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Should we prefer imipenem relebactam and ceftazidime-avibactam in infections with carbapenem-resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*?

Karbapenem dirençli *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* enfeksiyonlarında imipenem relebaktam ve seftazidime avibaktamı tercih edelim mi?

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ABSTRACT

Objective: Carbapenem-resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* serve as key reservoirs and transmitters of resistance, contributing to a rise in the antimicrobial-resistant globally. These bacteria have also been classified as urgent priority pathogens in terms of the need for new antibiotics. The purpose of this study was to determine the susceptibility of carbapenem resistant *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* isolates to imipenem-relebactam and ceftazidime-avibactam as described new drugs.

Methods: This study included a total of 183 isolates, comprising 82 *K. pneumoniae*, 45 *P. aeruginosa*, and 56 *A. baumannii* isolates, which were isolated from various clinical samples. The identification and antibiotic susceptibility testing of the isolates were performed using the Vitek 2 automated system (bioMérieux, France) according to the EUCAST criteria. Each isolate that exhibited resistance to one or more antibiotics from the carbapenem group underwent phenotypic confirmation for carbapenem resistance using the Carbapenem

ÖZET

Amaç: Karbapenem dirençli *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* ve *Acinetobacter baumannii* antibiotik direncin küresel olarak artmasına önemli katkı sağlayan ana rezervuarlar ve direnç taşıyıcıları olarak öne çıkmaktadırlar. Bu bakteriler aynı zamanda yeni antibiyotiklere duyulan ihtiyaç açısından da acil öncelikli patojenler olarak sınıflandırılmıştır. Bu çalışmanın amacı, karbapenem dirençli *K. pneumoniae*, *P. aeruginosa* ve *A. baumannii* izolatlarının, tanımlanan yeni ilaçlar olan imipenem-relebaktam ve seftazidim-avibaktama duyarlılığının belirlenmesidir.

Yöntem: Çalışmaya çeşitli klinik örneklerden izole edilen 82'si *K. pneumoniae*, 45'i *P. aeruginosa* ve 56'sı *A. baumannii* olmak üzere toplam 183 izolat dahil edildi. İzolatların identifikasyonu ve antibiyotik duyarlılık testleri, EUCAST kriterlerine göre Vitek 2 otomatik sistemi (bioMérieux, Fransa) kullanılarak yapıldı. Karbapenem grubundan bir veya daha fazla antibiyotiğe direnç tespit edilen her bir izolata Karbapenem inaktivasyon yöntemi (CIM) ve Blue-

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inactivation method (CIM) and the Blue-carba test (BCT). The susceptibility of all isolates to imipenem-relebactam (35 µg, Liofilchem, Italy), and ceftazidime-avibactam (10/4 µg, Bioanalyse, Turkey) was evaluated using the disk diffusion method according to EUCAST standards.

Results: The resistance to ceftazidime and ceftazidime-avibactam were found to be, respectively, 100%, 3.7% for *K. pneumoniae*, 24.4%, 8.9% for *P. aeruginosa*, and 100%, 98.2% for *A. baumannii*. The resistance rates of isolates to imipenem and imipenem-relebactam were found to be 80.5%, 85.4% for *K. pneumoniae*, 68.9%, 13.3% for *P. aeruginosa*, 100%, 98.2% for *A. baumannii* respectively. The positivity rates for CIM and BCT were determined as 79.3% and 80.5% for *K. pneumoniae*, 9% and 50% for *P. aeruginosa*, and 80.4% and 62.5% for *A. baumannii* isolates, respectively.

Conclusion: Ceftazidime-avibactam has been determined to be effective against carbapenem-resistant *K. pneumoniae* and *P. aeruginosa*. Imipenem-relebactam has been found to be effective in *P. aeruginosa* isolates, while being observed to be less effective against *K. pneumoniae*. It was concluded that ceftazidime-avibactam can be used as an alternative option in the treatment of carbapenem-resistant *K. pneumoniae* and *P. aeruginosa* infections and imipenem-relebactam can be used as an alternative option in the treatment of carbapenem-resistant *P. aeruginosa* infections.

Key Words: Imipenem relebactam, ceftazidime-avibaktam, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Carbapenem inactivation method, Blue-carba test

carba testi (BCT) yapıldı. Tüm izolatların imipenem-relebaktam (35 µg, Liofilchem, İtalya) ve seftazidime-avibaktama (10/4 µg, Bioanalyse, Türkiye) duyarlılığı EUCAST standartlarına göre disk difüzyon yöntemi kullanılarak değerlendirildi.

Bulgular: Seftazidim ve seftazidim-avibaktama karşı direnç sırasıyla *K. pneumoniae* için %100, %3.7, *P. aeruginosa* için %24.4, %8.9 ve *A. baumannii* için %100, %98.2 olarak belirlendi. İzolatların imipenem ve imipenem-relebaktam direnç oranları sırasıyla *K. pneumoniae* için %80.5, %85.4, *P. aeruginosa* için %68.9, %13.3, *A. baumannii* için %100, %98.2 olarak saptandı. CIM ve BCT pozitiflik oranları sırasıyla *K. pneumoniae* için %79.3 ve %80.5, *P. aeruginosa* için %9 ve %50, *A. baumannii* izolatları için %80.4 ve %62.5 olarak tespit edildi.

Sonuç: Ceftazidim-avibaktam, karbapenem dirençli *K. pneumoniae* ve *P. aeruginosa*'ya karşı etkili olarak tespit edilmiştir. İmipenem-relebaktam, *P. aeruginosa* izolatlarında da etkili bulunmuştur. Ceftazidim-avibaktamın karbapenem dirençli *K. pneumoniae*, imipenem-relebaktamın ise karbapenem dirençli *P. aeruginosa* enfeksiyonlarının tedavisinde alternatif bir seçenek olarak kullanılabileceği kanısına varılmıştır.

Anahtar Kelimeler: İmipenem relebaktam, Seftazidim-avibaktam, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Karbapenem inaktivasyon yöntemi, Blue-carba testi

INTRODUCTION

ESKAPE refers to a group of pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterobacter* spp.) that cause the majority of antimicrobial-resistant hospital infections (1,2). Gram-negative ESKAPE bacteria serve as key reservoirs and transmitters of resistance, contributing to a rise in the antimicrobial-resistant nosocomial infections globally (3). These bacteria have

developed resistance to a wide range of antibiotics, including carbapenems and third generation cephalosporins, which are the best medications available for treating multi-drug resistant bacteria. The World Health Organisation has also classified *A. baumannii*, *P. aeruginosa*, and carbapenem-resistant *K. pneumoniae* as urgent priority pathogens in terms of the need for new antibiotics. Despite the well-known need, there are very few novel antimicrobial medicines in development to treat Gram-negative ESKAPE infections (4).

Carbapenems are broad-spectrum lactam antibacterial drugs that play an important role in the treatment of complicated infections caused by such organisms, particularly against strains that produce extended-spectrum-lactamases (ESBLs) (5). The growth and spread of carbapenem-resistant bacteria, on the other hand, exacerbates the clinical problem of treating these infections (5,6). Polymyxins, tigecycline, and aminoglycosides are routinely used to treat carbapenem-resistant infections, but they have low efficacy and considerable toxicity (7,8). In recent years, the United States Food and Drug Administration (FDA) and the European Medical Agency (EMA) have approved numerous novel antibiotics with predominant activity against Gram-negative bacteria, including ceftazidime-avibactam and imipenem-relebactam (9).

The purpose of this study was to evaluate the susceptibility of carbapenem resistant *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* isolates to imipenem-relebactam and ceftazidime-avibactam.

MATERIAL and METHOD

Identification and antibiotic susceptibility of the isolates

This study included a total of 183 isolates, including 82 (44.8 %) *K. pneumoniae*, 45 (24.6 %) *P. aeruginosa*, and 56 (30.6 %) *A. baumannii* isolates, identified from various clinical samples sent to the Microbiology Laboratory of Tokat Gaziosmanpaşa University between December 2016-December 2019. The identification and antibiotic susceptibility testing of the isolates were performed using the Vitek 2 automated system (bioMérieux, France) according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (10). Each isolate that exhibited resistance or intermediate resistance to one or more antibiotics from the carbapenem group underwent phenotypic confirmation for carbapenem resistance using the Modified carbapenemase inactivation method (CIM) and the Blue-carba test (BCT). The susceptibility of all isolates to imipenem (10 µg, Bioanalyse, Turkey), meropenem (10 µg, Bioanalyse, Turkey), imipenem-relebactam (35 µg, Liofilchem, Italy), and ceftazidime-avibactam (10/4 µg, Bioanalyse, Turkey) was evaluated using the disk diffusion method according to EUCAST standards. The specified zone diameters for *A. baumannii* and *P. aeruginosa* were used (Figure 1) (10). *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were utilised as quality control strains. Samples sent from intensive care and all clinics were included in the study. Repetitive isolates from identical patient specimens were excluded from this study.

Blue Carba Test

Mueller-Hinton agar was used for the cultivation of the isolates. A five µL loop containing a pure bacterial culture was suspended in a test solution consisting of a 0.04% aqueous solution of bromothymol blue (Sigma) and 0.1 mmol/liter of ZnSO4 (Sigma), supplemented with 6 mg of Tienam (MSD) (equivalent to 3 mg of imipenem), and adjusted to a final pH 7. The mixture was then incubated at a temperature of 37°C for a duration of two hours. Both the test solution and negative-control solution changed colour, such as yellow or blue, yellow versus green, or green versus blue, the presence of carbapenemase activity was considered positive. Carbapenem-resistant bacteria appeared as blue or green in both solutions (11). The test was repeated for each individual isolate. (Figure 2).

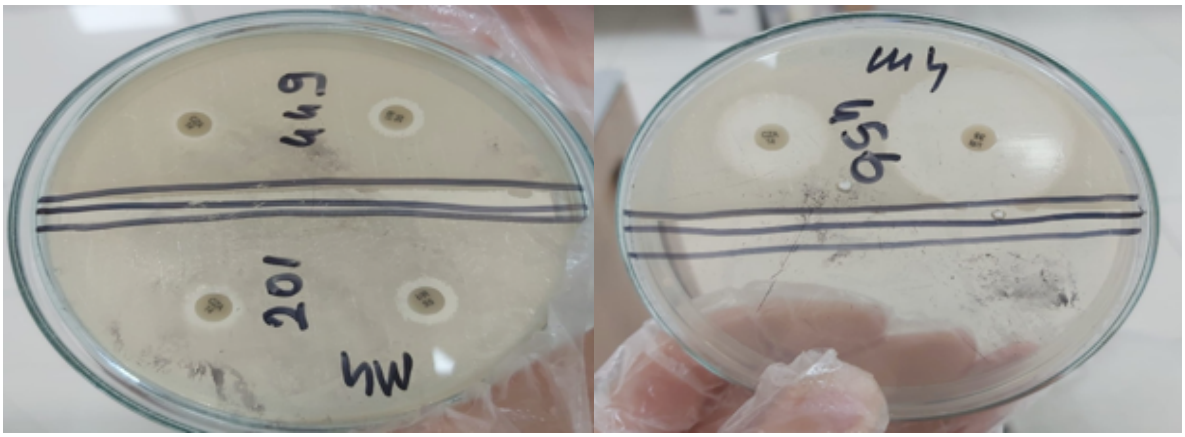

Figure 1. *K. pneumoniae* isolates detected as resistant and sensitive to imipenem relebkatam and ceftazidime avibactam

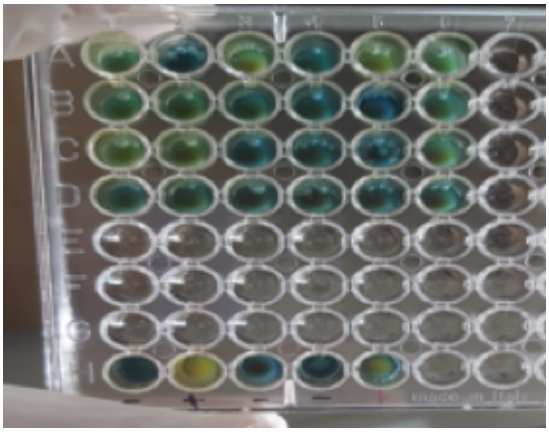

Figure 2. Blue-Carba test results
Carbapenem-resistant bacteria appeared as blue or green
Carbapenem-sensitive bacteria appeared as yellow

Modified Carbapenem Inactivation Method

For each *K. pneumoniae* and *P. aeruginosa* isolates, 10 µL loopfuls culture and 10 µg meropenem (Oxoid Ltd, Hampshire, United Kingdom) disk were suspended in 400 µL of distilled water and incubated at 35°C for four hours. Simultaneously, a 0.5% McFarland suspension of *Escherichia coli* ATCC was spread onto Mueller-Hinton agar and allowed to dry for 3-10 minutes at room temperature. After the incubation the meropenem disk withdrawn from the solution, and streaked onto Mueller-Hinton agar along with *Escherichia coli* ATCC. The plates were incubated at 37°C for two hours. Results were considered positive inhibitory zone diameters ranged from 0 to 16 mm or there was satellite expansion of colonies measuring 16-18 mm. Negative results were indicated by an inhibitory zone diameter of 19 mm (12) (Figure 3). For *A. baumannii* isolates modified carbapenem inactivation method was used suggested by Zhang et al. To create the inoculum, new bacteria cultivated overnight on LB agar or in broth were inoculated into TSB and adjusted to an OD600 of 8.0 in one mL. The bacteria were centrifuged and resuspended in 200µL TSB before incubating on the 10 µg meropenem (Oxoid Ltd, Hampshire, United Kingdom) disc. The next steps and evaluation of the test were carried out in the same way as the CIM method (13).

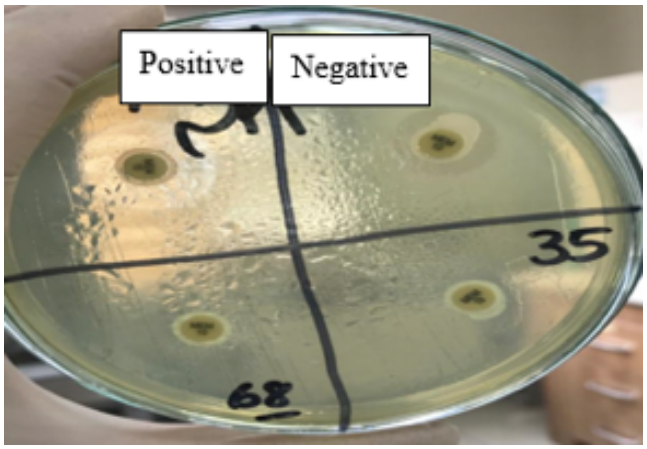

Figure 3. Carbapenem inactivation method results

The data was summarised using as frequencies and percentages whitin the scope of descriptive analysis.

The study was approved by the Ethics Committee of the Tokat Gaziosmanpaşa University (Date: 16.03.2023 and Number: 23/KAEK/067).

RESULTS

The study included a total of 183 carbapenem-resistant isolates consisting of 82 *K. pneumoniae*, 45 *P. aeruginosa*, 56 *A. baumannii* isolates. The majority of the isolates, 132 in total 72.1%, were obtained from the intensive care unit. The distribution of isolates according to clinical departments is presented in Table 1. The isolates were obtained from various clinical specimens, including tracheal aspirate (60, 32.8%), blood (44, 24%), urine (38, 20.8%), wound (35, 19.1%), sterile body fluid (4, 2.2%), and cerebrospinal fluid (2, 1.1%) specimens.

The resistance rates of isolates to ceftazidime and ceftazidime-avibactam were found to be, respectively, 100% and 3.7% for *K. pneumoniae*, 24.4% and 8.9% for *P. aeruginosa*, and 100% and 98.2% for *A. baumannii*. The resistance rates of isolates to imipenem and imipenem-relebactam were found to be, respectively, 80.5% and 85.4% for *K. pneumoniae*, 68.9% and 13.3% for *P. aeruginosa*, and 100% and 98.2% for *A. baumannii*.

Resistance to ceftazidime-avibactam was 3.7% in all *K. pneumoniae* isolates resistant to ceftazidime, 36.4% in *P. aeruginosa* isolates, and 98.2% in *A. baumannii* isolates. Resistance to imipenem-relebactam was 95.5% in all *K. pneumoniae* isolates resistant to imipenem, 16.1% in *P. aeruginosa* isolates, and 98.2% in *A. baumannii* isolates. The antibiotic resistance rates of all isolates are shown in Table 2.

The positivity rates for CIM and BCT were determined as 79.3% and 80.5% for *K. pneumoniae*, 9% and 50% for *P. aeruginosa*, 80.4% and 62.5% for *A. baumannii* isolates, respectively. The antibiotic resistance rates, along with CIM and BCT positivity, are presented in Table 2.

DISCUSSION

According to the findings, the susceptibility rates of isolates to ceftazidime-avibactam were higher for *K. pneumoniae* and *P. aeruginosa*. Additionally, susceptibility to imipenem-relebactam was high in *P. aeruginosa*. Several novel antibiotics with predominant in vitro action against Gram-negative bacteriae have been licenced in recent years, although they vary greatly in terms of range of activity, indications, and clinical experience. Ceftazidime avibactam and imipenem

Table 1. Distribution of isolates according to clinics

Clinics	n	%
Internal diseases	42	23
Neurology	23	12.6
Neurosurgery	19	10.4
General surgery	15	8.2
Oncology	14	7.7
Orthopedics	12	6.6
Chest intensive care	10	5.5
Pediatric	9	4.9
Urology	6	3.3
Cardiology	6	3.3
Infection	6	3.3
Gastroenterology	6	3.3
Anesthesia	5	2.7
Palliative care service	4	2.2
Oncology surgery	3	1.5
Others*	3	1,5
Total	**183**	**100**

* Gynecology, plastic surgery, radiation oncology

Table 2. Resistance rates of all isolates to antibiotics and Carbapenem Inactivation Method and Blue Carba Test results (%)

								CIM positive		CIM negative		BCT positive		BCT negative	
	Imipenem	Meropenem	Imipenem--elebactam	Ceftazidime	Cceftazidime-avibaktam	CIM [1]	BCT[2]	Imipenem--relebactam	Cceftazidime-avibaktam	Imipenem--relebactam	Cceftazidime-avibaktam	Imipenem--relebactam	Cceftazidime-avibaktam	Imipenem--relebactam	Cceftazidime-avibaktam
K. pneumoniae	93,9	84,1	80,5	100	3,7	79.3	80,5	98,5	3,1	11.8	5,9	98,5	3	6,3	6,3
P. aerugiosa	68,9	75,6	13,3	26.6	8,9	9	50	75	50	7,3	4,9	10,7	14,3	17,6	-
A. baumannii	100	100	98,2	98.2	98,2	80,4	62,5	97,8	97,8	100	100	100	97,1	95,2	100

1) Carbapenem Inactivation Method
2) Blue Carba Test

relebactam are among these new antibiotics (9).

One of the worldwide public health challenges facing humanity is antimicrobial resistance. Many gram-negative bacteria have developed resistance to carbapenem antibiotics, which are frequently used as a last choice in the treatment of severe infections caused by these organisms (1). Resistance to carbapenems is more common in *K. pneumoniae*, however it is also found in *P. aeruginosa* and *Acinetobacter* spp. According to the European Antimicrobial Resistance Surveillance Network, higher rates of resistance were recorded in the European Region in 2022 (4).

Ceftazidime-avibactam is a combination drug that contains a semi-synthetic third-generation cephalosporin as well as a new non-ß-lactam/ß-lactamase inhibitor. Avibactam protects ceftazidime from the hydrolytic activity of a variety of class A, C, and D -lactamases. (14). Relebactam is a new -lactamase inhibitor that inhibits both class A and class C -lactamases (15). Despite having no inherent antibacterial action, relebactam can protect imipenem from degradation by Ambler class A and class C -lactamases, as well as *Pseudomonas*-derived cephalosporinase (16). In vitro, relebactam significantly boosts imipenem's antibacterial activity against ESBL and Klebsiella pneumoniae carbapenemase (KPC) producing Enterobacterales, as well as multidrug resistance (MDR) or carbapenem resistant *P. aeruginosa* isolates (17).

In the "Study for Monitoring Antimicrobial Resistance Trends global surveillance program" relebactam restored imipenem susceptibility of imipenem-nonsusceptible *P. aeruginosa* and *K. pneumoniae*. Relebactam had no effect on the number of *Acinetobacter* spp. isolates sensitive to imipenem (18). A total of 150 clinical carbapenem resistance *Enterobacterales* (CRE) with a large proportion of *K. pneumoniae* isolates were investigated, and 63% were responsive to ceftazidime-avibactam and 62% were susceptible to imipenem-relebactam (19). According to Garca-Fernández et al. imipenem/relebactam inhibited 98.8% of *Enterobacterales* isolates and 92.2% of *P. aeruginosa* isolates. In addition, imipenem/relebactam remained efficacious against ceftazidime-resistant *P. aeruginosa* isolates (76.3%) and imipenem-resistant isolates (71.5%). A total of 75.1% and 46.2% of all multidrug-resistant or difficult-to-treat *P. aeruginosa* isolates were susceptible to imipenem/relebactam, respectively (20). Tamma et al. observed imipenem-relebactam was active against 88% of KPC-producing isolates and ceftazidime-avibactam was active against all of OXA-48-like carbapenemases (21). Hilbert et al. indicated the addition of relebactam raised imipenem susceptibility from 63.8% to 87.0% in *P. aeruginosa* isolates (22). Several in vitro experiments have been conducted to assess the activity of imipenem-relebactam against *P. aeruginosa*. In total, 94% of *P. aeruginosa* were susceptible to imipenem-relebactam. However, sensitivity to imipenem-relebactam was frequently greater than 70% in imipenem-resistant *P. aeruginosa* (23-26). In the current study resistance to imipenem-relebactam was observed 13.3% in *P. aeruginosa* isolates, which was consistent with prior research findings.

In a study conducted in 2021, relebactam was found to restore imipenem activity in KPC or AmpC-producing imipenem resistant *K. pneumoniae* strains. However, relebactam exhibited no activity against MBL-producing isolates. Relebactam restored imipenem susceptibility in 100%, 60%, and 49% of carbapenem-resistant *K. pneumoniae* isolates that exclusively harbored AmpC, extended-spectrum beta-lactamase (ESBL), and carbapenemases, respectively. The study emphasized the need for further research to evaluate the activity of relebaktam against isolates carrying bla OXA-48 or with altered efflux pump hyperactivity (27). Studies have shown that relebactam is susceptible in all KPC positive CRKPs (27,28). However, while a significant proportion of Oxa 48 positive strains were susceptible to relebactam, all MBL-producing strains were resistant to relebactam. Relebactam was found to have the highest activity on KPC carbapenemase and AmpC

ß-lactamase and no activity on MBL genes and efflux pump overactivity (27). In the current study resistance to imipenem-relebactam was reported 80.5% in *K. pneumoniae* isolates. This finding may be related to the possibility that the isolates in this study contained a significant number of MBL genes. Carbapenemases that are frequently identified in carbapenem resistant *A. baumannii* mainly belong to class B and D (29). Therefore there are studies in the literature reporting that relebactam does not potentiate the antibacterial effect of imipenem against carbapenem-resistant *A. baumannii* (18,30,31). In this study, 98.2% of A. baumanni isolates were resistant to imiipenem relebactam and our results are similar to previous studies.

Ceftazidime-avibactam inhibited 97.8% of all Enterobacterales and 91.7% of *P. aeruginosa* isolates, including those that were resistant to meropenem and ceftazidime (32). According to EUCAST, only ceftazidime was reported as intrinsic resistant for A. baummanni (33) and some studies investigated the efficacy of ceftazidime avibactam against A. baumanii.(32,34,35) When compared to other Gram-negative bacteria, *A. baumannii* has significantly greater resistance to ceftazidime-avibactam (32,34). Sader et al reported ceftazidime/avibactam exhibited limited activity against Acinetobacter spp. (34). MDR *A. baumannii* with blaOXA-51-like genes are totally resistant to ceftazidime-avibactam (36). In the current study, resistance to ceftazidime-avibactam was detected in 98.2% of cases, and the efficacy of ceftazidime-avibactam against *A. baumannii* isolates was found to be very low, consistent with findings in other studies. This is attributed to the overexpression of AmpC and/or blaOXA-51 ß-lactamase by *A. baumannii* isolates (23).

The current study provides in vitro data on the potential of two novel antimicrobial drugs, imipenem-relebactam and ceftazidim-avibactam, as tools for the treatment of carbapenem-resistant infections in *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*. The fact that genotyping resistance and metallo-beta-lactamase phenotyping were not conducted represents a limitation of the study. On the other hand, in vitro activity is an element of the complex decision-making process involved in selecting the most effective antibiotic (21).

In conclusion; controlling carbapenem-resistant bacterial infections, which are challenging to treat, plays a vital role, especially in hospitalized patients. Our results suggest that ceftazidime-avibactam could be beneficial and effective against carbapenem-resistant *K. pneumoniae* and *P. aeruginosa*. It has been observed that imipenem-relebactam is highly effective in *P. aeruginosa* isolates while less effective against *K. pneumoniae*. The impact of these antibiotics on *A. baumannii* isolates is also found to be quite limited in this study, as in previous research. These findings highlight the importance of conducting more comprehensive research aimed at developing effective diagnosis and treatment strategies against antimicrobial resistance. According to the current study, ceftazidime-avibactam are important alternatives, especially in the treatment of *K. pneumoniae* and *P. aeruginosa* isolates.

ETHICS COMMITTEE APPROVAL

* The study was approved by the Ethics Committee of the Tokat Gaziosmanpaşa University (Date: 16.03.2023 and Number: 23/KAEK/067).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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