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In vitro evaluation of colistin and ceftazidime-avibactam activity against multi-drug resistant klebiella pneumoniae isolates

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Abstract

This study aimed to evaluate the in vitro effectiveness of colistin and ceftazidime-avibactam (CZA) antibiotics against multidrug-resistant (MDR) *Klebsiella pneumoniae* isolates. The study included 54 clinical isolates sent to the Medical Microbiology Laboratory of Kirsehir Education and Research Hospital between 2022 and 2023, which were resistant to multiple drugs in routine antibiotic susceptibility tests. Colistin susceptibility was evaluated using the microdilution method, while CZA susceptibility was assessed using the disk diffusion method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. It was determined that 31.4% of the isolates were resistant to colistin, and 22.2% were resistant to CZA. No isolates were resistant to both antibiotics. Statistical analyses did not reveal a significant relationship between antibiotic susceptibility and gender, age, underlying disease, and sample type ($p>0.05$). However, colistin resistance has been found to be higher in intensive care units, whereas resistance to CZA has significantly increased in internal medicine units ($p =0.025$). The study's findings indicate that colistin and CZA may be important in treating multidrug-resistant *K. pneumoniae* infections. CZA provides an effective alternative for colistin-resistant isolates, while colistin is an effective alternative for CZA-resistant isolates. However, to enhance the efficacy of these agents, larger-scale studies and ongoing monitoring of resistance mechanisms are necessary.

Keywords: colistin, ceftazidime avibactam, klebsiella pneumoniae

1. Introduction

Klebsiella pneumoniae, although a component of the flora in the human body's gastrointestinal system and nasopharynx, is a Gram-negative bacillus that commonly acts as a pathogen in urinary tract infections, septicemia, pneumonia, nosocomial infections, surgical and catheter-related infections (1). *K. pneumoniae* is a significant nosocomial pathogen due to its rapidly increasing resistance to all currently available antibiotics, particularly carbapenems (2). The capsule structure, presence of siderophores, lipopolysaccharides, and fimbriae are essential virulence factors of these strains (1).

Resistance to at least one agent from three or more antimicrobial groups is defined as multidrug resistance (MDR); resistance to bacteria that are susceptible to two or fewer antimicrobial categories is termed extensive drug resistance (XDR); and resistance to all agents in all antimicrobial categories is known as pandrug resistance (PDR) (3). An infection caused by a multidrug-resistant microorganism can result in inadequate or delayed antimicrobial treatment and is linked to poorer patient outcomes. Among multidrug-resistant organisms, bacteria such as *K. pneumoniae* and *Acinetobacter spp.* can resist all currently available antimicrobial agents or may only be sensitive to older, potentially more toxic agents like polymyxins (3). The rising prevalence of multidrug-resistant Gram-negative bacterial pathogens worldwide is a primary global public health concern (4).

Antimicrobial resistance among Gram-negative pathogens, particularly resistance to β-lactam antimicrobials, often arises from the production of β-lactamases, which can significantly limit treatment options for serious bacterial infections. The rising prevalence of pathogens producing extended-spectrum β-lactamases (ESBLs) has resulted in increased use of carbapenems and growing dependence on them (4). Carbapenems are a class of beta-lactam antibiotics used to treat infections caused by *Enterobacterales* that produce ESBL and/or AmpC cephalosporinase. Although limited antibiotic options like colistin, tigecycline, and aminoglycosides are used to treat carbapenemase-producing pathogens, this has highlighted the urgent need for new antimicrobial agents (3,5). Antimicrobial resistance poses serious threats to modern medical practices. It is associated with the spread of resistance, treatment failures, and increased mortality rates. *K. pneumoniae* has emerged as a critical pathogen in this context. Strains that have developed resistance to last-resort antibiotics, such as carbapenems, have made treatment protocols much more complex (6,7). Colistin and ceftazidime-avibactam (CZA) are significant treatment options for these resistant infections. This study aims to evaluate the in vitro efficacy of these two agents against multidrug-resistant *K. pneumoniae* isolates.

2. Materials and Methods

This study included *K. pneumoniae* isolates from various

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clinics sent to the Medical Microbiology Laboratory of Kirsehir Education and Research Hospital between February 2022 and December 2023. These isolates were found to exhibit multidrug resistance in routine antibiotic susceptibility tests (Amikacin, amoxicillin-clavulanate, ampicillin, ampicillin-sulbactam, cefazolin, cefepime, ceftazidime, ceftolozane-tazobactam, ceftriaxone, cefuroxime, ciprofloxacin, levofloxacin, ertapenem, imipenem, meropenem, gentamicin, piperacillin-tazobactam, tigecycline, trimethoprim-sulfamethoxazole) and were stored as stock. Repeating isolates were not included in the study. The demographic data of the patients whose strains were included in the study (age, gender, sample type, clinical, and comorbidity status) were retrospectively obtained from the hospital automation system. Identifying isolates and antibiotic susceptibility tests in routine laboratory were determined using the VITEK2 compact system (bio-Merieux, France). Strains exhibiting multidrug resistance were stored at -20°C until the day of in vitro testing. On the day of the study, the preserved strains were revived by inoculating them onto blood agar and incubating them for 24 hours in an incubator. The colistin and CZA antibiotic susceptibility tests of the growing bacteria were conducted and evaluated as specified by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. The colistin antibiotic susceptibility test was performed using the microdilution method. Antibiotic stock solutions were created based on the manufacturer's guidelines and stored at -80°C in a frozen state. For colistin, concentrations in the range of 64-0.25 µg/ml were prepared by performing serial two-fold dilutions in 96-well microplates containing freshly prepared cation-adjusted Mueller-Hinton liquid medium. The microplates were covered and incubated at 35 ± 2°C for 18-20 hours. At the end of the incubation, the wells with growth were visually evaluated. The CZA antibiotic susceptibility test was performed using the Kirby-Bauer disk diffusion method, and the CZA (10-4 µ) (Bioanalyse, Turkey) antibiotic disk was examined. Isolates with an inhibition zone diameter of ≥13 mm according to EUCAST criteria were considered CZA sensitive and were evaluated as sensitive. The data obtained were recorded in the study file and subjected to statistical analysis. The data analysis used the "IBM SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, USA) 30.0 for Windows" package. The results obtained from the SPSS software were interpreted based on variables such as gender, age, sample type, diagnosis, mortality, and type of service, as well as the effectiveness of these two agents. The variables in the descriptive statistics were shown as the number of cases, with the percentage (%) displayed. Pearson's chi-square and Fisher's exact tests were used in the data analysis, and a $p<0.05$ value was considered statistically significant.

3. Results

The colistin and CZA antibiotic susceptibility results of multidrug-resistant *K. pneumoniae* isolates obtained from clinical samples of 54 patients referred from various clinics were examined. Of the patients, 35 were male, 19 were female, and the average age was 72,22 (14,48). Among all the isolates, 17 (31.4%) were found to be resistant to colistin, while 12 (22.2%) exhibited resistance to CZA (Fig. 1). There are no isolates resistant to both antibiotics simultaneously. The susceptibility data for both antibiotics were analyzed using cross tables and the chi-square test, considering factors such as gender, age, underlying diseases, mortality, sample type, and the clinic from which the sample originated. According to the data results, no statistically significant relationship was found between the susceptibility of both antibiotics and gender, age, underlying disease, mortality, and sample type ($p > 0.05$). Although not statistically significant, the resistance rates for both antibiotics were higher in males, patients over 65 years old, patients diagnosed with pneumonia, respiratory samples for colistin, and blood-catheter samples for CZA. Statistically significant differences were found in the sensitivity rates to CZA among clinical units ($p = 0.025$), and the resistance rate was higher in patients from the internal medicine unit. Although not statistically significant, colistin resistance was observed to be higher in percentage among patients in intensive care units compared to those in other wards (Table 1).

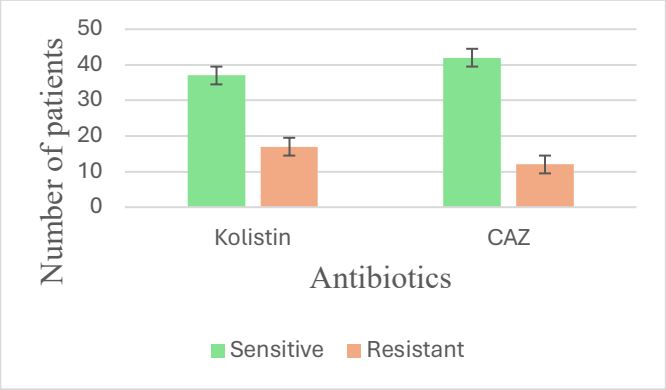

Fig. 1. Number of patients resistant and sensitive to colistin and ceftazidime avibactam

Table 1. Distribution of patients from whom colistin and ceftazidime-avibactam-sensitive and resistant strains were isolated according to demographic data [(%)]

	Colistin		p	CZA		p	Total
	Sensitive	*Resistant*		*Sensitive*	*Resistant*		
Gender			**0.547**			**0.879**	
Female	14 (%73.3)	5(%26.3)		15 (%78.9)	4 (%21.1)		19 (%100)
Male	23 (%65.7)	12 (%34.3)		27 (%77.1)	8 (%22.9)		35 (%100)
Age			**0.949**			**0.148**	
<65	9 (%69.2)	4 (%30.8)		12 (%92.3)	1 (%7.7)		13 (%100)
≥65	28 (%68.3)	13 (%31.7)		30 (%73.2)	11 (%26.8)		41 (%100)
Diagnosis			**0.378**			**0.368**	

UTI	7 (%70)	3(%30)		7 (%70)	3 (%30)		10 (%100)
Pneumonia	12 (%63.1)	7 (%36.9)		15 (%78.9)	4 (%21.1)		19 (%100)
Sepsis	5 (%100)	0 (%0)		2 (%40)	3 (%60)		5 (%100)
CVD	5 (%83.3)	1 (%19.7)		6 (%100)	0 (%0)		6 (%100)
AKI	1 (%33.3)	2 (%66.7)		3 (%100)	0 (%0)		3 (%100)
Wound Infection	2 (%50)	2 (%50)		3 (%75)	1 (%25)		3 (%100)
Others	5 (%71.4)	2 (%28.6)		6 (%85.7)	1 (%14.3)		7 (%100)
Mortality	15 (%65.2)	8 (%34.8)	**0.653**	16 (%69.6)	7 (%30.4)	**0.211**	23 (%100)
Sample Type			**0.741**			**0.386**	
Respiratory Track	14 (%60.9)	9 (%39.1)		20 (%87)	3 (%13)		23 (%100)
Urine	12 (%75)	4 (%25)		12(%75)	4(%25)		16 (%100)
Blood-Catheter	7(%70)	3 (%30)		6 (%60)	4 (%40)		10 (%100)
Wound	4(%80)	1 (%20)		4(%80)	1 (%20)		5 (%100)
Department			**0.138**			**0.025**	
ICU	26 (%61.9)	16 (%38.1)		35 (%83.3)	7(%16.7)		42 (%100)
Internal Medicine Service	8 (%88.9)	1 (%11.1)		4 (%44.4)	5 (%55.6)		9 (%100)
Surgery Service	3 (%100)	0 (%0)		3 (%100)	0 (%0)		3 (%100)
Total	**37 (%68.5)**	**17(%31.5)**		**42 (%77.8)**	**12(%22.2)**		**54 (%100)**

CZA: Ceftazidime-avibactam, UTI: Urinary tract infection, CVD: Cerebrovascular disease, AKI: Acute kidney injury, ICU: Intensive care unit, Other: malignancy, arrhythmia, cirrhosis, chronic kidney disease, hernia, etc

4. Discussion

In this study, we investigated the distribution of colistin and ceftazidime-avibactam (CZA) resistance among patients based on demographic factors, diagnosis, sample type, and hospital department. Our findings revealed no statistically significant association between gender and resistance to either colistin (p=0.547) or CZA (p=0.879). Similarly, age did not significantly affect resistance rates for colistin (p=0.949) or CZA (p=0.148). While most colistin-resistant strains were isolated from patients over 65 years old, the difference was not statistically significant. Regarding diagnosis, sepsis cases were exclusively linked to colistin-sensitive strains, while resistance was more common in pneumonia cases. Interestingly, acute kidney injury (AKI) showed the highest proportion of colistin resistance (66.7%), despite the limited number of cases. Regarding the department of hospitalization, resistance to colistin was more prevalent in patients from the intensive care unit (ICU) (38.1%) than in other departments. In comparison, the CZA resistance rate was significantly lower in ICU patients (16.7%) compared to those from internal medicine services (55.6%) (p=0.025). This finding highlights the importance of closely monitoring resistance patterns in ICUs, where antimicrobial resistance is typically higher. Furthermore, the distribution of resistant strains by sample type did not differ significantly, although respiratory tract samples showed a higher resistance rate to colistin (39.1%) than urine (25%). These findings suggest that while colistin resistance remains relatively consistent across demographic factors, ICU admission and specific diagnoses may increase the risk, warranting targeted antimicrobial stewardship interventions (Table 1).

It has been observed that various beta-lactamase genes (KPC, NDM, and OXA-48) are commonly found alongside the mcr-1 gene among the resistance mechanisms in MDR *K. pneumoniae* strains. This situation has brought treatment strategies to the forefront, particularly those involving broad-spectrum antibiotics (6). Colistin and CZA have been reported as critical agents for treating multidrug-resistant *K. pneumoniae* infections (8). CZA has been developed as a new β-lactam/β-lactamase inhibitor combination with in vitro and in vivo activity against *Enterobacterales* members that produce carbapenemase and OXA-48 (9). This drug has been found particularly effective in treating infections caused by multidrug-resistant Gram-negative bacteria (9,10). Colistin is an antibiotic from the polymyxin group, used as an effective agent against Gram-negative bacteria. However, serious side effects such as nephrotoxicity and neurotoxicity restrict its therapeutic use (8). The use of colistin has increased due to the rise in multidrug resistance among Gram-negative bacteria and the lack of new antibiotics to combat them. However, colistin resistance has also been frequently encountered in hospitalized patients (11,12).

According to data from a total of 10,998 Klebsiella isolates (9,098 *K. pneumoniae* and 1,900 *K. oxytoca* isolates) collected from 176 centers in 39 countries across Asia/Pacific, Europe, Latin America, and Africa/Middle East between 2012 and 2014, 2,821 isolates (25,7%) were found to be multidrug-resistant. The percentages of multidrug-resistant isolates varied among different countries; in some countries, relatively high rates of multidrug-resistant isolates were found (Brazil, Nigeria, Russia (>50%)), while in others, lower rates were observed (Australia, Denmark, Netherlands, Sweden, United Kingdom (<5%)). It was reported that 88.1% of meropenem-resistant multidrug-resistant isolates were sensitive to CZA (13). In a study by Van Duin et al., the first group of 38 patients with carbapenem-resistant *Enterobacteriaceae* infection was treated with CZA, while the second group of 99 patients was treated with colistin. At the end of 30 days, hospital mortality was reported to be significantly lower in the CZA group (9%) compared to the colistin group (32%), indicating that CZA could be a reasonable alternative to colistin in the treatment of carbapenemase-producing *K. pneumoniae* infections (14). Almangour et al. conducted a study comparing the efficacy of

CZA and colistin in treating carbapenem-resistant *Enterobacteriaceae* bacteremia, including a total of 230 patients; 149 patients received CZA and 81 patients received colistin-based treatment. *K. pneumoniae* was identified as the most prevalent isolated pathogen (n = 201; 87%). Of the isolates, 116 (78%) were sensitive to CZA, whereas 62 (76%) were sensitive to colistin. CZA proved superior for treating infections caused by carbapenem-resistant *Enterobacteriaceae*, showing higher clinical treatment rates, lower incidence of acute kidney injury, and reduced mortality rates compared to colistin-based regimens (15). In another study conducted in India, the effectiveness of colistin and CZA against multidrug-resistant *K. pneumoniae* was compared, with observations indicating that CZA had fewer side effects than colistin. However, continuous monitoring is necessary for resistance development (16). When the results of these studies were compared with our data, it was found that CZA (22.2%) had a lower resistance rate than colistin (31.5%), indicating similarity (Fig. 1).

The 2016 annual report from the Türkiye Public Health Institution, part of the Ministry of Health, indicated that the prevalence of multidrug-resistant *K. pneumoniae* in our country was 46.1%. In 961 of the 1394 multidrug-resistant *K. pneumoniae* isolates, colistin susceptibility was tested, and 271 (28.2%) were found colistin-resistant. Among 1229 carbapenem-resistant *K. pneumoniae* isolates, colistin resistance was 31.7% (17). In a study conducted in Ankara between September 2018 and December 2018, colistin resistance was determined to be 39.51% in 81 *K. pneumoniae* isolates with identified carbapenem resistance (18). In the study by Kaya et al., 95.7% of the multidrug-resistant *K. pneumoniae* were sensitive to CZA. In contrast, CZA resistance was not detected in the carbapenem and colistin-resistant *K. pneumoniae* isolates (19). In the study by Hosbul et al., 150 carbapenem-resistant *K. pneumoniae* isolates were examined between January 1, 2018, and February 1, 2021. Colistin resistance was 52% (n=78), while CZA resistance was 7.3% (n=11). Except for one of the 78 colistin-resistant isolates, all other colistin-resistant isolates were found to be sensitive to ceftazidime-avibactam. Colistin resistance was observed to be high in recent studies and in this study (31.4%) and it has been thought that colistin resistance in *K. pneumoniae* isolates in our country is increasingly becoming a dangerous issue. CZA resistance was higher in our data (22.2%) compared to other studies. This has been interpreted as using this newly developed drug to treat resistant isolates over time.

The study by Jayol et al. further suggests that ceftazidime/avibactam is an effective therapeutic option for treating infections caused by colistin-resistant and KPC- or OXA-48-producing *K. pneumoniae (20*). CZA therapy demonstrates lower mortality rates compared to colistin-based treatments in bloodstream infections caused by carbapenem-resistant *K. pneumoniae* producing OXA-48. In a multicenter study, the mortality rate was 14.3% when CZA was used as the initial therapy, whereas it was 37.7% when patients were switched from last-resort treatments such as colistin (p = 0.04). Additionally, initiating CZA on the same day the blood culture was obtained significantly reduced the mortality risk. These findings indicate that CZA is more effective than colistin in treating carbapenem-resistant *K. pneumoniae* infections, particularly in OXA-48 endemic regions (21). Like this study, the findings of our research, in which no *K. pneumoniae* isolate was found to be resistant to both colistin and CZA, showed that CZA can be used as an alternative in vitro for isolates resistant to colistin and that colistin can be used for isolates resistant to CZA. However, it should not be forgotten that more evidence is needed to prove this, and it must be supported by clinical studies. In a study evaluating the in vitro efficacy of the combination of CZA with various antimicrobial agents against carbapenem-resistant *K. pneumoniae*, the in vitro efficacy of the combination of CZA and COL shows irrelevant effects against the tested clinical isolates (22). Although ceftazidime/avibactam has emerged as a valuable therapeutic option against KPC-producing *K. pneumoniae*, evidence regarding its combination with colistin remains inconclusive and clinically problematic. In vitro time-kill assays conducted by Wang et al. demonstrated that the ceftazidime/avibactam-colistin combination exhibited only partial synergistic effects in a minority of isolates and failed to achieve superior bactericidal activity compared to monotherapy in most cases (23). Similarly, Borjan et al. reported a lack of synergy and no significant enhancement in survival outcomes in an in vivo *Galleria mellonella* model, further questioning the utility of this combination (24). Notably, the addition of colistin may not only lack synergistic benefit but also introduce substantial risk due to its well-documented nephrotoxicity (23,24). These findings collectively suggest that the ceftazidime/avibactam-colistin combination should be approached with caution and reserved only for cases where alternative regimens are either unavailable or ineffective, with careful consideration of potential toxicities and the absence of an additive antimicrobial effect.

There are some limitations in this study. One limitation is that the resistance test was conducted using different methods for the two types of antibiotics in the study's methodology. Colistin was examined with broth microdilution, while CZA was assessed using the disk diffusion method. Additionally, limitations include obtaining study data from a single center, a small number of patients, and the inability to determine resistance mechanisms in resistant strains.

The study suggests that colistin and CZA may be important agents in treating multidrug-resistant *K. pneumoniae* infections. However, antibiotic susceptibility varies according to patient characteristics. The study data indicate that the increasing resistance rates in patients over 65 years old

necessitate special attention when treating this group. The high resistance rates of CZA in blood-catheter samples may pose challenges for using this drug in treating invasive infections, and the high colistin resistance rates in intensive care units highlight the critical importance of antibiotic management in these settings (Table 1). Although CZA stands out as an effective alternative against carbapenemase-producing strains, the presence of resistant strains shows that this drug alone is not sufficient. Advanced studies involving larger patient populations, optimizing treatment strategies, understanding resistance mechanisms better, and ensuring continuous monitoring will help validate these results comprehensively.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: T.A.M., Design: T.A.M., Data Collection or Processing: T.A.M., Analysis or Interpretation: T.A.M., Literature Search: T.A.M., Writing: T.A.M.

Ethical Statement

Approval was obtained from Kirsehir Ahi Evran University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee with decision number 2024-4/15 dated 06/02/2024.

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