Journal of Izmir Chest Hospital 2023;37(2):84–88
DOI: 10.14744/IGH.2023.85547

RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

# Ceftazidime-Avibactam Susceptibility of *Klebsiella pneumoniae* Isolates Obtained from Intensive Care Patients

# Yoğun Bakım Hastalarından Elde Edilen *Klebsiella pneumoniae* İzolatlarının Seftazidim-Avibaktam Duyarlılığı

[1]Güneş ŞENOL
[2]Mete DEMİREL
[2]Ayrız GÜNDÜZ
[2]Tuba ATAY
[2]Can BİÇMEN
[3]Süleyman Yıldırım

[1]Department of Infectious Diseases and Clinical Microbiology, İzmir Bakırçay University Faculty of Medicine, İzmir, Türkiye
[2]Department of Medical Microbiology, Health Science University, Suat Seren Chest Diseases Teaching Hospital, İzmir, Türkiye
[3]Department of Intensive Care Unit, Health Science University, Suat Seren Chest Diseases Teaching Hospital, İzmir, Türkiye

**ORCID ID**
**GŞ** : 0000-0002-1027-7578
**MD** : 0000-0003-0292-5296
**ATG** : 0000-0001-5133-7250
**TA** : 0000-0002-3471-5907
**CB** : 0000-0001-5392-570X
**SY** : 0000-0001-9856-3431

**ABSTRACT**

**Objective:** Antibiotic resistance encountered in agents causing intensive care unit (ICU) infections is a considerable problem in treatment. In recent years, multiple antibiotic resistances have been detected, especially in *Klebsiella pneumonia* isolates. Infections caused by these bacteria are difficult to handle and have a high mortality. In this study, the *in vitro* antimicrobial susceptibility rate of ceftazidime/avibactam (CAZ-AVI). on *K. pneumonia* isolates obtained from the samples of ICU patients was investigated.

**Material and Methods:** The study is designed as a cross-sectional cohort. CAZ-AVI susceptibility of *K. pneumonia* isolates obtained from patients diagnosed with ICU infection was studied by disc diffusion method.

**Results:** Among 37 *K. pneumonia* isolates isolated from 20 blood, 16 bronchial aspirate and one urine samples from ICU patients, 31 (83.7%) were found to be CAZ-AVI susceptible and 6 (16.3%) were resistant. 12 of the isolates are panresistant. It was observed that 3 (25%) of the panresistant strains were resistant to CAZ-AVI and 9 (75%) were susceptible.

**Conclusion:** In our study, it was determined that CAZ-AVI showed a low resistance rate even in *K. pneumoniae* strains that showed multi-antibiotic resistance. It was thought that it could be an alternative treatment option in ICU infections with antibiotic resistance problems.

**Keywords:** Ceftazidime/avibactam, drug resistance, *Enterobacteriaceae*, *Klebsiella pneumoniae*.

**ÖZ**

**Amaç:** Yoğun bakım ünitesi enfeksiyonlarına neden olan etkenlerde karşılaşılan antibiyotik direnci tedavide önemli bir sorundur. Son yıllarda özellikle *Klebsiella pneumoniae* izolatlarında çoklu antibiyotik direnci saptandı. Bu bakterilerin neden olduğu

**Cite this article as:** Şenol G, Demirel M, Gündüz A, Atay T, Biçmen C, Yıldırım S. Ceftazidime-Avibactam Susceptibility of *Klebsiella pneumoniae* Isolates Obtained from Intensive Care Patients. Journal of Izmir Chest Hospital 2023;37(2):84–88.

**Received (Geliş):** April 09, 2023 **Accepted (Kabul):** August 01, 2023 **Online (Çevrimiçi):** August 17, 2023
**Correspondence author (Sorumlu yazar):** Güneş ŞENOL, MD. İzmir Bakırçay Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, İzmir, Türkiye.
**Tel:** +90 536 257 16 87 **e-mail:** drshenol@yahoo.com

enfeksiyonların tedavisi zordur ve ölüm oranı yüksektir. Bu çalışmada, yoğun bakım ünitesi hastalarından alınan örneklerden elde edilen *K. pneumoniae* izolatlarının seftazidim/avibaktama karşı *in vitro* antimikrobakteriyel duyarlılık oranı çalışıldı.

**Gereç ve Yöntemler:** Çalışma kesitsel bir kohort olarak tasarlandı. Yoğun bakım ünitesi enfeksiyonu tanısı alan hastalardan elde edilen *K. pneumoniae* izolatlarının seftazidim/avibactam duyarlılığı disk difüzyon yöntemi ile çalışıldı.

**Bulgular:** Yoğun bakım hastalarından alınan 20 kan, 16 bronş aspiratı ve bir idrar örneğinden izole edilen 37 *K. pneumoniae* izolatlarının 31'i (%83,7) seftazidim/avibaktama duyarlı, 6'sı (%16,3) dirençli bulundu. İzolatların 12'si pandirençli olarak saptandı. Pandirençli suşların 3'ünün (%25) seftazidim/avibaktama dirençli, 9'unun (%75) duyarlı olduğu görüldü.

**Sonuç:** Çalışmamızda çoklu antibiyotik direnci gösteren *K. pneumoniae* suşlarında bile CAZ-AVI'nin düşük direnç oranı gösterdiği belirlendi. Antibiyotik direnci sorunu olan yoğun bakım ünitesi enfeksiyonlarında alternatif bir tedavi seçeneği olabileceği düşünülmüştür.

**Anahtar kelimeler:** *Enterobacteriaceae*, *Klebsiella pneumoniae*, ilaç direnci, seftazidim/avibaktam.

## INTRODUCTION

Multidrug-resistant (MDR) *Enterobacteriaceae*, leading *Klebsiella pneumoniae*, are important menace to hospitalized patients, being related with high mortality rates and bad clinical consequences.[1] Limitations of available treatment options may cause to a delay in treatment time that patients with MDR *K. pneumoniae* (MDR-Kp) infections tend to be critically ill.[2] According to the World Health Organization's antimicrobial resistance report, carbapenem resistant *Enterobacteriaceae* are considered as a special group for drug- resistant infections.[3] Centers for disease control have defined CRE such as *Klebsiella* species, *Escherichia coli*, and *Enterobacter* species as foremost global threat for the drug resistance.[4]

The increased resistance rates of Gram-negative bacteria have restricted the treatment alternatives.[5] At present, there are new antibiotics that they might have been as options to cope with these resistant agents; however, their efficacy is scarce due to reported variable resistance rates.[6]

Recently, ceftazidime/avibactam (CAZ-AVI) was launched as alternative antibiotic which is a combination of a third-generation cephalosporin with a synthetic-lactamase inhibitor. It has efficiency against Gram-negative bacteria such *Enterobacteriaceae* with produces of extended spectrum beta-lactamase, *K. pneumoniae* carbapenemases, and AmpC.[7]

The data indicate that the adding of avibactam expands (4-to-1024-fold MIC reduction) the activity of ceftazidime against most *Enterobacteriaceae* species with or without having a b-lactamase enzymes.[8]

CAZ-AVI is approved by the US food and drug administration and European medicines agency for the treatment of intra-abdominal infections, complicated urinary tract infections (UTI) and hospital-acquired bacterial *pneumonia*.[9,10] Nevertheless, the increasing resistance rate to CAZ-AVI should be noted.[11]

At present, in Türkiye colistin, polymyxin B, tigecycline, and fosfomycin are available, in combination with carbapenems the most common treatments for MDR-Kp infection. In this report, it is aimed to discuss the data on the *in vitro* activity of CAZ-AVI in MDR-Kp isolates obtained from patients with intensive care unit (ICU) infection.

## MATERIAL AND METHODS

The study was conducted at a Chest Diseases and Chest Surgery referral hospital ICU with 29 beds.

*K. pneumonia* isolates isolated from ICU patient samples from patients diagnosed with ICU infection in the first 6 months of 2021 was studied. Only one isolate per patient was collected. Conventional microbiological culture method was used for isolation of bacteria. Identification was applied by standard biochemical tests and Phonix semi-automated system (Becton-Dickinson Microbiology Systems, Sparks, MD, USA).

CAZ-AVI and other antibiotic susceptibilities were studied by disc diffusion method according to EUCAST standards.[12] Isolates with an inhibition diameter of 13 mm and above were determined as susceptible, and strains below 13 mm were determined as resistant.

*E. coli* ATCC 25922 is used as the quality control strain.

Descriptive statistical analysis was performed.

Ethical approval was taken as date and number: June 18, 2021/41-37.

## RESULTS

Among 37 *K. pneumonia* isolates isolated from 16 blood, 20 bronchial aspirate and 1 urine samples from ICU patients, 31 (83.7%) were found to be CAZ-AVI susceptible and 6 (16.3%) were resistant. Twelve of the isolates are panresistant. It was observed that 3 (25%) of the panresistant isolates were resistant to CAZ-AVI and 9 (75%) were susceptible. Distribution of isolates according to infection types is given in Figure 1. Five of 6 CAZ-AVI resistant isolates (83%) originate from blood samples. The susceptibility rates of isolates to antibiotic groups and resistance rates to other antibiotics according to CAZ-AVI susceptibility status are also shown in Table 1.

## DISCUSSION

This study reports on the activity of CAZ-AVI in MDR-Kp isolates recovered from patients with ICU infections.

As shown in other publications, CAZ-AVI is an effective antibiotic against MDR *Enterobacteriaceae* isolates.

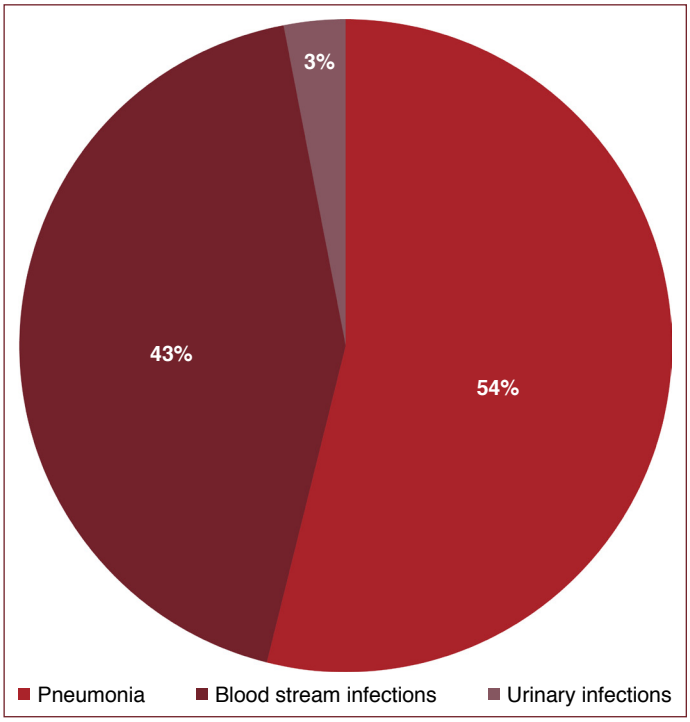


**Figure 1:** Distribution of *Klebsiella pneumoniae* isolates according to infection site.

In very recent study by Kiratisin et al.[13] was reported that all isolates of carbapenemase-producing *Enterobacteria* other than metallo-β-lactamase from Africa/Middle East or Latin America were sensitive to CAZ-AVI; resistance rates in Europe and Asia/South Pacific were ≤4.5. While isolates producing NDM carbapenemases were susceptible only to colistin, the lowest resistance rate was found to CAZ-AVI (1.5%) among all *Enterobacteria* carrying KPC carbapenemases.

Many similar articles have been published. The rate of resistance of CAZ-AVI against 121 carbapenem-resistant *K. pneumoniae* (CARB-R Kp) strains obtained from ICU patients was reported 19.01% (23/121) by Chen et al.[14] They indicated that 15 out of 23 CAZ-AVI-resistant CARB-R Kp isolates have been expressed NDM type beta-lactamase.

Flamm et al.[15] indicated that for *Klebsiella* spp., CAZ-AVI were very high active against isolates from each of the blood stream infections (BSI), intra-abdominal infections and UTI. Against *Klebsiella* spp. CAZ-AVI MIC values were ≤4 mg/L. There were two isolates from patients with *pneumonia*, both carbapenem resistant *K. pneumoniae* with CAZ-AVI MICs were 32 mg/L; the rest of the *Klebsiella* spp. Isolates from *pneumonia* patients (99.7%) had CAZ-AVI MIC levels were ≤4 mg/L. For CAZ-AVI, MIC90 values of *Klebsiella* spp. with the extended-spectrum beta lactamase (ESBL) producing isolates ranged from 1 to 2 mg/L for from all infection types while 0.25 mg/L for non-ESBL phenotype isolates. A total of 99.2% of ESBL phenotype *Klebsiella* spp. isolates showed CAZ-AVI MIC values ≤2 mg/L, except only two isolates with both 32 mg/L.

All *K. pneumoniae* isolates (n=350; including ESBL positive= 84; non-meropenem susceptible= 12) were found susceptible to CAZ-AVI in another study by Flamm et al.[16]

Jean et al.[17] reported that while 99.1% of all blood isolates were susceptible, two of the four KPC-resistant isolates were also resistant to CAZ-AVI.

Mavroidi et al.[18] had studied during 2014–2016, a total of 248 CAR-R Kp were isolated from a Greek ICU unit. Molecular characterization of the susceptibility of CAZ-AVI against to CAR-R Kp was studied. The mostly CAR-R Kp from BSIs (n=53) were OXA-48 (43.4%) and KPC (33.9%) producers. CAR-R Kp (n=28) consisted 52.8% of 53 CARB-R Kp obtained from BSIs. CAZ-AVI was effective against all OXA-48 and KPC producers.

Sader et al.[19] reported that *Klebsiella* species (n=433) isolated from hospitalized patients with *pneumonia*, containing ventilator-associated *pneumonia* patients, from 76 U.S. medical centers have been showed that ESBL producers were 99.5%, CR strains were 98.1% susceptible to CZA.

CAZ-AVI was found effective in ICU infections generally. Sader et al.[20] analyzed antibiotic resistance rates in another study comparing 4381 ICU unit bacterial isolates and 14 483 organisms from non-ICU infections. CAZ-AVI was active against 99.8 and 100.0% of *Enterobacteriaceae* from ICU and non-ICU patients, respectively, including MDR strains (99.3%), extensively drug-resistant strains (96.5%) and CR strains (98.0%).[21]

Treating ICU patients within 24 h with a beginning therapy containing two or more antibiotics having *in vitro* activity against the KPC-Kp isolates are also more likely to associate with survival.[22,23]

In the presence of non-NDM beta-lactamase, CAZ-AVI sensitivity is splendid. CAZ-AVI may be involved in the treatment of non-NDM B-lactamase-secreting isolates with known KPC resistance gene.[24]

When treatments with CAZ-AVI are compared with antibiotics known to be susceptible, better results are obtained in 14-day microbiological suppression, 14- and 28-day survival rates.[25]

## Limitations of Our Study

The number of studied isolates is small. Antibiotic resistance analyzes at the molecular level could not be performed. We did not have

**Table 1: Resistance rates of other antibiotics according to CAZ-AVI susceptibility status n (%)**

| | Carbapenems | | Ceftazidime | | Quinolones | | Aminoglycosides | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| CAZ-AVI-S (n=31) | 15 | 48.6 | 28 | 90.3 | 18 | 58 | 9 | 29 |
| CAZ-AVI-R (n=6) | 6 | 100 | 6 | 100 | 6 | 100 | 3 | 50 |

CAZ-AVI-S: CAZ-AVI-susceptible, CAZ-AVI-R: CAZ-AVI-resistant

data related to the carbapenemase genes, which were associated with the mechanisms responsible for resistance.

## CONCLUSION

Knowing the local antibiotic resistance profile, rapid and appropriate antibiotic selection is very critical in the management of ICU infections caused by antibiotic resistant bacteria. According to our experience, the use of CAZ-AVI will both reduce the consumption of carbapenems and increase the chance of treatment success in infection with resistant agents. Given the limited treatment options to treat infections caused by carbapenemase producing Enterobacterales continued surveillance of CAZ-AVI activity is crucial.

### Disclosures

**Ethics Committee Approval:** The study was approved by The Health Science University, Suat Seren Chest Diseases Teaching Hospital Clinical Research Ethics Committee (date: 18.06.2021, number: 41-37).

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – G.Ş., M.D., A.G., T.A., C.B., S.Y.; Design – G.Ş., M.D., A.G., T.A., C.B., S.Y.; Supervision – G.Ş., M.D., A.G., T.A., C.B., S.Y.; Fundings – G.Ş., S.Y.; Materials – G.Ş., M.D.; Data Collection and/or Processing – G.Ş., M.D., S.Y.; Analysis and/or Interpretation – G.Ş., M.D.; Literature Search – G.Ş., S.Y.; Writing – G.Ş.; Critical Reviews – G.Ş.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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