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ORIGINAL ARTICLE

Frequency of Ceftazidime-Avibactam resistance in Pseudomonas aeruginosa: Experience at a Tertiary Care Hospital.

Mahnoor Chaudhry[1], Kokab Jabeen[2], Zainab Tufail[3], Sana Mustafa[4], Seerat Fatima Tu Zahra[5], Sara Mahmood[6]

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ABSTRACT... Objective: To isolate Pseudomonas aeruginosa from different clinical samples and determine the antimicrobial activity of Ceftazidime/avibactam against these isolates. **Study Design:** Prospective Cross-sectional study. **Setting:** Pathology Laboratory of Lahore General Hospital, Lahore. **Period:** July 2023 to June 2024. **Methods:** One hundred thirteen Pseudomonas aeruginosa were identified from different samples Bacterial identification was done by gram staining, bench tests, and API20NE. The antimicrobial sensitivity testing of the causative bacteria was conducted, using commercially available discs, by Kirby Bauer disc diffusion assay and reported in accordance with Clinical & Laboratory Standards Institute (CLSI) 2022. **Results:** Out of 113 resistant strains of Pseudomonas aeruginosa obtained from different clinical samples Ceftazidime/avibactam was only sensitive to 43.4% of strains and resistant to 56.6% of them. **Conclusion:** According to the findings of this study, Pseudomonas aeruginosa, a nosocomial organism is isolated from many different clinical samples. The findings of this study also indicate that even a new combination antibiotic fails to show sensitivity in more than half of the isolates. This is a frightening situation that places stress on avoiding the misuse of antibiotics and following anti-microbial stewardship.

Key words: Anti-microbial Resistance, Ceftazidime/Avibactam, Pseudomonas Aeruginosa.

INTRODUCTION

Pseudomonas aeruginosa are Gram-negative bacteria that cause nosocomial infections. It has many virulence factors and causes a variety of infections.[1] In the hospital setting, they might be present on mattresses, ventilator machines, humidifiers, other types of equipment, and on the skin of healthcare workers.[2] It leads to both acute and chronic infections. Acute infections like respiratory infections, urinary tract infections, keratitis, otitis media, and bacteremia occur. Chronic infections are mostly in patients with burns, HIV (Human Immunodeficiency Virus), cystic fibrosis (CF), and cancer patients undergoing chemotherapy. These infections frequently result in significant morbidity and mortality due to the organism's ability to easily modify by environmental changes and potentially develop antibiotic resistance.[3] In cystic fibrosis patients Pseudomonas spp. colonizes the airway leading to worsening and gradual lung function decline.[4]

Antimicrobial resistance develops due to the outer membrane which is thick in lipopolysaccharide, reduced permeability of the outer membrane, production of enzymes that inactivate antimicrobials, and efflux pumps.[5] Because of multidrug efflux pumps and endogenous antimicrobial inactivation, P. aeruginosa has primary resistance to many antimicrobial agents. P. aeruginosa's ability to develop resistance to multiple classes of antibacterial agents complicates antibiotic selection, and the selection of appropriate antibiotics to begin treatment is crucial in optimizing clinical outcomes.[6]

Ceftazidime-Avibactam is a combination antimicrobial consisting of ceftazidime, third-generation cephalosporin, and avibactam,

1. MBBS, M.Phil, Senior Demonstrator Microbiology, Shalamar Medical and Dental College, Lahore.
2. MBBS, M.Phil, Ph.D, Professor Pathology, Sahiwal Medical College, Sahiwal.
3. MBBS, Resident Microbiology, Lahore General Hospital, Lahore.
4. MBBS, Resident Microbiology, Lahore General Hospital, Lahore.
5. MBBS. M.Phil (Microbiology), Senior Demonstrator Pathology, Shalamar Medical and Dental College, Lahore.
6. MBBS, M.Phil (Microbiology), Senior Demonstrator Pathology, Fatima Memorial Medical and Dental College, Lahore.

Correspondence Address:
Dr. Mahnoor Chaudhry
Department Microbiology
Shalamar Medical and Dental College, Lahore.
mahnoorchaudhry474@gmail.com

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a non-beta lactam- beta-lactamase inhibitor. Comparable to amikacin and ceftolozane–tazobactam, ceftazidime–avibactam shows better in vitro activity against P. aeruginosa compared to fluoroquinolones and beta-lactam agents.[7] Antibiotic therapies designed to overcome carbapenem-resistance mechanisms are required to potentially treat carbapenem-resistant bacteria and other MDR organisms. Ceftolozane/tazobactam and ceftazidime/avibactam were the first cephalosporin and beta-lactamase inhibitor combinations approved by the US Food and Drug Administration (FDA). Like certain other beta-lactam antibiotics, ceftazidime/avibactam and ceftolozane/tazobactam are bactericidal inhibitors of bacterial cell wall synthesis and could be used for the treatment of complicated intra-abdominal infections (cIAI) due to resistant Enterobacteriaceae and P.aeruginosa.[8] Ceftazidime-avibactam is a combination antibiotic that was granted approval by the Food and Drug Administration (FDA) in 2015 for the medical management of complicated intra-abdominal infections (cIAI), Hospital-acquired pneumonia (HAP), complicated urinary tract infections (cUTI), and Ventilator-associated pneumonia (VAP) in children as well as adults. Additionally, the European-Medicines-Agency (EMA) has expanded its use to include infections brought on by aerobic Gram-negative bacteria in patients who have few available treatment alternatives. This Beta-lactam/Beta-lactamase Inhibitor combination has rapidly established itself as a primary treatment option for difficult-to-treat Gram-negative bacterial infection.[9]

OBJECTIVE

To isolate Pseudomonas aeruginosa from clinical samples and to determine the activity of ceftazidime/avibactam against them.

METHODS

The Prospective cross-sectional study was carried out in the Pathology Laboratory of Lahore General Hospital, Lahore. Ethical approval was taken from research and ethical committee, PGMI/ AMC/ LGH Lahore with reference number: UHS/Education /126-23/3306.The samples (Blood, Urine, CSF, Sputum, Pus, Wound Swab, Tracheal secretions, External Ventricular drain tips, Fluids, Tissues and Ear swabs) received in the Microbiology laboratory from July 2023 to June 2024 were evaluated. Clinical isolates taken from blood, pus, urine, etc. were included. Repeated samples from the same patients in the same course of illness were excluded.

The samples for blood culture were received in blood culture bottles. These were incubated at 35°C for 5 days. The first subculture was performed on blood agar and MacConkey agar after 24 hours. In case of no growth, the second subculture was performed on the same media on day 3 and then on day 5. If no growth was isolated after the subcultures, the report of no growth was finalized after 5 days of incubation. Samples other than blood were immediately sub-cultured on Blood agar and MacConkey agar and incubated at 37C for 24 hours. If no growth was observed, a report of no growth was finalized. However, the positive cultures were processed for bacterial identification using colony morphology, gram staining, oxidase test, and API 20NE. The antibiotic susceptibility testing of the isolated bacteria was conducted by using the Modified Kirby Bauer disc diffusion assay. The bacterial suspension equivalent to 0.5 McFarland turbidity standard was prepared by emulsifying 3-4 colonies of bacteria in normal saline. The suspension was lawned on the Mueller-Hinton agar plates with sterile swabs followed by putting antibiotic discs. These plates were incubated overnight at 35°C and the zones of inhibition were interpreted in accordance with Clinical & Laboratory Standards Institute (CLSI) 2022.[16]

Data management and analysis were performed using the Statistical Package for Social Sciences (SPSS; Version 26.0) Categorical descriptive variables like gender, and ceftazidime-avibactam resistance, were presented as frequencies and percentages. Continuous numerical variables like age were described as mean and standard deviation.

RESULTS

A total of 113 Pseudomonas aeruginosa strains were taken 75(66.37%) of them were isolated

from males and 38(33.63%) were isolated from females. Ceftazidime/avibactam is only sensitive to 43.4% of strains and resistant to 56.6% of them. (Table-I). The susceptibility pattern of other drugs is mentioned in (Table-II).

Pseudomonas. Aeruginosa Strains	Frequency n=113	Percent
Resistant	64	56.6
Sensitive	49	43.4
Total	113	100.0

Table-I. Distribution of Pseudomonas. aeruginosa strains concerning activity of Ceftazidime/avibactam

Drugs	Resistant		Sensitive	
	Frequency	Percentage	Frequency	Percentage
PRL	112	99.1%	1	0.9%
TZP	79	69.9%	34	30.1%
CAZ	89	78.8%	24	21.2%
FEP	86	76.1%	27	23.9%
IPM	75	66.4%	38	33.6%
MEM	75	66.4%	38	33.6%
AK	67	59.3%	46	40.7%
CN	75	66.4%	38	33.6%
CIP	97	85.8%	16	14.2%
LEV	100	88.5%	13	11.5%
NOR	17	15.05	3	2.7%

Table-II. Frequency of activity of P.aeruginosa panel (CLSI 2022)

NOR was not applicable for 93 samples.

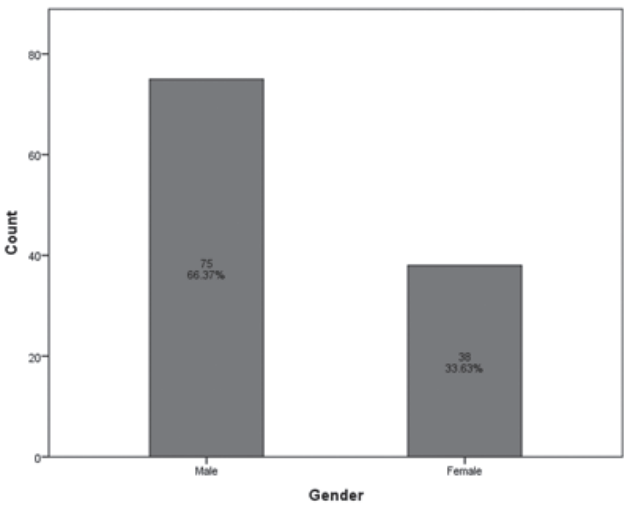

Figure-1. Gender-wise distribution of Pseudomonas aeruginosa

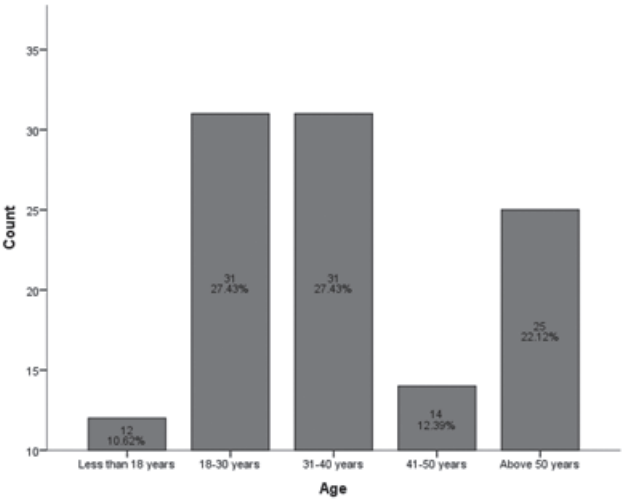

Figure-2. Age- distribution of pseudomonas aeruginosa

DISCUSSION

Pseudomonas aeruginosa contributes to 10% of nosocomial infections and is considered to be one of the most significant causes of healthcare-associated infections. Pseudomonas aeruginosa has a high propensity to develop resistance to a wide variety of antibiotics; hence, there has been an instant emergence of multidrug-resistant Pseudomonas aeruginosa in recent times, which is regarded as a significant difficulty for medical professionals.[10]

The current study shows that 66.37% of Pseudomonas aeruginosa is isolated from male patients and 33.63% is isolated from female patients with a prevalence of 10.62% among people less than 18 years of age, 27.43% in 18-30 years of age, the same prevalence was found in people between 31-40 years of age, 41-50 years showed 12.39% above 50 years of people showed the prevalence of 22.12%. According to a study conducted in Iraq Kirkuk University, this bacterium is isolated from 56.2% of males and 43.7% of females with 30% among young patients (23-28 years). Geographical location and variations in hygiene practices may be the cause of the variability in prevalence rates across multiple research based on age and gender.[11] The outcome is similar to the study conducted in Nigeria which revealed that 52.8% of the patients were male the age group that had the

highest prevalence of this bacteria (20.7%) was individuals under the age of 29.[12] Conversely, these outcomes conflict with findings in the Iraqi city of Karbala, research studies conducted by Shewatatek et al. in Ethiopia and Ekrem and Rokan in Al-Sulaimania City, Iraq, revealed higher bacteria presence in older and female patients.[13]

The activity of Ceftazidime/avibactam in our current study shows resistance in 56.6% of isolates and susceptibility to 43.4% of resistant strains isolated. This is contrary to a global surveillance program checking susceptibility patterns of CZA and colistin against Pseudomonas aeruginosa, which showed 91.5% sensitivity for CZA and 96.2% sensitivity for colistin.[14] According to Nichols et al., It was found that 93.2% of Pseudomonas aeruginosa isolated from a total of nine Asia-Pacific nations (about 41 laboratories, 1,392 isolates) were sensitive to CAZ-AVI, and around half of the resistant isolates possessed genes expressing MBLs, which could explain for their resistance. Additionally, Nichols et al. found that 71.7% of strains that were non-susceptible to meropenem and 68.9% of strains that were non-susceptible to ceftazidime were sensitive to CAZ-AVI. These results were based on the fact that a combination of antibiotics was used. The current examination, which is a continuation of the Nichols et al. study with one extra year of data, found that 92.6% of all P. aeruginosa isolates were sensitive to CAZ-AVI, with an MIC90 of 8 ug/ml.[15]

CONCLUSION

This research indicates that a nosocomial bacteria known as Pseudomonas aeruginosa can be isolated from a wide variety of clinical samples. According to the results of this research even a newly developed antibiotic combination does not demonstrate sensitivity in the treatment of more than half of the isolates. This is a terrifying situation that highlights the importance of avoiding the improper use of antibiotics and adhering to anti-microbial stewardship practices.

LIMITATIONS

This study is based on data collected only from Lahore General Hospital (Single centered study). This data is only about the antimicrobial susceptibility pattern of Pseudomonas aeruginosa. In the future studies must be conducted on genetic mechanisms conveying resistance in these multidrug resistance pathogens.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Mahnoor Chaudhry	Manuscript writing, Description.	
2	Kokab Jabeen	Data analysis, Review and Final approval.	
3	Zainab Tufail	Data collection, Proof reading.	
4	Sana Mustafa	Data analysis, Manuscript writing.	
5	Seerat Fatima Tu Zahra	Statistical analysis, Discussion.	
6	Sara Mahmood	Data analysis and discussion.