Original Article Acta Med Eur. 2024;6(2):9-13

Acta Medica Europa

ISSN Online: 2996-1211 doi: 10.5281/zenodo.10701658

Ceftazidime-Avibactam Resistance Rates Increased in Gram-Negative Bacteria with the COVID-19 Pandemic

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Article Info

Received: 10 February 2024

Revised: 24 February 2024

Accepted: 24 February 2024

Published: 24 February 2024

Keywords:

Ceftazidime-avibactam, COVID-19, pandemic, resistance, Gram negative, Acinetobacter.

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ABSTRACT

Ceftazidime-avibactam combination is frequently used especially in hospital-acquired infections caused by Gram-negative bacteria. However, during the Coronavirus Disease 2019 (COVID-19) pandemic, which manifested itself in 2020, it has been reported that there has been an increase in the rates of resistance to antibiotics in general in many bacteria. In this study, it was aimed to investigate the resistance rates to ceftazidime-avibactam in Gram-negative bacterial isolates obtained from hospitalized patients, to compare the resistance rates according to years and the pandemic process, and thus to examine the effect of the pandemic on the resistance rates. A total of 2570 clinical samples taken from patients hospitalized in various wards of our secondary care hospital between January 2018 and December 2023 and sent to the microbiology laboratory for culture and where Gram-negative bacterial growth was detected as a result of culture were included in the study. Ceftazidime-avibactam resistance in all samples was tested by the disk diffusion method. The average age of the patients was 68.6±22.4 (range 0-102) and 997 (38.8%) were male. 86% of the samples came from intensive care units, and 32.0% belonged to the pre-pandemic period, 32.9% to the pandemic period, and 35.1% to the post-pandemic period. 57.0% of the samples were urine culture and 36.1% were tracheal aspirate. 2222 (86.5%) of the isolates obtained were enteric Gram-negative bacteria. The most frequently detected isolates were *Klebsiella* spp. (46.6%) and *Escherichia coli* (28.5%). *Acinetobacter* spp. (p<0.001), *Pseudomonas aeruginosa* (p=0.011), *E. coli* (p=0.001), *Klebsiella* spp. (p=0.003) and *Enterobacter* spp. (p=0.017) resistance rates to ceftazidime-avibactam in the pre-pandemic period were found to be significantly lower compared to the pandemic and post-pandemic periods. The findings obtained in our study showed that there was a sudden increase in the resistance rates to ceftazidime-avibactam in all Gram-negative enteric and non-fermenter bacterial isolates with the pandemic process, and that the resistance rates were especially high in non-fermenter bacteria, but ceftazidime-avibactam still maintained its effectiveness to some extent in enteric bacteria.

Cite as: Yanik K, Özkan A, Hepsev A, Coskun N, Yilmaz F, Görgün S. Ceftazidime-Avibactam Resistance Rates Increased in Gram-Negative Bacteria with the COVID-19 Pandemic. Acta Med Eur. 2024;6(2):9-13. doi: 10.5281/zenodo.10701658

INTRODUCTION

Ceftazidime is a third-generation cephalosporin that acts by inhibiting cell wall synthesis in Gram-negative bacteria. Avibactam is a beta lactamase inhibitor. Ceftazidime-avibactam combination is a good treatment option used due to the mechanism of increasing the effectiveness of ceftazidime due to the effect of avibactam against beta-lactamase production of bacteria (1-4).

Ceftazidime-avibactam is frequently used, especially in cases of hospital-acquired infections caused by Gram-negative bacteria. However, it has been reported that there has been an increase in resistance rates in recent years (3-7). It has been reported that the great increase in the number of patients in hospitals and the intensity of antibiotic administration to these patients, especially during the Coronavirus Disease 2019 (COVID-19) pandemic, which manifested itself in 2020, caused a general increase in antibiotic resistance in most bacteria. It has been shown that, with the pandemic all over the world, resistance rates against many antibiotics in bacteria have increased suddenly in 2020 (8-12).

Table 1. Distributions of some variables.

	n	%
n	2570	100.0
Year		
2018	404	15.7
2019	419	16.3
2020	431	16.8
2021	415	16.1
2022	429	16.7
2023	472	18.4
Period		
Pre-pandemic	823	32.0
Pandemic	846	32.9
Post-pandemic	901	35.1
Gender		
Male	997	38.8
Female	1573	61.2
Clinics		
Intensive care units	2210	86.0
Pediatrics	121	4.7
Internal medicine	81	3.2
Urology	55	2.1
Gynecology and obstetrics	24	0.9
General surgery	19	0.7
Orthopedics	19	0.7
Neurochirurgy	18	0.7
Chest diseases	12	0.5
Neurology	11	0.4
Specimen		
Urine	1465	57.0
Tracheal aspirate	929	36.1
Wound	104	4.0
Catheter tip	27	1.1
Sputum	26	1.0
Abcess	13	0.5
Cerepro-spinal fluid	6	0.2
Bacteria group		
Enteric	2222	86.5
Non-fermentary	348	13.5
Bacteria species		
***Klebsiella* spp.**	1198	46.6
Escherichia coli	732	28.5
Acinetobacter baumannii	237	9.2
***Enterobacter* spp.**	214	8.3
Pseudomonas aeruginosa	111	4.3
Other	78	3.0

In this study, it was aimed to investigate the resistance rates to ceftazidime-avibactam in Gram-negative bacterial isolates obtained from hospitalized patients, to compare the resistance rates according to years and the pandemic process, and thus to examine the effect of the pandemic on the resistance rates.

METHODS

Samples, identification and antibiotic susceptibility tests

A total of 2570 clinical samples taken from patients hospitalized in various wards of our secondary care hospital between January 2018 and December 2023 and sent to the microbiology laboratory for culture and where Gram-negative bacterial growth was detected as a result of culture were included in the study. Identification of the samples coming to the laboratory was done using traditional methods. Antibiotic susceptibility tests were performed by disk diffusion method. Isolates whose ceftazidime-avibactam resistance status was not tested in the relevant period were removed from the stocks at -20 °C and revived, and antibiotic susceptibility tests were performed for ceftazidime-avibactam. Susceptibility evaluations were made according to CLSI and EUCAST criteria (13,14). Data on previously studied tests were obtained by retrospectively scanning hospital records. Repeated samples from the same patient and cultures that were not tested for ceftazidime-avibactam were not included in the study.

Statistical analysis

All statistical analyzes in the study were performed using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were given as mean and standard deviation in numerical data, and distributions of nominal or ordinal variables were given as numbers and percentages. Comparisons between groups in terms of categorical variables were made with the Chi Square test. The results were evaluated within the 95% confidence interval and p values <0.05 were considered significant. Bonferroni correction was made where necessary.

RESULTS

The average age of the patients was 68.6±22.4 (range 0-102) and 997 (38.8%) were male. 86% of the samples came from intensive care units, and 32.0% belonged to the pre-pandemic period, 32.9% to the pandemic period, and 35.1% to the post-pandemic period. 57.0% of the samples were urine culture and 36.1% were tracheal aspirate. 2222 (86.5%) of the isolates obtained were enteric Gram-negative bacteria. The most frequently detected isolates were *Klebsiella* spp. (46.6%) and *Escherichia coli* (28.5%) (Table 1).

Ceftazidime-avibactam resistance rates of bacterial species by year are shown in Table 2. Acinetobacter spp. ($p<0.001$), Pseudomonas aeruginosa ($p=0.011$), E. coli ($p=0.001$), Klebsiella spp. ($p=0.003$) and Enterobacter spp. ($p=0.017$) resistance rates to ceftazidime-avibactam in the pre-pandemic period were found to be significantly lower compared to the pandemic and post-pandemic periods (Table 3).

Table 2. Resistance rates of the bacteria species according to the years.

	Ceftazidime avibactam resistant		**Total**	**p**
	n	**%**	**n**	
Acinetobacter baumannii				**0.003**
2018	18	**51.4**	35	
2019	16	**50.0**	32	
2020	35	74.5	47	
2021	27	79.4	34	
2022	33	78.6	42	
2023	38	80.9	47	
Pseudomonas aeruginosa				**0.014**
2018	3	**23.1**	13	
2019	7	**35.0**	20	
2020	7	43.8	16	
2021	13	76.5	17	
2022	13	72.2	18	
2023	15	55.6	27	
Escherichia coli				**0.001**
2018	1	**0.9**	111	
2019	2	**1.6**	123	
2020	3	**2.5**	122	
2021	13	10.8	120	
2022	10	8.1	123	
2023	12	9.0	133	
***Klebsiella* spp.**				**0.021**
2018	11	**5.7**	194	
2019	12	**6.3**	192	
2020	24	12.0	200	
2021	25	12.4	201	
2022	21	10.4	202	
2023	30	14.4	209	
***Enterobacter* spp.**				0.145
2018	3	8.1	37	
2019	3	7.5	40	
2020	8	23.5	34	
2021	7	23.3	30	
2022	7	22.6	31	
2023	10	23.8	42	

DISCUSSION

Ceftazidime-avibactam is an antibiotic combination that has been frequently used in many hospital-acquired infection cases in recent years. It has been reported to be very effective, especially in cases caused by Gram-negative bacteria. It is among the best treatment options for infections caused by carbapenem-resistant enteric bacteria. However, in recent years, it has been shown that there has been an increase in resistance rates in general (15-17). In our study, it was shown that resistance rates to ceftazidime-avibactam increased in Gram-negative bacterial isolates, especially during the pandemic period.

During the COVID-19 pandemic, there was an intense number of admissions to hospitals due to COVID-19 in hospitals all over the world, and there was a great increase in the inpatient rates due to their severe clinical condition. In addition, most of the patients were administered multiple antibiotics during the COVID-19 treatment process. In addition, due to the increasing patient density, there was a shortage of space and therefore there were significant deficiencies in taking the necessary precautions regarding isolation between patients, and as a result, there was an increase in hospital infections. In addition, there has been a significant decrease in the number of healthcare professionals in hospitals due to reasons such as contracting COVID-19 or shifting healthcare professionals to many different regions, and there have been disruptions in the necessary services for patients. These factors have led to an increase in the amount and variety of antibiotics used by patients. All these reasons have led to a significant jump in antibiotic resistance rates throughout the world during the pandemic period, especially in bacterial species that cause hospital infections (8-12,18). Bianco et al. (19) reported an outbreak of ceftazidime-avibactam-resistant Klebsiella in the COVID-19 pandemic. In our study, ceftazidime-avibactam resistance rates of Gram-negative bacterial isolates obtained from various clinical samples of patients hospitalized in our hospital were examined. Accordingly, while the ceftazidime-avibactam resistance rate in Acinetobacter isolates was 50.7% before the pandemic, it increased to 76.5% with the pandemic; From 30.3% to 60.6% in *Pseudomonas* isolates; From 1.3% to 6.6% in *E. coli* isolates; From 6.0% to 12.2% in *Klebsiella* isolates; It was observed that it increased from 7.8% to 23.4% in *Enterobacter* isolates. All these increases were found to be statistically significant. In addition, it was determined that the resistance rates to ceftazidime-avibactam did not continue to increase in all these bacterial species after the pandemic, and that there were similar resistance rates during the pandemic period and the post-pandemic period.

When the ceftazidime-avibactam resistance rates of the isolates were examined by years in our study, it was seen that the resistance rates in 2018 and 2019 were generally low, and there was a significant increase in the resistance rates in each bacterial species in 2020. It was determined that this increase did not continue in the years after 2020 and generally continued at similar rates. All these findings show that the resistance rates to ceftazidime-avibactam, especially in these Gram-negative enteric and non-fermenter bacterial species that frequently cause nosocomial infections, increased significantly with the pandemic process, and that the main reason for this increase was the pandemic.

Nosocomial infections caused by resistant Gram-negative bacteria develop frequently in hospital intensive care units. Broad-spectrum antibiotics, especially used before and after surgical interventions, are one of the important factors leading to the development of this resistance. However, determining the resistance profile of the infectious agent in these patients is of great importance, especially for surgeons (20-22). The findings from our study, which mostly included patients in intensive care units, show that the resistance rate to ceftazidime-avibactam is generally high in non-fermenter Gram-negative bacterial species, and ceftazidime-avibactam may not be a very good option in cases of infection caused by these species. However, it is observed that resistance rates to ceftazidime-avibactam are lower in Gram-negative enteric bacterial species and ceftazidime-avibactam can still be used as a treatment alternative in cases related to these factors.

Table 3. Resistance rates of the bacteria species according to the periods.

	Ceftazidime avibactam resistant		**Total**	**p**
	n	**%**	**n**	
Acinetobacter baumani				**<0.001**
Pre-pandemic	34	50.7	67	
Pandemi	62	76.5	81	
Post-pandemic	71	79.8	89	
Pseudomonas aeruginosa				**0.011**
Pre-pandemic	10	30.3	33	
Pandemi	20	60.6	33	
Post-pandemic	28	62.2	45	
Escherichia coli				**0.001**
Pre-pandemic	3	1.3	234	
Pandemi	16	6.6	242	
Post-pandemic	22	8.6	256	
***Klebsiella* spp.**				**0.003**
Pre-pandemic	23	6.0	386	
Pandemi	49	12.2	401	
Post-pandemic	51	12.4	411	
***Enterobacter* spp.**				**0.017**
Pre-pandemic	6	7.8	77	
Pandemi	15	23.4	64	
Post-pandemic	17	23.3	73	
Other				0.732
Pre-pandemic	1	3.8	26	
Pandemi	2	8.0	25	
Post-pandemic	1	3.7	27	

There were some limitations in our study. Since the study only aimed to examine the effectiveness of ceftazidime-avibactam on Gram-negative bacteria, the fact that resistance rates to other antibiotics were not evaluated can be seen as a limitation. However, the fact that the number of isolates is so high and that it is one of the rare current studies in the world examining the ceftazidime-avibactam resistance rate is an advantage of our study.

The findings obtained in our study showed that there was a sudden increase in the resistance rates to ceftazidime-avibactam in all Gram-negative enteric and non-fermenter bacterial isolates with the pandemic process, that the resistance rates were especially high in non-fermenter bacteria, but ceftazidime-avibactam still maintained its effectiveness to some extent in enteric bacteria.

Funding

This research received no external funding.

Conflict of Interest

The authors declares no conflict of interest.

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