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FREQUENCY OF CEFTAZIDIME-AVIBACTAM SUSCEPTIBILITY IN SPECIMENS OF CARBAPENEM-RESISTANT PSEUDOMONAS AERUGINOSA IN A TERTIARY CARE HOSPITAL

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Abstract

Objective: *To determine the frequency of Ceftazidime-avibactam (CAZ-AVI) susceptibility in specimens of Carbapenem-resistant Pseudomonas aeruginosa (CRPA) at a tertiary care hospital.*

Study design: *Cross-Sectional Study*

Place and duration of study: *Department of Microbiology, Combined Military Hospital Multan six months from December to May 2024.*

Methodology: *Specimens of carbapenem-resistant Pseudomonas aeruginosa were included in the study to find the susceptibility of Ceftazidime-avibactam using the standard Kirby Bauer disc diffusion method. Zones were interpreted following clinical standard institute (CLSI) 2023*

Results: *Out of a total of 103 CRPA specimens, 45.6% (47) were found to be sensitive to CAZ-AVI with an average zone of inhibition of 16.9 ± 8.8 mm. The male population of our study showed more susceptibility to CAZ-AVI as compared to females (55.3% vs. 44.7%). The majority (78.6%) of resistant cases were from inpatient department as compared to the outpatient department 21.4% (p-value <0.001). The majority of the resistant cases belonged to the (60-80) age group. In our study the most sensitivity was shown by BAL and sputum (87.5% and 75% respectively) whereas the most resistant cases were of Tracheal aspirate and blood i.e. 100% both (p-value <0.001).*

Conclusion*: High susceptibility of Ceftazidime-avibactam against Carbapenem resistant Pseudomonas aeruginosa is found in our study.*

INTRODUCTION

With the irrational use of broad-spectrum antibiotics, the emergence of multidrug-resistant Pseudomonas aeruginosa isolates has become a significant health problem worldwide[1]. It is reported the infection caused by CRPA is related to high level of morbidity and mortality[2].It is one of the leading causes of healthcare associated infections around the world[3]. In hospitals it can leads to prolonged hospital stay, immunosuppression and overall increase in resistance which accounts for greater healthcare costs[4]. It can cause complicated abdominal infections, blood stream infections, surgical site

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infections, urinary tract infections including nephritis, skin infections predominantly in burn patients, health care associated pneumonia and ventilator associated pneumoniae in intensive care units[5]. In patients with cystic fibrosis and bronchiectasis it may develop chronic and recurrent infections.

Currently, Carbapenems are considered as first line antimicrobial agents for the treatment of severe gram negative infections[6]. But it is not cost effective, have adverse effects and its excessive use in seriously ill patients has increased the resistance of the drug to serious life-threatening infections worldwide. However, with misuse the detection of Carbapenem-resistant Pseudomonas aeruginosa (CR-PA) patterns are on the rise globally. The resistance is attributed by the presence of enzymes Carbapenemsases that inactivate most β-lactam antibiotics[7]. One of the factors of its increase resistance in developing countries is use of medication without proper prescription or proper culture and sensitivity as per protocol.

Due to soaring of multi drug resistant and emergence of extensively drug resistant Pseudomonas aeruginosa in recent years highlights the fact that it is the high time to search for newer antimicrobial drugs. The aim is to search for the drug with maximum benefits for the better outcomes of the patients in hospital setups along with that implementation of strict antimicrobial stewardship policies and strong microbiological surveillance.

Ceftazidime-avibactam consisting of third generation cephalosporin - Ceftazidime and novel beta lactamase inhibitor avibactam was approved by Food and Drug administration in February 2015 for the treatment of complicated infections caused by multi drug resistant or extended drug resistant gram negative bacteria[8].

A review study regarding the global frequency of Carbapenem-resistant Pseudomonas aeruginosa showed the frequency to be ranging from 16.8 to 50%[9]. A study conducted in tertiary care hospital in Pakistan analyzed 155 (30.6%) CRPA strains isolated from different clinical specimens i.e. pus, blood, urine and endotracheal aspirate out of which 131 (84.5% were susceptible and 24 (15.5%) were found to be resistant. The age groups were between 18 to 86 years[10].

The rationale of the study is to increase the evidence base for the use of Ceftazidime-avibactam (CAZ-AVI) in patients with Carbapenem-resistant Pseudomonas aeruginosa infection. This will improve patient outcome by decreasing hospital stay and decrease the cost of treatment. This study aims to determine the frequency of Ceftazidime-avibactam susceptibility in specimens of Carbapenem-resistant Pseudomonas aeruginosa at a tertiary care hospital.

METHODOLOGY

This cross-sectional study was conducted in Department of Microbiology, Combined Military Hospital Multan six months after approval of the synopsis from December to May 2024. Ethical approval was obtained from the institutional ethics committee of Combined Military Hospital Multan (04/2024).

Inclusion criteria

All microbiological samples (blood, urine, pus) positive for Carbapenem resistant Pseudomonas aeruginosa, of either gender with age ranging from 18 - 65 years of age, admitted or outdoor patients were included in the study.

Exlusion criteria

Samples of the patients with comorbidities, recurrent and duplicate samples of Carbapenem resistant Pseudomonas aeruginosa were excluded from the study.

A sample size of 103 was calculated through WHO sample size calculator using the formula for single proportion keeping the frequency of Pseudomonas aeruginosa infection susceptibility to Ceftazidime-avibactam as 84.5%, desired precision 7% and level of confidence as 95%.

Patient characteristics including age (years), gender (male/female), type of specimen, indoor / outdoor cases were noted. Kirby-Bauer disk diffusion method was used to determine the antibiotics susceptibility of Pseudomonas aeruginosa by preparing inoculum of 0.5 Mc Farland standard. The suspension was streaked on Muller Hinton agar and antibiotic discs were applied as per standard guidelines. Plates were

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incubated at 37 degree for 24 hours and results were interpreted according to CLSI 2023 with caliper in Carbapenem resistant cases. Ceftazidime-avibactam (CAZ-AVI) discs were applied and results were interpreted according to CLSI guidelines. The zone of >=21 was considered as sensitive and zone of < 20 is considered as resistant.

Descriptive statistics were run for qualitative and quantitative variables in the form of mean±SD and frequency and percentages using SPSS version 23. Relation of CAZ-AVI susceptibility with age groups and type of specimen was assessed through chi-square test taking p-value < 0.05 as significant.

RESULTS

Out of a total of 103 specimens, 45.6% (47) were found to be sensitive to CAZ-AVI CRPA with an average zone of inhibition of 16.9 ± 8.8. The male population of our study showed more susceptibility to CAZ-AVI as compared to females (55.3% vs. 44.7%). The majority of resistant cases were from the Inpatient department 78.6% as compared to the Outpatient department 21.4% with significant p-value i.e. <0.001. Table 1

The majority of the sensitive cases belonged to the 14-25 age group whereas the majority of the resistant cases belonged to the 60-77 age group. Table 2. Moreover, a significant correlation (p-value <0.001) was found between age and zone of susceptibility with intermediate strength of association (r = -.58). This showed that with advancing age there was a decrease in the sensitivity to Ceftazidime avibactam. Table 3.

In our study the most sensitivity was shown by BAL and sputum (87.5% and 75% respectively) whereas the most resistant cases were of Tracheal aspirate and blood i.e. 100% both. Table 4. Furthermore, a significant association was found between the zone of susceptibility and specimen type (p-value <0.001).

Figure 1: Frequency of CRPA Specimen

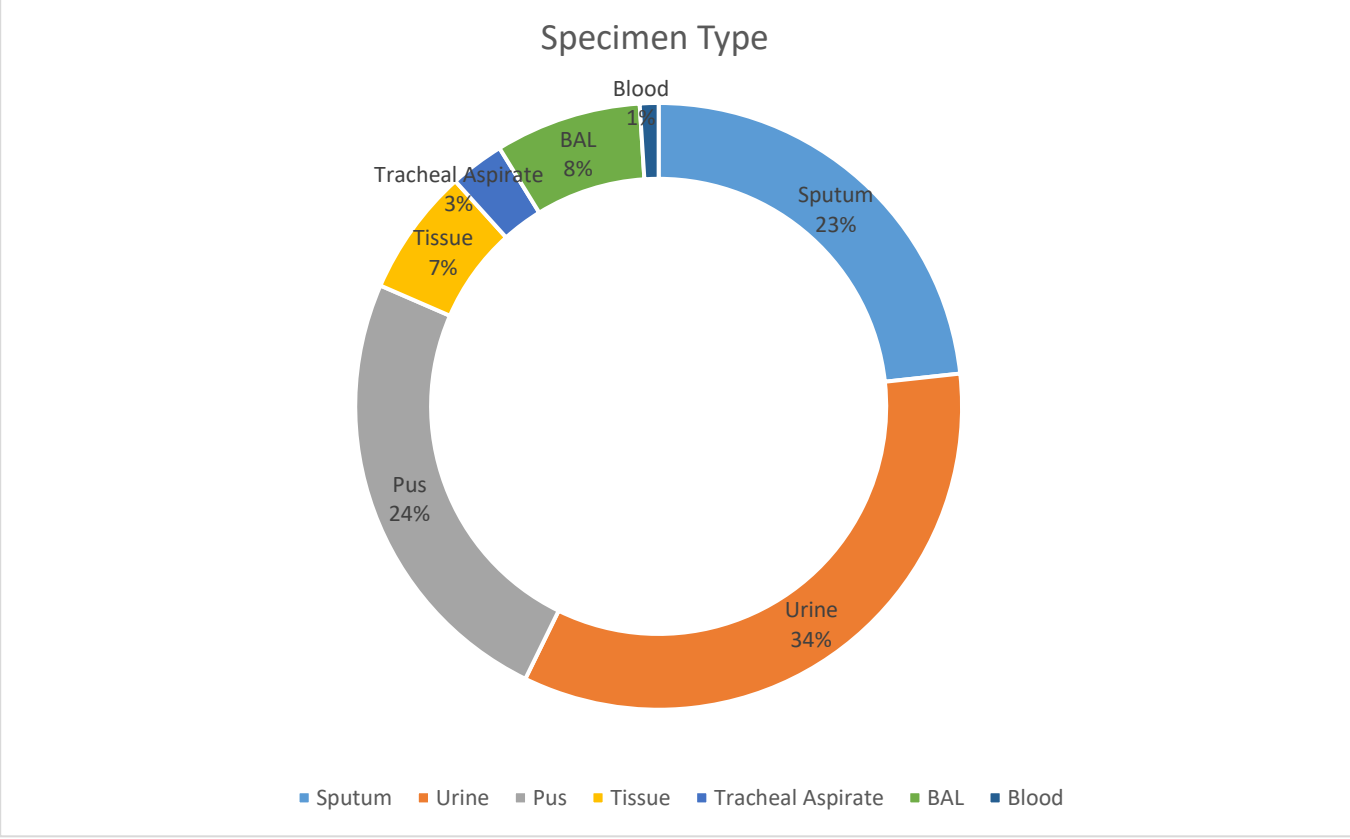

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Table 1: Location-wise Caz-Avi susceptibility in CRPA isolates

Location	Resistant n (%)	Sensitive n (%)	p-Value
IPD	44 (68.8)	20 (31.3)	<0.001
OPD	12 (30.8)	27 (69.2)	
Total	**56 (54.4)**	**47 (45.6)**	

Table 2: Age distribution and CAZ-AVI susceptibility in CRPA isolates (N=103)

Age Group	Resistant n (%)	Sensitive n (%)	p-value
14-25	1 (8.3)	11 (91.7)	<0.001
26-39	4 (17.4)	19 (82.6)	
40-59	20 (60.6)	13 (39.4)	
60-77	31 (88.6)	4(11.4)	
Total	**56 (54.4)**	**47 (45.6)**	

Specimen Type	Resistant n (%)	Sensitive n (%)	p-Value
Sputum	6 (25)	18 (75)	<0.001
Urine	19 (54.3)	16 (45.7)	
Pus	21 (84)	4 (16)	
Tissue	5 (71.4)	2 (28.6)	
Tracheal Aspirate	3 (100)	0 (0)	
BAL	1 (12.5)	7 (87.5)	
Blood	1 (100)	0 (0)	
Total	**56 (54.4)**	**47 (45.6)**	

Table 3: Correlation of Age and Caz-Avi Zone of susceptibility in CRPA isolates

Table 4: Distribution of specimen type and CAZ-AVI susceptibility in CRPA isolates (N=103)

Variable		Age	Zone of susceptibility
Age	r	1.000	-0.584
	p	-	<0.001
Zone of susceptibility	r	-0.584	1.000
	p	<0.001	-

DISCUSSION

In this study susceptibility Ceftazidime-avibactam in MDR Carbapenem resistant Pseudomonas aeruginosa came out to be 45.67%. This study will be helpful to overcome infections to overcome increasing rate of morbidity and mortality due to increase in resistant cases.

Currently, multi-drug resistant and extensive drug resistant, Pseudomonas aeruginosa is one of the leading causes of death in hospitals particularly in ICUs, severely ill patients with impaired immune system such as cancer patients or neutropenic patients[12]. Despite that, the impact of antimicrobial resistance on clinical outcomes of the patients and health care cost cannot be overlooked. Hospitalized patients are prone to other opportunistic infections as well. The need for better treatment options and speedy patient recovery always remains the first priority of the physician. So, that the right medications and good patient care both are crucial to overcome the increasing resistance.

In that scenario, testing the susceptibility of newer antibiotics is crucial. Susceptible antimicrobials drugs will provide us with better treatment options for

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seriously ill patients along in hospitals with good infection control practices particularly in intensive care units in particular.

In this study there is a significant susceptibility to newer antibiotic ceftazidime avibactam which will have positive impact in recovery of the patients with MDR Pseudomonas aeruginosa with limited treatment options.

Similarly, a study conducted in tertiary care hospital in Turkey showed greater susceptibility to ceftazidime avibactam than the conducted study as 84.5%[13]. This drug responded more in developed countries than under developed countries this may be due to lack of good hospital care and infection control measures in under privileged countries. Particularly the malpractice in rural areas are one of the culprit of increase in overall resistance.

A study was conducted in twelve different hospitals in Spain, Greece showed the frequency in their patients of MDR Pseudomonas aeruginosa is 30.2% whereas in this study it is 56%. The susceptibility was low in our countries may be due to advising antibiotics when necessary and strict compliance of infection control strategies[14]. The testing of susceptibility pattern of antimicrobial drugs MDR Pseudomonas aeruginosa is critical in under developed counties where there is misuse of antibiotics and due to contemporary antimicrobial stewardship in our hospital settings.

A study conducted in ten different Latin countries, the susceptibility of Ceftazidime-avibactam was found to be 86% whereas it is 47% in our study[15]. This trend showed that the response of the drug is relatively less but it will be helpful in critical situation where there will be no other treatment options. There is a limitation in the conducted study in comparison to the study conducted in Latin, that in-vitro activity of CAZ-AVI is not studied due to financial constraints. A study conducted in Sub Saharan Africa showed the resistance of Pseudomonas aeruginosa as 14% which was found to be less resistant[16].it means it has a negative correlation to this study.

In a study conducted in Qatar, 205 samples were taken, out which 68.8% were found to be susceptible to ceftazidime avibactam. Most commonly the organism was isolated from respiratory samples 44% followed by skin and soft tissue 26% and urinary isolates 23.4%[17]. Whereas in the conducted study, predominately organism was isolated from urine specimen 34%, followed by pus 24.34%, sputum 23.3%, bronchoalveolar lavage, 7.8%, tissue 6.8%, tracheal aspirate 2.9% and blood 1%[18].

A study conducted in tertiary care hospital predominately showed that the sensitivity of respiratory samples was found to be 85% whereas in the conducted study bronchoalveolar lavage was 87.5% followed by sputum 75%[19]. Respiratory samples are more sensitive to ceftazidi me in both the studs shows a positive co-relation.

The frequency of Ceftazidime-Avibactam (CAZ-AVI) in the treatment of Carbapenem-Resistant Pseudomonas aeruginosa (CRPA) round the globe is increasing drastically CAZ-AVI represents a novel therapeutic option, particularly in the context of multidrug-resistant organisms where treatment options are too limited.

In Iran, similar study was conducted the mean age of MRD Pseudomonas aeruginosa was 49 %, whereas in this study conducted it is also 49% and were mostly from the out- patient department. This may support the fact that majority of infections occurs in middle age[20]

The results vary in different geographical regions of the world it may be due to drug prescription strategies, surveillance, stewardship and infection control practices.

CONCLUSION: The susceptibility of Ceftazidime avibactam is found to be significant to treat multidrug resistant Pseudomonas aeruginosa in tertiary care hospital

LIMITATIONS

Due to lack of resources the in vitro activity of ceftazidime avibactam is not studied

CONFLICT OF INTEREST:

There is no conflict of interest.

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