Iranian Journal of Microbiology
Volume 17 Number 2 (April 2025) 253-260

ORIGINAL ARTICLE

Evaluating the susceptibility to ceftazidime-avibactam in clinical isolates of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* recovered from an apex medical hospital in north India

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Received: July 2024**, Accepted:** January 2025

ABSTRACT

Background and Objectives: We assessed the susceptibility of ceftazidime+avibactam (CZA/AVI) in *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolated from intensive care units of our hospital.
Materials and Methods: Clinical samples from Jan 2022 to Dec 2023 at SKIMS Soura, were processed for the recovery of *K. pneumoniae* and *P. aeruginosa*. Susceptibility testing was done by disc diffusion (DD) method and minimum inhibitory concentration (MIC) for CZA/AVI and meropenem was assessed using E-test strips. Categorical agreement (CA), very major errors (VME), major errors (ME) and minor errors (mE) between DD and MIC were measured. Statistical analyses were performed using SPSS version 22.0.
Results: A total of 111 *K. pneumoniae* and 81 *P. aeruginosa* were part of the study. Of these, 56.8% *K. pneumoniae* and 45.7% *P. aeruginosa* isolates were susceptible to CZA/AVI. MIC of CZA/AVI for *K. pneumoniae* ranged from 0.125 to ≥ 256 µg/ml and for *P. aeruginosa* it ranged from 0.032 to 128 µg/ml. CA was 97.29% between DD and E-Test for CZA/AVI in *K. pneumoniae* isolates, with a ME of 2.70%. For *P. aeruginosa* CA between DD and E-Test for CZA/AVI was 98.76% with a VME of 1.23%. MIC values of meropenem were higher than CZA/AVI even in sensitive isolates.
Conclusion: CZA/AVI shows good in-vitro activity against clinical isolates of *K. pneumoniae* and *P. aeruginosa* and can be part of empirical therapy for treating infections caused by these bacteria.

Keywords: Antimicrobial drug resistance; Carbapenem antibiotics; Disc diffusion method; Intensive care unit

INTRODUCTION

Reserved category antibiotics like polymyxins and tigecycline are the only therapeutic options available against carbapenem resistant Enterbacterales (CRE). However, side effects like nephrotoxicity in case of polymyxins and low plasma concentration achieved in case of tigecycline greatly limit their use (1). Newer beta-lactam and beta-lactamase inhibitor (BL-BLIs) combinations have been developed to circumvent this therapeutic dilemma, which can be a potential game changer in the treatment of infections caused by Gram negative bacteria (GNB). Ceftazidime-avibactam (CZA/AVI) is one such novel BL-BLIs which

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combines ceftazidime, the anti-pseudomonal cephalosporin and the novel β-lactamase inhibitor avibactam. Avibactam is a diazabicyclooctane which has in vitro activity against β-lactamases of Ambler class A (ESBLs and KPCs), class C (AmpC cephalosporinases) and some class D (e.g OXA-48-type), but not class B metallo-β-lactamases (MBLs) (2). This enhanced microbiological profile covers most carbapenem resistant and multi drug resistant strains of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* with the exception of those producing MBLs.

In India CZA/AVI has been approved for treatment of complicated intra-abdominal infections, urinary tract infections and hospital-acquired pneumonia (including ventilator-associated pneumonia) caused by GNB (3). Several reports have been published globally (including Asia) regarding the in vitro activity of CZA/AVI against CRE (2, 3-5). In India however, very few studies have documented the in vitro activity of CZA/AVI against GNB (1). Accurate susceptibility testing is essential to optimize the use and limit the misuse of CZA/AVI. Even though broth microdilution (BMD) is the reference susceptibility testing method for CZA/AVI; disc diffusion (DD) and E-Test strips are more frequently used owing to feasibility and less technical expertise required (4). This study intends to evaluate the in-vitro susceptibility pattern of CZA/AVI against clinical isolates of *P. aeruginosa* and *K. pneumoniae* recovered from patients admitted in various intensive care units (ICU's) of an apex health care institute in the northern part of the country.

MATERIALS AND METHODS

Study design and settings. This observational study was carried out in the Department of Microbiology at the Sher-i-Kashmir Institute of Medical Sciences (SKIMS) Soura, Kashmir India; from January 2022 to December 2023 (24 months). Demographic information of patients admitted in the ICU's was obtained from electronic Medical Records Department of the hospital.

Inclusion criteria. All samples sent to the bacteriology section during the study period from patients admitted to the ICU's were included in the study. Only the first isolate recovered from a patient's sample was considered.

Exclusion criteria. Polymicrobial cultures, repeated isolation of the same organism from the patient, bacteria other than *K. pneumoniae* and *P. aeruginosa*, improperly labelled or transported specimens and patients on CZA/AVI therapy were excluded from the study.

Sample processing. Samples such as urine, pus and body fluids, sputum, endotracheal aspirates and bronchoalveolar lavage (BAL) were processed within 2 hours of receipt in the laboratory as per the standard microbiological guidelines (6). *K. pneumoniae* and *P. aeruginosa* were identified by conventional biochemical tests and antimicrobial susceptibility testing (AST) was performed by Kirby-Bauer disc diffusion (DD) method on Mueller-Hinton agar plates according to Clinical and Laboratory Standards Institute guidelines (7). Discs used included; ceftazidime (30 μg), ceftriaxone (30 μg), cefotaxime (30 μg), cefipime (30 μg), imipenem (10 μg), meropenem (10 μg), gentamicin (10 μg), amikacin (30 μg), ciprofloxacin (5 μg), levofloxacin (5 μg), sulfamethoxazole/trimethoprim (1.25/23.75 μg), piperacillin/tazobactam (100/10 μg), aztreonam (30 μg), ticarcillin/clavulanic acid (75/10 μg), ceftazidime/avibactam (30/20 μg), and tigecycline (15 μg). In addition, nitrofurantoin (300 μg) and norfloxacin (10 μg) were tested in urinary isolates. Colistin susceptibility was done by micro broth dilution method. *E. coli* ATCC (25922), and *P. aeruginosa* ATCC (27853) were used as control strains. All the discs and media were procured from HiMedia Mumbai. Minimum inhibitory concentration (MIC) for CZA/AVI and meropenem (MRP) against *K. pneumoniae* and *P. aeruginosa* was calculated using E-Test strips (Pfizer and Hi-media).

The MICs and zone diameter of CZA/AVI and MRP were interpreted using CLSI guidelines (7). MDR phenotype was defined as resistance to at least one agent in three or more drug classes. Categorical agreement (CA) along with very major error (VME), major error (ME) and minor error (mE) between DD and E-Test was determined according to CLSI guidelines (8). Specifically, CA was defined as the agreement between the E-test and DD interpretive results. ME was defined as misclassification of a susceptible isolate as resistant and VME was defined as misclassification of a resistant isolate as susceptible. mE was classified as any other discrepancy (e.g., intermediate by one method but not the other).

Statistical analysis. All statistical analyses were performed using SPSS version 22.0. Statistical significance was defined for P<0.05.

Ethical approval for the study was given by the Institutes ethical clearance committee bearing number: IEC/SKIMS# RP152/2022.

RESULTS

A total of 1098 samples were received during the study period, which were in accordance with the inclusion criteria of the study. Out of these, 406 (36.9%) samples were positive for bacterial growth which included *K. pneumoniae* (n=111, 27.3%), *P. aeruginosa* (n=81, 19.9%), *Acinetobacter baumannii* (n=119, 29.3%), methicillin resistant coagulase negative *Staphylococcus* (n=5, 1.2%), methicillin resistant *Staphylococcus aureus* (n=8, 2%), *Escherichia coli* (n=25, 6.2%), *Enterococcus* spp. (n=20, 4.9%), *Burkholderia cepecia* (n=17, 4.2%), *Proteus* spp. (n=8, 2%), *Enterobacter* cloacae (n=9, 2.2%) and *Citrobacter* spp. (n=3, 0.7%). Only *K. pneumoniae* and *P. aeruginosa* (n=192) isolates were processed further.

The mean age of the studied population was 35.41 (range 11-81 years) and males comprised 53.1% (n=102) of the sample group. Majority of the samples received were pus/body fluids (n=86, 44.8%) followed by respiratory samples (n=77, 40.1%), urine (n=23, 12%), and CSF (n=6, 3.1%). Samples were mostly received from the surgical intensive care unit (n=96, 50%) followed by the neurosurgical ICU (n=48, 25%), cardiac ICU (n=28, 14.6%) and neonatal ICU (n=20, 10.4%). Clinical profile of the patients is given in Table 1. The overall susceptibility profile of the *K. pneumoniae* and *P. aeruginosa* isolates is shown in Table 2. Most of the strains were MDR, however, all the isolates were susceptible to colistin (100%). There was a significant difference in the susceptibility of CZA/AVI and MRP among the *K. pneumoniae* isolates. However, no such difference was seen in *P. aeruginosa* isolates (Table 3).

A total of 100 isolates; [63/111 (56.8%) *K. pneumoniae* and 37/81 (45.7%) *P. aeruginosa*] were susceptible to CZA/AVI and 92; [48/111 (43.2%) *K. pneumoniae* and 44/81 (54.3%) *P. aeruginosa*] were resistant to it on DD. MIC of CZA/AVI for *K. pneumoniae* ranged from 0.125 μg/ml to ≥ 256 μg/ml and for *P. aeruginosa* it ranged from 0.032 μg/ml to 128 μg/ml (Table 4 and Fig. 3). Zone sizes of the tested isolates and their MIC's are given in Table 5. The MIC for 3 isolates of *K. pneumoniae* was in the susceptible range (< 2mg/ml) even though they were resistant by disc diffusion (zone size 16 and 18 mm respectively) (Fig. 1). And 1 isolate of *P. aeruginosa* had an MIC value of >32μg/ml even though it was sensitive on disc diffusion (zone size 23 mm) (Fig. 2). For *P. aeruginosa* categorical agreement (CA) between DD and MIC by E-Test for CZA/AVI was 98.76% with a VME of 1.23%. For *K. pneumoniae* CA between DD and MIC by E-Test for CZA/AVI was 97.29% with a ME of 2.70%. No VME or mE was seen in *K. pneumoniae* and no ME or mE was seen in *P. aeruginosa*. MIC values of MRP for *K. pneumoniae* and *P. aeruginosa* ranged from 0.064 to >32mg/ml.

DISCUSSION

CZA/AVI was launched in 2015 to treat various infections caused by carbapenem resistant Enterobacterales. To our knowledge, this is the first in vitro surveillance conducted to assess the activity of CZA/AVI in clinical isolates of *K. pneumoniae* and *P. aeruginosa* recovered from our hospital. An overall susceptibility of 52.1% to CZA/AVI was seen amongst the 192 isolates tested (56.8% *K. pneumoniae* and 45.7% *P. aeruginosa*) which is lower than what has been reported earlier.

Many global surveillance studies have reported susceptibility rates of greater than 90% to this combination, especially against Enterobacterales. The Antimicrobial Testing Leadership and Surveillance (ATLAS) program carried out in 10 Latin American countries reported an overall susceptibility of 98.1% and 86.9% to CAZ/AVI, among Enterobacterales and *P. aeruginosa* isolates respectively (2). A similar study carried out in South Korea reported a susceptibility rate of 95% to CZA/AVI in Enterobacterales and 92.6% in *P. aeruginosa* isolates (8). In India an earlier study reported an overall sensitivity rate of 72% to CZA/AVI in *K. pneumoniae* isolates, collected from 9 centers across the country (1). Clinical isolates of Enterobacterales and *P. aeruginosa* collected from Europe, between 2015-2017, were found to be highly susceptible to CZA/AVI (9). On the other hand, lower sensitivity rates of CZA/AVI in MDR isolates of Enterobacterales (77.4%) and *P. aeruginosa* (40.7%) were reported in a study from

Table 1. Clinical profile of the patients from whom *K. pneumoniae* and *P. aeruginosa* was recovered

	Data available (n)	*K. pneumoniae* n (%)	*P. aeruginosa* n (%)	P-value
Sample type	192			
Pus & body fluids	86	47 (54.7)	39 (45.3)	0.561
Sputum	37	25 (67.6)	12 (32.4)	
Endotracheal aspirates	29	16 (55.2)	13 (44.8)	
BAL	11	6 (54.5)	5 (45.5)	
Urine	23	15 (65.2)	8 (34.8)	
CSF	6	2 (33.3)	4 (66.6)	
Location	192			
Surgical ICU	96	62 (64.6)	34 (35.4)	0.215
Neurosurgical ICU	48	23 (47.9)	25 (52.1)	
Cardiac ICU	28	14 (50)	14 (50)	
Neonatal ICU	20	12 (60)	8 (40)	
Diagnosis	136			
Respiratory failure /ARDS	24	15 (62.5)	9 (37.5)	0.475
Myocardial infarction	17	8 (47.1)	9 (52.9)	
Acute abdomen	10	7 (70)	3 (30)	
Intra cranial haemorrhage/cerebral infarction	13	8 (61.5)	5 (38.5)	
Trauma	21	13 (61.9)	8 (38.1)	
Pneumonia (CAP/VAP/HAP)	14	8 (57.1)	6 (42.9)	
Sepsis/sepsis syndrome	28	17 (60.7)	11 (39.3)	
Meningitis	6	5 (83.3)	1 (16.7)	
Others	3	0	3 (100)	

Morocco (10).

The most predominant carbapenemases in South East Asia, especially in India are MBLs, whereas serine β-lactamases dominate other parts of the globe. The reduced susceptibility among isolates of *K. pneumoniae* and *P. aeruginosa* seen in our study could be due to increased production of MBLs in them. Aztreonam-avibactam is another antibiotic combination that has been studied for its use in infections caused by CRE expressing serine β-lactamases, MBLs or both. In a study conducted to access the activity of aztreonam-avibactam in a large number of isolates collected in Europe, Latin America and Asia Pacific region from 2020-2022, it was found that this combination exhibited potent activity against CRE isolates resistant to CZA/AVI, meropenem-vaborbactam and imipenem-relebactam independent of the type of carbapenemases produced (11). This proposition can serve as a stepping stone for further research; wherein the types of β-lactamases can be delineated and specific guidelines formulated for our institution after testing both CZA/AVI and aztreonam-avibactam in CRE isolates.

Majority of the isolates (n=86, 44.8%) in our study were recovered from pus and body fluids followed by respiratory samples (n=77, 40.1%). Similarly, most of the isolates were recovered from patient admitted in the SICU (n=96, 50%). Clinical diagnosis available in 136 patients ranged from sepsis (n=28, 21.2%) to respiratory failure/ARDS (n=24, 17.6%) to trauma (n=21, 15.4%) among others. All the isolates showed 100% susceptibility to colistin. Among the other antibiotics classes tested, good sensitivity was seen for aminoglycosides with variable sensitivity to other antibiotcs. Imipenem was sensitive in 23% of the isolates whereas 31.8% isolates were sensitive to meropenem. This low sensitivity profile is worrisome as patients admitted in the ICUs are generally very sick. These patients are often on a cocktail of high end anti-microbial agents. Furthermore, interventions like placement of central lines, peripheral lines, urinary catheters and the need of mechanical ventilation provides a fair ground for resistant microorganisms to cause infections in them. A vicious cycle ensues

Table 2. Antimicrobial susceptibility profile of *K. pneumoniae* and *P. aeruginosa* isolates.

Antibiotics	No tested	*K. pneumoniae* (n=111)		*P. aeruginosa* (n=81)	
		Sensitive n (%)	Resistant n (%)	Sensitive n (%)	Resistant n (%)
Amikacin	192	78 (70.3)	33 (29.7)	47 (58)	34 (42)
Gentamicin	192	81 (73)	30 (27)	47 (58)	34 (42)
Tobramycin	192	64 (57.7)	47 (42.3)	38 (47)	43 (53)
Piperacillin +tazaobactam	192	24 (21.6)	87 (78.4)	29 (35.8)	52 (64.2)
Ticarcillin +clavulanic acid	*81	-	-	31 (38.3)	50 (61.7)
Aztreonam	192	47 (42.3)	64 (57.7)	38 (47)	43 (53)
Co-trimoxazole	111	27 (24.3)	84 (75.7)	-	-
Levofloxacin	192	51 (46)	60 (54)	31 (38.3)	50 (61.7)
Ciprofloxacin	192	30 (27.0)	81 (73)	23 (28.4)	58 (71.6)
Norfloxacin	**23	6 (30)	14 (70)	0	3 (100)
Ceftazidime	192	47 (42.3)	64 (57.7)	29 (35.8)	52 (64.2)
Ceftriaxone	***111	43 (38.7)	68 (61.3)	-	-
Cefotaxime	192	47 (42.3)	64 (57.7)	31 (38.3)	50 (61.7)
Cefipime	192	44 (39.6)	67 (60.4)	29 (35.8)	52 (64.2)
Nitrofurantoin	**23	16 (80)	4 (20)	0	3 (100)
Imipenem	192	22 (19.8)	89 (80.2)	22 (27.2)	59 (72.8)
Meropenem	192	31 (27.9)	80 (72.1)	30 (37)	51 (63)
Colistin	192	111 (100)	0	81 (100)	0
Cefatzidime+avibactam	192	63 (56.8)	48 (43.2)	37 (45.7)	44 (54.3)

* Ticarcillin +clavulanic acid was tested in *P. aeruginosa* only (n=81).

**Norfloxacin and Nitrofurantoin were tested in urinary isolates only (*K. pneumoniae*, n=20; *P. aeruginosa*, n=3).

***Ceftriaxone was tested in *K. pneumoniae* only (n=111)

Table 3. Comparison of MRP susceptibility with CZA susceptibility for *K. pneumoniae* and *P. aeruginosa*.

Antimicrobial agent	*K. pneumonia*		*P. aeruginosa*	
	Sensitive n (%)	Resistant n (%)	Sensitive n (%)	Resistant n (%)
CZA/AVI	63 (56.8)	48 (43.2)	37 (45.7)	44 (54.3)
MRP	31 (27.9)	80 (72.1)	30 (37)	51 (63)
P-value	0.000014		0.264	

Table 4. The MICs of CZA/AVI determined by the E-Test strip

Isolate category	Antimicrobial agent	Number of isolates at each MIC (µg/mL) for CZA/AVI									
		0.032	0.125	0.25	1.5	2	8	16	32	64	128	>256
K. pneumoniae n=111	CZA-AVI	-	10	23	11	19	-	9	8	11	16	4
P. aeruginosa n=81	CZA-AVI	9	16	7	4	-	-	8	14	17	6	-

where the patients ends up staying for extended period of time in an environment that poses substantial risks to them. Needless to say that the costs of treatment in these patients and the mortality rates go up.

MIC values of CZA/AVI were compared with the MIC values of meropenem, which is the most common carbapenem prescribed in our ICUs (as part of empirical therapy). It was seen that the average MIC

Table 5. The MICs of MRP determined by the E-Test strip

Isolate category	Antimicrobial agent	Number of isolates at each MIC (µg/mL) for MRP										
		0.064	0.125	0.25	0.50	1.0	2	4	6	8	16	32
K. pneumoniae n=111	MRP	8	4	7	11	-	1	13	9	19	11	28
P. aeruginosa n=81	MRP	2	2	4	10	7	5	-	7	10	5	29

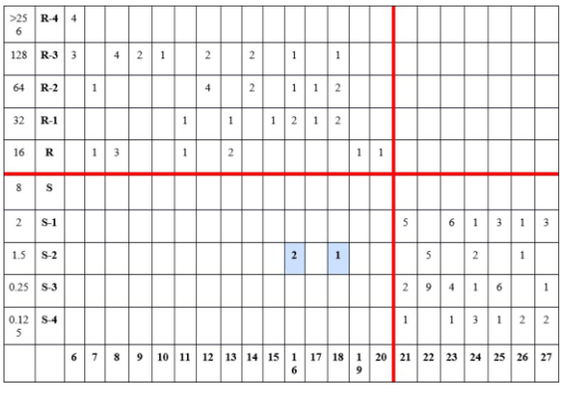

Fig. 1. Scattergram comparing CZA/AVI MIC values (E-Test) and disk diffusion zone diameters with 30/20-mg disks among *K. pneumoniae* isolates (n=111). The red lines indicate CZA/AVI breakpoints (CLSI). The blue background indicates that ME occurred for the disk diffusion method, compared to the E-Test.

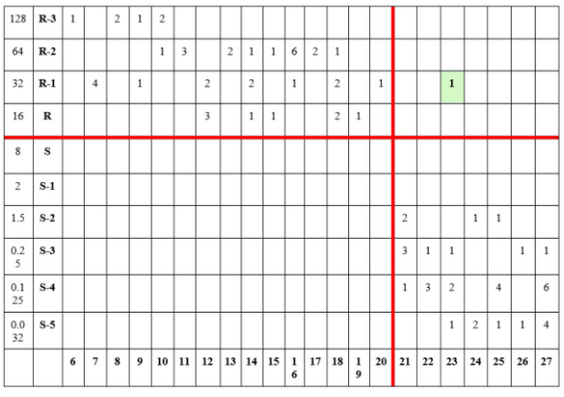

Fig. 2. Scattergram comparing CZA/AVI MIC values (E-Test) and disk diffusion zone diameters with 30/20-mg disks among *P. aeruginosa* isolates (n=81). The red lines indicate CZA/AVI breakpoints (CLSI). The green background indicates that VME occurred for the disk diffusion method, compared to the E-Test.

of CZA/AVI was lower than the MIC of meropenem in organisms sensitive to these antimicrobial agents. This could make a case for using CZA/AVI in treating patients where CRE are isolated. A clinical trial found CZA/AVI to be a safer alternative to carbapenems in treating cases like catheter associated urinary tract infection and complicated intra-abdominal infections (12). A previous study carried out to assess the effectiveness of CZA/AVI versus colistin in treating CRE bacteremia reported a significantly higher success rate with the use of CZA/AVI as compared to colistin (13). CZA/AVI has been found to be clinically efficacious in phase III non-inferiority trials as well as in real world settings (14, 15). A decreased mortality rate was observed with early use of CZA/AVI for managing infections caused by organisms which are sensitive to this inhibitor combination (16).

CA between DD and E-Test for testing CZA/AVI in *K. pneumoniae* was 97.29%. Whereas for *P. aeruginosa* the CA between the two methods was 98.76%. ME (2.70%) was seen between DD and E-Test in *K. pneumoniae* and VME (1.23%) was seen in *P. aeruginosa*. The parameters of CZA/AVI (30/20-mg) DD test for the isolates tested in our study were in line with the criteria of acceptability (VME rates <1.5% and ME rates <3%). In a study comparing the susceptibility testing methods for the combination of CZA/AVI with aztreonam in MBL producing organisms, the authors found that all the three methods namely DD, E-Test fixed ratio method and E-Test agar synergy method showed 100% correlation with each other (17). In another study, that compared the performance of DD and E-Test with broth micro dilution method, E-test and the DD test for CZA/AVI depicted an acceptable performance as an alternative to the reference broth microdilution method (BMD). VME by both disk diffusion and E-test were found in 2.1% and ME were found in 7.8% isolates with an overall CA of 94.6% (18). Likewise, in another study the performance of the E-test and DD using 30/20 µg and 10/4 µg discs were evaluated against BMD for 102 Gram negative bacteria. The authors found that the E-test performed the best, with CA of 95% and major errors of 6.3% (19).

The limitations of our study stems from the fact that the in-vitro performance of CZA/AVI was stud-

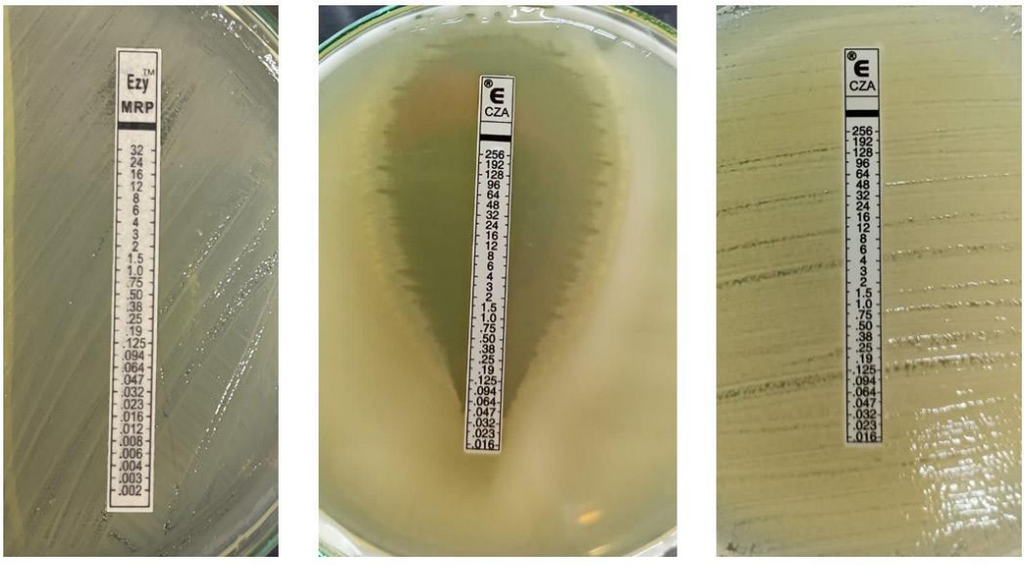

Fig. 3. Photograpahs of E-test strips of MRP and CZA/AVI
A. An isolate of *P. aeruginosa* showing an MIC of >32µg/ml
B. An isolate of *K. pneumoniae* showing an MIC of 0.032µg/ml
C. An isolate of *K. pneumoniae* showing an MIC of >256µg/ml

ied in two microorganisms only, isolated from the ICUs. The performance of this inhibitor combination in Enterobacterales other than *K. pneumoniae* and other non-fermenters can further strengthen the clinicians' faith in using it for treating life threatening infections. Also the molecular analysis of the type of β-lactamases present in the studied pathogens is missing in our study. The scientific interpretation of our results paired together with the molecular profile of the pathogens would be more meaningful.

CONCLUSION

In conclusion the results of this study point to the fact that the in-vitro susceptibility of CZA/AVI is better than or equal to the commonly tested antibiotics recommended by CLSI for *K. pneumoniae* and *P. aeruginosa* at our institution. How this combination fares in-vivo remains to be investigated. Continued surveillance of the susceptibility profile of CZA/AVI cannot be overemphasized. As bacteria continue to evolve and the scientific community continues to come up with better diagnostic modalities, it is just a matter of time before this resource is exhausted, unless we learn from the trends in the past and use antimicrobial agents judiciously.

ACKNOWLEDGEMENTS

The authors express their profound gratitude to the technical staff of the Department of Microbiology for their contribution and support and also to the Medical Records Department for facilitating the retrieval of patient data.

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