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Original Article

Prevalence and Antimicrobial Susceptibility Pattern of Mono therapy and combination therapy of Cefepime in *Pseudomonas aeruginosa* isolates of patients from a tertiary care hospital in Karachi, Pakistan

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ABSTRACT

Introduction: *Pseudomonas aeruginosa* is a bothersome pathogen on the rise and prone to developing resistance during treatment. Hospitalized patients are especially prone to its detrimental effects.

Aims: To determine the prevalence and antimicrobial susceptibility pattern of Mono therapy and combination therapy of Cefepime in *Pseudomonas aeruginosa* isolates obtained from patients at a tertiary care hospital in Karachi, Pakistan.

Methods: This study was conducted at a university-affiliated, urban teaching hospital. During a 2-year period (January 2013 to December 2015), all hospitalized patients with a positive blood culture for *P. aeruginosa* were eligible for this investigation, amounting to a sample size of 634, and a cross sectional study was performed. Standard microbiological methods were used to identify the clinical isolates. The isolates were cultured on chocolate and MacConkey agar.

Results: Throughout the duration of this study, 634 isolates of *P. aeruginosa* were cultured. Positive cultures were then tested against the following drugs: Cefepime, Meropenem, Amikacin and Ciprofloxacin. Cefepime was 76.2% (483) sensitive for isolates while the age and sex relationship analysis showed that isolates gathered from 0-18 year old females were 94.6% sensitive to Cefepime. Around 63.25% isolates were sensitive to the combination of Cefepime and Amikacin while the combination offering the least resistance was that of Cefepime and Ciprofloxacin (71%).

Conclusions: *P. aeruginosa* isolates show a progressive trend of resistance to Cefepime. Cefepime when used in combination with Ciprofloxacin, potentially will be more effective than monotherapy with Cefepime.

Key words: *P. aeruginosa,* Cefepime, B-lactam, Susceptibility pattern, Antimicrobials, Karachi.

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INTRODUCTION

Pseudomonas aeruginosa has emerged as quite a challenging pathogen for clinicians. Resistant strains of *P. aeruginosa* were first detected in Western Europe in the 1980s, and then in 1991 they were reported in Japan, leading this to become a growing concern worldwide.[1] *Pseudomonas aeruginosa* bacteremia occurs most frequently in critically ill patients, particularly those who are immunocompromised such as cystic fibrosis patients,burn victims and ICU patients.[2,3] It stands to reason then that there is an increased predisposition amongst hospitalized HIV positive patients for contracting this pathogen as demonstrated by Tacconelli E *et al.*[5] Chronic *P. aeruginosa* infections lead to lung tissue destruction which ultimately results in an untimely death for the patient[4] *P. aeruginosa* demonstrates staggering statistics when it comes to nosocomial infections; being the 2nd most common pathogen to cause pneumonia, 8th most common for bacteremia, and 3rd most common for urinary tract infections as demonstrated by the Center of Disease Control and Prevention (CDC), Nosocomial Infection Surveillance System in the United States of America.[6] With this pathogen contributing 10-20% to nosocomial infections ,it is regarded as the bane of a hospitalized patient.

The Carbapenems, namely Imipenem and Meropenem were known for their effectuality against this dreaded pathogen, but recent studies have shown that the efficacy of these drugs has decreased due to a growing resistance to these compounds, which is a cause of apprehension for clinicians.[7] Since *P. aeruginosa* develops resistance to antibiotics during the course of treatment[8] and is also intrinsically resistant to a myriad of drugs owing to the

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broadly specific drug efflux pump and its synergy with the low degree of outer membrane permeability,[10,11] it is quite a vexing pathogen.

Cefepime is a 4th gen cephalosporin that has a broad spectrum antibacterial activity. Its coverage is better than 3rd gen cephalosporins[10] which is why Cefepime was recommended as a treatment of pneumonia and cystic fibrosis.[12,13] The objective of the current study was to determine the anti microbial susceptibility patterns of Mono therapy and combination therapy using Cefepime against *Pseudomonas aeruginosa* isolates obtained from patients at a tertiary care hospital in Karachi, Pakistan.

MATERIAL AND METHODS

This cross sectional study was conducted at the Microbiology Department of Ziauddin Medical University Hospital Karachi, Pakistan from January 2013 to January 2015, over a period of two years. Patient records from the microbiology department were used to gather the data and a total of 634 patients from all age groups had a positive culture for *P. aeruginosa*. These cultures were obtained from samples of tracheal aspirate, blood, pus, body fluids, urine and broncoalveolar lavage.

The samples were cultured on Chocolate and MacConkey agar and incubated at 37°C for a duration of 18 hours. The isolates were identified according to standard microbiological methods.[14] *P. aeruginosa* by its colony morphology, on gram staining shows up as a pleomorphic gram negative rod. On MacConkey agar it shows up as a non-lactose fermenter which produces a pigment that has a characteristic grape like odor. *P. aeruginosa* is oxidase positive and a non-motile bacterium which has the ability to reduce nitrate to nitrite. Api 20 NE was used for the confirmation of isolates.

The antibiotic sensitivity patterns of these isolates were studied by using the Kirby Bauer Disc Diffusion method on Mueller–Hinton agar, in accordance with CLSI 2014 Guidelines,[15] and using Hi-media antibiotic discs. The antibiotics which were tested included, Amikacin (30 mcg), Cefepime (30 mcg), Ciprofloxacin (5 mcg) and Meropenem (10 mcg). Strains which had similar resistance patterns (antibiotype) were considered to be from the same clone. The *Pseudomonas aeruginosa* ATCC 27853 strain was used for quality control during this study.

Statistical analysis was performed using SPSS version 20 and the prevalence and susceptibility pattern of Cefepime for *P. aeruginosa was* calculated.

RESULTS

From January 2013 till January 2015, a total of 634 patients from all age groups were included in this study since they had a positive culture for *P. aeruginosa*. They were further divided into 3 categories of ages 0-18 years, 19-60 years and 60 years and above. Table 1 shows the distribution of samples between different age groups and sex.

We found Cefepime to be sensitive in 76.2% (483) of cases and 23.8% resistant. Cefepime was found to be the most sensitive drug amongst female patients aged 0-18 years, being effective for 94.6% of the cases, while it was least sensitive in males over the age of 60, around 73.3%. Thus the pattern that emerges, indicates that increasing age shows an increased resistance to this drug. Table 2. Shows the susceptibility pattern according to sex amongst different age groups, indicating a progressive decrease in sensitivity with age.

Tables 3 show the susceptibility pattern of *P. aeruginosa* when treated with combinations of Cefepime with Amikacin, Meropenem and Ciprofloxacin respectively.

Table 3 shows that Cefepime, a 4th gen cephalosporin has a different sensitivity pattern against *P. aeruginosa* when used in combination with other antibiotics. The most sensitive combination was found to be that of Cefepime and Amikacin, being 63.25% sensitive, followed by Cefepime and Meropenem at a sensitivity of 59.78%, and Cefepime and Ciprofloxacin being 49.2% sensitive. The least resistive pattern found was that of the combination of Cefepime and Ciprofloxacin (7.1%), followed by Cefepime and Amikacin (16.5%) and the most resistance was noted for the combination of Cefepime and Meropenem (17.5%). Tables 4-6 show different combination therapies with their sensitivity and resistance patterns according to age and sex. Our data strongly supports the use of Cefepime and Ciprofloxacin as combination therapy on account of its low resistance to the isolates.

DISCUSSION

Pseudomonas aeruginosa is a non-fermenting, gram negative, pleomorphic bacillus which is freely found in nature and the environment (ubiquitous). *P. aeruginosa* gives rise to a multitude of nosocomial infections ranging from UTI, to pneumonia and septicemia.

In our study we found Cefepime to be sensitive in 76.2% (483) which was slightly higher than the one reported in Pakistan by Ahmad Ullah H. *et al* in 2013. Their study showed this drug to be resistant in 15% of the isolates.[19] Our figures were also in stark contrast to a study done in Urmia, Iran, where Cefepime was found to be 75.4% resistant, with 22.4% of the isolates found to be of intermediate resistance and 2.1% isolates showing sensitivity to Cefepime.[16] From India, Patel *et al* reported Cefepime to be 15.63 % resistant in isolates of *P. aeruginosa*[17] where as Endimiani *et al* reported that 10-35% of the isolates of the clinical population in North America are resistant to Cefepime.[18]

It has been strongly recommended that when *Pseudomonas aeruginosa* is the insinuated culprit, combination therapy trumps mono therapy due to the various resistance mechanisms in action, namely porin channel mutations, bacterial efflux pumps, alteration in the target site of the antibiotic, loss of membrane proteins, IMP-type metalloenzymes or carbapenemases etc.[20,21] Assorted variations of combination therapies are standard for different sites of infection. Patients suffering from VAP and neutropenia are treated rigorously with anti Pseudomonal drugs in order to treat or further prevent Pseudomonal infections. In such patients, Piperacillin/Tazobactum in combination with Amikacin was proposed for the treatment while in another study, Levofloxacin (Fluoroquinolone) in combination with Cefepime was recommended,[22,23] this is in concordance with our study which showed that the most effective treatment that can be proposed would be Ciprofloxacin (Fluoroquinolone) and Cefepime because of its low resistance of 7.1% . Drago L *et al* demonstrated that the synergistic effect of combination therapy against *P. aeruginosa* showed there was enhanced activity when Fluoroquinolones were used in conjunction with B-Lactams and Amikacin.[24]

Various combination of antibiotics have been used for the treatment of *P. aeruginosa* such as B-lactams and fluoroquinolones or B-lactams and aminoglycosides[25] and the appropriate concoction of drugs should be administered to the patient as soon as possible since a delay in combination therapy has been known to cause an increase in mortality.[26] A meta-analysis reported that in conditions where there is a blood stream infection of *P. aeruginosa,* only combination therapy can yield favorable results.[27] B-lactams and fluoroquinolones are known for their effect on *P. aeruginosa* because of their excellent penetration in different sites of the body as well as being less nephrotoxic, but with the use of fluoroquinolones there is a concurrent rise in *C. difficile* infections.[28]

There is an increasing trend of increased Cefepime resistance in Pakistan as shown by our study when compared with a study done previously. Awareness should be spread about *P. aeruginosa* being a diverse organism that is able to gain resistance while being treated, so that physicians make it a point to use combination therapy as opposed to mono therapy, when they suspect *P. aeruginosa* infections in patients.

Table 1: 'Age and Sex distribution of sample'

Age Group	No. of Male Patients (N=368)	No. of Female Patients (N=266)
0-18 years (N=90)	53 (8.36%)	37 (5.8%)
19-60 years (N=257)	139 (21.92%)	118 (18.61%)
60 years and above (N=287)	176 (27.7%)	111 (17.51%)

Table 2: 'Susceptibility pattern of Cefepime'

	MALE			FEMALE		
	0-18	19-60	60 above	0-18	19-60	60 above
Sensitive	40 (75.5%))	103(74.1%)	129(73.3%)	35 (94.6%)	92 (77.9%)	84(75.7%)
Resistance	13 (24.5%)	36(25.9%)	47(26.7%)	2(5.41%)	26(22.0%)	27(24.3%)

Table 3: 'Cefepime combined with Amikacin, Meropenem and Ciprofloxacin' combination

		CEFEPIME	
		Sensitive	Resistant
Amikacin	Sensitive	401 (63.25%)	46 (7.25%)
	Resistant	82 (12.93%)	105 (16.56%)
		Sensitive	Resistant
Meropenem	Sensitive	379 (59.8%)	40 (6.31%)
	Resistant	104 (16.4%)	111 (17.5%)
		Sensitive	Resistant
Ciprofloxacin	Sensitive	312 (49.2%)	106 (16.7%)
	Resistant	171 (27%)	45 (7.1%)

Table 4: 'Sensitivity and Resistance Pattern of Cefepime with Amikacin against *P. aeruginosa*'

Age	Sex	Sensitivity	Resistance	Intermediate Resistance
0-18	Male (N=53)	62.3%(n=33)	16.9% (n=9)	20.7% (n=11)
	Female (N=37)	62.2%(n=23)	2.7% (n=1)	35.1% (n=13)
19-59	Male (N=139)	64.02%(n=89)	15.1% (n=21)	20.8% (n=29)
	Female (N=118)	61.01%(n=72)	12.7% (n=15)	26.2% (n=31)
60 and above	Male (N=176)	64.8%(n=114)	21.5% (n=38)	13.6% (n=24)
	Female (N=111)	63.1%(n=70)	18.9% (n=21)	18.01% (n=20)

Table 5: 'Sensitivity and Resistance Pattern of Cefepime with Ciprofloxacin against *P. aeruginosa*'

Age	Sex	Sensitivity	Resistance	Intermediate Resistance
0-18	Male (N=53)	47.25% (n=25)	5.6% (n=3)	47.25% (n=25)
	Female (N=37)	67.5% (n=25)	0%(n=0)	32.4% (n=12)
19-59	Male (N=139)	47.5% (n=66)	7.9% (n=11)	44.6% (n=62)
	Female (N=118)	56.8% (n=67)	5.9% (n=7)	37.29% (n=44)
60 and above	Male (N=176)	43.2% (n=76)	10.2% (n=18)	46.5% (n=82)
	Female (N=111)	47.7 (n=53)	5.4% (n=6)	46.8% (n=52)

Table 6: 'Sensitivity and Resistance Pattern of Cefepime with Meropenem against *P. aeruginosa*'

Age	Sex	Sensitivity	Resistance	Intermediate Resistance
0-18	Male (N=53)	58.5%(n=31)	18.9% (n=10)	22.6% (n=12)
	Female (N=37)	62.2% (n=23)	2.7% (n=1)	35.1% (n=13)
19-59	Male (N=139)	59.7% (n=83)	18.7% (n=26)	21.6% (n=30)
	Female (N=118)	60.1% (n=71)	11.0% (n=13)	28.8% (n=34)
60 and above	Male (N=176)	58.5% (n=103)	22.2% (n=39)	19.3% (n=34)
	Female (N=111)	61.3% (n=68)	19.8% (n=22)	18.9% (n=21)

CONCLUSION

Cefepime for many years has been considered to be one of the most reliable drugs that can safely be used for patients with *P. aeruginosa* infections. There is a progressive trend that shows that *P. aeruginosa* is found be resistant to this antibiotic now. Thus this awareness should be promptly spread so that physicians administer prompt combination therapy. We suggest that a combination of Cefepime and Ciprofloxacin is the most effective therapy to battle this pathogen. More research is warranted so that new drugs are discovered to deal with *P. aeruginosa infections* effectively.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

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