0%)	3 (33.3%)	6 (66.7%)	20 (86.9%)	3 (13.0%)
LEV	6 (54.5%)	5 (45.5%)	29 (87.9%)	4 (12.1%)	4 (44.4%)	5 (55.6%)	21 (91.3%)	2 (8.7%)
SXT	4 (36.4%)	7 (63.6%)	23 (69.7%)	10 (30.3%)	0 (0.0%)	9 (100.0%)	19 (82.6%)	4 (17.4%)
FM	6 (54.5%)	5 (45.5%)	30 (90.9%)	3 (9.1%)	1 (11.1%)	8 (88.9%)	14 (60.9%)	9 (39.1%)
ATM	4 (36.4%)	7 (63.6%)	28 (84.8%)	5 (15.2%)	1 (11.1%)	8 (88.9%)	16 (69.7%)	7 (30.4%)
AMP	0 (0.0%)	11 (100.0%)	23 (69.7%)	10 (30.3%)	3 (33.3%)	6 (66.7%)	9 (39.1%)	14 (60.9%)
CFM	2 (18.2%)	9 (81.8%)	11 (33.3%)	22 (66.7%)	3 (33.3%)	6 (66.7%)	13 (56.5%)	10 (43.5%)

CREC; carbapenem-resistant *E. coli*, CSEC; carbapenem-sensitive *E. coli*, CRKP; carbapenem-resistant *K. pneumoniae*, CSKP; carbapenem-sensitive *K. pneumoniae*, Cefazolin (CZ), meropenem (MEN), azithromycin (AZT), gentamicin (GN), tobramycin (TOB), ceftazidime (CAZ), ceftazidime-avibactam (CZA), amikacin (AN), levofloxacin (LEV), trimethoprim-sulfamethoxazole (SXT), fosfomycin (FM), aztreonam (ATM;30 µg), ampicillin (AMP), and cefixime (CFM), sensitive (S) and R (resistance).

Table 3. Distribution of MDR Patterns across in *E. coli* and *K. pneumoniae* Isolates

Classes of Antibiotic	[N (%)] of MDR isolates	
	<i>E. coli</i> (N; 23)	<i>K. pneumoniae</i> (N; 18)
β-lactams- Aminoglycosides- Fluoroquinolones	6 (26.1%)	6 (33.3%)
β-lactams- Aminoglycosides- Folate pathway inhibitors	3 (13.0%)	4 (22.2%)
Aminoglycosides- Fluoroquinolones-Phosphonic acids	3 (13.0%)	2 (11.1%)
Aminoglycosides- Folate pathway inhibitors- Phosphonic acids	5 (21.7%)	3 (16.7%)
Folate pathway inhibitors- Phosphonic acids- β-lactams	4 (17.4%)	2 (11.1%)
Folate pathway inhibitors- Phosphonic acids- Fluoroquinolones	2 (8.6%)	1 (5.6%)

β-lactams (CZ; Cefazolin, CAZ; Ceftazidime, CZA; Ceftazidime/Avibactam, CFM; Cefixime, AZT; Aztreonam, ATM; Aztreonam), Aminoglycosides (GN; Gentamicin, TOB; Tobramycin, AN; Amikacin), Fluoroquinolones (LEV; Levofloxacin), Folate pathway inhibitors (SXT; Trimethoprim-Sulfamethoxazole), Phosphonic acids FM; Fosfomycin, MDR; multidrug resistance.

ported a substantial prevalence of ESBL production among *E. coli* and *K. pneumoniae* isolates, with ESBL-producing strains demonstrating higher levels of resistance to cephalosporins (20). Such differences may be associated with antimicrobial exposure, infection-control practices, and the molecular epidemiology of circulating strains.

Among the tested antimicrobials, aminoglycosides, levofloxacin, and CZA showed comparatively higher in vitro activity against both species. However, these findings should not be interpreted as evidence for empirical treatment efficacy, as therapeutic decisions require consideration of clinical characteristics and individual susceptibility results. Fosfomycin retained considerable in vitro activity against *E. coli*, with susceptibility observed in 81.8% of isolates, whereas its activity against *K. pneumoniae* was notably lower, with only 46.9% of isolates remaining susceptible. This species-specific difference may reflect differences in intrinsic and acquired resistance mechanisms, although these mechanisms were not investigated in the present study. An important finding was the reduced activity of CZA against carbapenem-resistant isolates. While overall CZA susceptibility was approximately 68% in both species, only 27.3% of carbapenem-resistant *E. coli* and 22.2% of carbapenem-resistant *K. pneumoniae* isolates remained susceptible. Thus, 25.0% of all carbapenem-resistant isolates were susceptible to CZA, demonstrating that carbapenem resistance in this population was frequently associated with reduced CZA activity, but not uniformly with CZA resistance. Similarly, fosfomycin remained active against 54.5% of carbapenem-resistant *E. coli* and 11.1% of carbapenem-resis-

tant *K. pneumoniae*. These findings emphasize the importance of susceptibility testing before selecting antimicrobial therapy for carbapenem-resistant urinary pathogens. The relatively reduced CZA activity observed among carbapenem-resistant isolates may be associated with resistance mechanisms such as metallo-β-lactamase production, class D carbapenemases, alterations in outer-membrane permeability, or combinations of β-lactamase production and porin changes. However, because molecular characterization was not performed in this study, these mechanisms cannot be directly attributed to the observed resistance patterns. Previous surveillance studies have demonstrated that CZA generally retains substantial in vitro activity against many ESBL-producing and multidrug-resistant Enterobacterales, supporting its potential role in the treatment of selected resistant infections when susceptibility is confirmed (21).

This study has several limitations. The relatively small sample size and inclusion of isolates from a limited population may restrict the generalizability of the findings. In addition, the study did not include molecular characterization of β-lactamase or carbapenemase genes, and therefore the genetic mechanisms underlying resistance could not be determined. Larger multicenter studies incorporating molecular and, where appropriate, MIC-based characterization are warranted to clarify the epidemiology and mechanisms of CZA resistance among carbapenem-resistant uropathogens. Continued antimicrobial resistance surveillance, together with susceptibility-guided antimicrobial therapy and appropriate antimicrobial stewardship, remains essential for limiting the spread of MDR urinary pathogens.

CONCLUSION

This study demonstrates a substantial burden of carbapenem and ESBL resistance among urinary *E. coli* and *K. pneumoniae* isolates from women presenting with UTI symptoms. Aminoglycosides, levofloxacin, and ceftazidime-avibactam showed comparatively higher in vitro activity against the tested isolates, although CZA activity was markedly reduced among carbapenem-resistant strains. These findings underscore the importance of continuous antimicrobial resistance surveillance, susceptibility-guided antibiotic therapy, prudent use of broad-spectrum agents, and effective infection prevention and control measures to limit the spread of MDR uropathogens.

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