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Phenotypic detection of carbapenem-resistant *Enterobacterales* and carbapenem-resistant *Pseudomonas aeruginosa* by mCIM and eCIM and their ceftazidime-avibactam with aztreonam synergy profile in a tertiary care hospital in Eastern India

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ABSTRACT

Background: Worldwide, the emergence of carbapenem-resistant enterobacterales (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) is a global concern to public health as they are responsible for several serious infections that lead to elevated treatment expenses, prolonged hospitalization, and a higher mortality rate. **Aims and Objectives:** To detect Carbapenem resistance in Enterobacterales and Pseudomonas aeruginosa by phenotypic methods such as mCIM and eCIM. To determine synergism between Ceftazidime-Avibactum and Aztreonum in metallobetalactamase producing isolates. **Materials and Methods:** Total 217 isolates including enterobacterales and *Pseudomonas aeruginosa* from patient's samples such as urine, pus, blood, wound swab, sputum, and ET tube were processed as per standard protocol during the study period from July 2023 to January 2024 at Calcutta National Medical College, Kolkata. **Results:** Resistance to carbapenem was observed in 110/217 (50.69%) isolates. Phenotypically, 99/110 (90%) produced metallo-β-lactamase and 11/110 (10%) produced serine carbapenemase by mCIM with eCIM test. MBLs producing organisms were most commonly isolated from blood culture samples. On an average, 76% of the MBL producing isolates shows positive synergy result to the combination of CZA + AT by disk elution method. **Conclusion:** eCIM and mCIM test was performed for identification of carbapenemase producing CRE and CRPA, which causes serious infection in patients with no definitive treatment. The combination of CZA-AT is a potential treatment option to manage CRE and CRPA-associated infections.

Key words: Modified carbapenem inactivation method; EDTA-modified carbapenem inactivation method; Carbapenem-resistant Enterobacterales; Carbapenem-resistant *Pseudomonas aeruginosa*, Ceftazidime-avibactam, Aztreonam

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INTRODUCTION

Emergence of multidrug-resistant organisms is a threat to the mankind. Carbapenems the "Last resort antibiotics" are highly potent and broad-spectrum and hence are widely used in treating several critically ill patients.[1] Carbapenem resistance among Enterobacterales and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) is quite prevalent and in India, it ranges from 18% to 31%.[2] The mortality rate among patients infected with carbapenem-resistant

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Enterobacterales (CRE) is very high and ranges from 18% to 48% depending on immune status of the patient, presence of associated comorbidities and organ infected.[3] As per the Centers for Disease Control and prevention, the high mortality rates among hospitalized patients infected with CRE and CRPA isolates may be up to 50%[4]. Carbapenems belong to the group of beta-lactam antimicrobial agents.[5] Phenotypic resistance to carbapenems can occur due to the production of Carbapenemases which are enzymes responsible for hydrolysis of carbapenem beta-lactam ring leading to inactivation of the molecule or production of cephalosporinases like extended spectrum beta-lactamase or AmpC beta lactamases along with mutation of bacterial cell leading to decreased permeability to carbapenems.[6] Beta lactamases can be classified into 4 molecular classes: Ambler Class A, B, C, or D. Class A (e.g., KPC), Class C (Cephalosporinases), Class D (e.g. OXA-48), and Class B (e.g., IMP, NDM, and VIM enzymes).[5] Classes A, C, D belong to serine beta lactamases while Class B belongs to the metallo-beta-lactamases (MBLs).[5] This Class B is inhibited by EDTA and requires zinc ions for catalysis.[6,7] Few newer beta lactam-beta lactamase inhibitor combinations such as ceftazidime-avibactam (CZA), imipenem/cilastatin-relebactam, and meropenem-vaborbactam are active against most serine carbapenemase but not against MBLs.[8] The modified carbapenem inactivation method (mCIM) is used for phenotypic detection of carbapenemase producing CRE and CRPA isolated in culture and is highly sensitive and specific. Another method is EDTA-modified carbapenem inactivation method (eCIM) which helps in differentiation of serine enzymes and MBLs.[8] CZA is a potent inhibitor of serine betalactamases producing isolates but not against MBLs. Aztreonam (AT), a monobactam group of drug, is stable in the presence of MBL enzymes. Thus, the combination of CZA and AT is likely to be effective against MBL-producing organisms where avibactam prevents Class A and C enzymes from causing hydrolysis of AT, and hence, AT is able to evade Class B enzymes and can retain its bactericidal property.[9] Furthermore, there is some probable synergistic activity when CZA and AT are combined. As there are surprisingly lesser studies in this field, so we aimed to evaluate phenotypic detection methods such as mCIM and eCIM for detecting CREs. Furthermore, the synergism between CZA and AT was assessed by broth disk elution method in MBL-producing isolates from different samples. This study was conducted in the Department of Microbiology, Calcutta National Medical College and Hospital, Kolkata.

Aims and objectives

1. Phenotypic detection of carbapenem resistance by eCIM and mCIM methods among different Enterobacterales and *Pseudomonas aeruginosa*
2. To assess synergism between CZA+AT in MBLs-positive isolates.

MATERIALS AND METHODS

An observational cross-sectional study was conducted for 7 months (June-December 2023) in the Department of Microbiology at Calcutta National Medical College and Hospital, Kolkata, including different samples such as urine, pus, blood, wound swab, sputum, and ET tube including 217 patients from different departments of our hospital which were sent to our department. Relevant history was taken from patient's relative in a pro forma sheet. These samples were processed as per M100 CLSI guidelines, 33rd edition.[10] Antibiotic susceptibility was performed by Kirby-Bauer disk diffusion method. The CREs were tested by mCIM. In addition to it, eCIM was also performed to differentiate MBLs from serine carbapenemases.

mCIM

Test reagents used were trypticase soy broth (TSB) – 2 mL aliquot, meropenem disk (10 mcg), 1 mcl inoculation loop, Mueller–Hinton agar plates (MHA), and meropenem susceptible indicator strain *Escherichia coli* (ATCC25922). 1 mcl loopful of bacteria from enterobacterales isolated on blood agar media was collected and dissolved into 2 mL TSB. It was vortexed for 10–15 s. A 10 mcg meropenem disk was added to each tube using sterile forceps and was immersed into the suspension. It was incubated at 35±2°C in ambient air for 4 h. After 4 h, an MHA plate was inoculated with a meropenem-sensitive *E. coli* strain (ATCC25922) of 0.5 McFarland turbidity from nutrient broth by lawn culture method on MHA plate. The plate was allowed to dry for 3–5 min before adding meropenem (MRP) disk. The MRP disk was put on the inoculated plate and incubated at 35±2°C in ambient air for 18–24 h, and then, the zone of inhibition was measured. Interpretation of the test was done as the mCIM was reported as positive when the inhibition zone diameter was 6–15 mm or 16–18 mm with small colonies in the inhibitory zone.

eCIM

The test reagents were same as mCIM along with 0.5M EDTA. For each isolate, a second 2 mL TSB tube was labeled for eCIM test. 20 mcl of 0.5M EDTA was added to 2 mL TSB tube to obtain a final concentration of 5 mM EDTA, and then, all other steps as in mCIM were repeated. Interpretation of the test was done as for the isolated positive for mCIM, if there were an increase in zone diameter of meropenem by >5 mm as in eCIM as compared to mCIM. Then, it was reported as positive. If increase in zone diameter was <4 mm in eCIM as compared to mCIM, it was considered as negative.

Furthermore, broth disk elution method was performed to assess synergism between CZA+AT in MBL-positive cases.

CZA-AT synergism testing (disk elution method)

2 mL of Mueller–Hinton broth was added to 4 sterile culture tubes which were labeled as "0" where no disk was added, "1" where 1 CZA disk was added, "2" where 1 AT disk was added, and "3" where 1 CZA and 1 AT disk were added. The tubes were incubated at room temperature for 30 min to allow the drug to elute from the disks. A 0.5 McFarland standard inoculums were prepared from the isolate in normal saline followed by 12 mcl of this suspension was added to the culture tube with eluted disks. Now, the final inoculum was around 1.5×10^5 CFU/mL. Then, this was incubated for 16–20 h at 35°C. The strain was considered synergy positive if it was resistant to both CZA and AT alone by microbroth dilution while no turbidity was seen in the tube with combination of AT and CZA disks.

Inclusion criteria

All samples selected by simple random sampling during our study period were included.

Exclusion criteria

Patients who did not give consent to participate in this study were excluded.

Ethical clearance

For the present study, the ethical approval was taken from the Institutional Ethics Committee, Calcutta National Medical College and Hospital, Kolkata.

RESULTS

An observational cross-sectional study including 217 isolates including enterobacterales and *Pseudomonas aeruginosa* from patient's samples such as urine, pus, blood, wound swab, sputum, and ET tube was processed as per standard protocol during the study period from July 2023 to January 2024 at Calcutta National Medical College, Kolkata (Tables 1-6 and Figures 1-3).

Table 1: Demographic profile among patients with CRE and CR-PA isolates based on age and gender

Variables	Percentage
Gender	
Male	65.43
Female	34.57
Age groups	
0–20 years	2
21–40 years	8
41–60 years	18
61–80 years	72

CRE: Carbapenem-resistant *Enterobacterales*, CR-PA: Carbapenem-resistant *Pseudomonas aeruginosa*

Statistical analysis

The data obtained were analyzed with the statistical tool R. The different percentages were calculated. Fisher's exact test/one-way Chi-square test was used for comparative analysis. The tests were evaluated at a confidence level of 95% and $P<0.05$ was considered statistically significant. Out of all risk factors in the study, the use of broad spectrum antimicrobial agents was statistically significant (<0.05) and other factors though statistically not significant may be contributory.

DISCUSSION

The present study was conducted in the Department of Microbiology, Calcutta National Medical College and Hospital, Kolkata, with objectives of phenotypic detection of carbapenem resistance by eCIM and mCIM methods among Enterobacterales and *Pseudomonas aeruginosa* and to determine synergism between CZA+AT in MBL-positive isolates. The key findings of our study were that males were more commonly affected than females and 61–80-year age group was most commonly affected. Inpatient department (IPD) patients (74%) were more commonly infected with CRE and CRPA isolates as compared to outpatient department (OPD) patients. Out of IPD patients, maximum infections were found to be from intensive care unit (ICU). Most common sample was urine and most common micro-organisms isolated was *E. coli*. Most common associated sensitivity was seen in doxycycline and isolates from urine samples were most commonly sensitive to fosfomycin. The percentage of eCIM positivity (i.e., MBL) was highest in *Klebsiella pneumoniae*. CZA-AT synergism was maximally seen in isolates from blood samples and most commonly in *K. pneumoniae*. Most common risk factor among patients infected with CRE and CRPA was prolonged use of broad spectrum antimicrobial agents.

In our study, males (65.43%) were more commonly infected with CRE and CRPA as compared to females (34.57%) and the most common age group affected was 61–80 years (72%). Furthermore, in another study by Sharma et al., males were found to be more commonly infected with CRE and CRPA than females.[11] Hence, our study results corroborates. Another study by Thomas and Sarwat 21–40 years was predominantly affected followed by 41–65-year age group.[12] This discrepancy may be due to difference in demographic pattern. In our study, there were 26% OPD patients and 74% IPD patients and out of all IPD patients, 32% was from ICU, 18% from intensive treatment unit, 10% from general medicine, 5% from dialysis unit, 4% from gastroenterology, 2% from surgery department, 2% from gynecology and obstetrics, and 1% from pediatrics department. Another study by Gao et al.,

Table 2: Analysis of different type of samples and different isolates studied with their mCIM and eCIM results

Sample	*Escherichia coli*			*Klebsiella pneumoniae*			*Pseudomonas aeruginosa*		
	No. of isolates	mCIM +ve	eCIM +ve	No. of isolates	mCIM +ve	eCIM +ve	No. of isolates	mCIM +ve	eCIM +ve
Urine	48	26	26	32	17	16	5	2	1
Pus	23	12	8	13	6	6	4	1	1
Blood	27	15	15	10	5	5	1	0	0
Wound swab	18	6	6	4	2	1	0	0	0
Sputum	12	5	2	9	4	4	0	0	0
ET tube	7	5	4	2	2	2	2	2	2

mCIM: Modified carbapenem inactivation method, eCIM: EDTA-modified carbapenem inactivation method, ET tube: Endotracheal tube

Table 3: Associated sensitivity pattern of CRE and CR-PA isolates detected in patients

Antibiotic used	Sensitive (%)	Resistant (%)
Amoxicillin clavulanic acid	0	100
Amikacin	3	97
Cefotaxime	0	100
Cefoperazone sulbactam	4	96
Ciprofloxacin	8	92
Doxycycline	24	76
Levofloxacin	4	96
Piperacillin tazobactam	18	82
Nitrofurantoin (for urine samples only)	20	80
Fosfomycin (for urine samples only)	62	38
Tigecycline	40	60

CRE: Carbapenem-resistant *Enterobacterales*, CR-PA: Carbapenem-resistant *Pseudomonas aeruginosa*

showed that maximum samples isolating CRE or CRPA were from ICU.[13] Hence, our study results corroborates with this study. In our study, most common organism isolated was *E. coli* out of all samples followed by *K. pneumoniae*. Most common sample was urine (85 samples) with 26 were eCIM-positive *E. coli*, 16 were eCIM-positive *K. pneumoniae,* and 1 was eCIM-positive *P. aeruginosa*. In another study by Pudpong et al., the most common sample was sputum followed by urine samples and the predominant organism isolated was *K. pneumoniae* with most common eCIM-positive cases.[14] Hence, some discrepancy is noted here. In the present study, the maximum sensitivity among the carbapenem-resistant isolates was found most commonly in doxycycline followed by piperacillin-tazobactam among samples other than urine and in urine samples, maximum sensitivity was found to fosfomycin. A study by Armin et al., showed that CRE and CRPA isolates had good sensitivity to aminoglycosides, tigecycline, fosfomycin, etc.[15] These differences in susceptibility may be due to differences in antibiogram pattern in different geographical regions. In the present study, the percentage of MBL production was highest in *K. pneumoniae* and percentage of serine carbapenemases was highest in *P. aeruginosa*. Similar results were found in a study by Codjoe and Donkor.[16] Our study showed CZA-AT synergy to be maximum

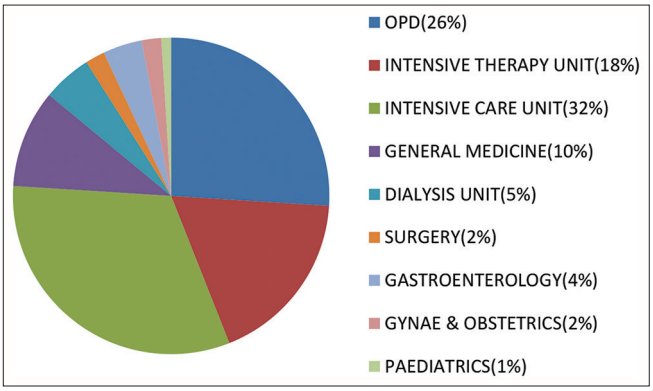

Figure 1: Percentage of patients infected with carbapenem-resistant isolates in different departments

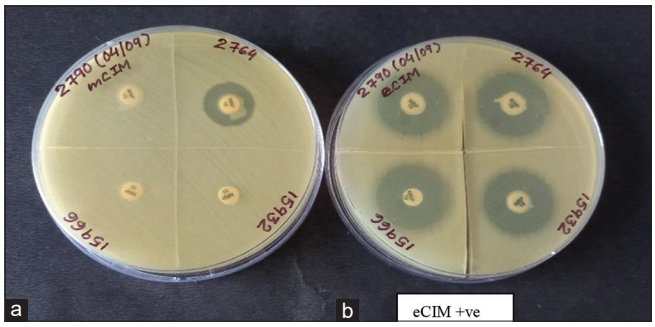

Figure 2: (a) Results of modified carbapenem inactivation method positive and negative isolates. (b) Results of EDTA modified carbapenem inactivation method positive isolates

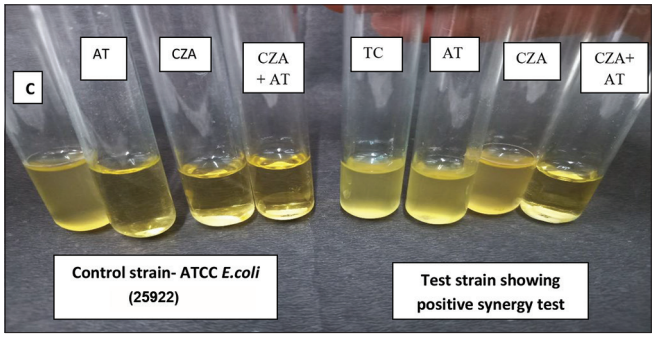

Figure 3: Results of positive ceftazidime-avibactam and aztreonam synergy test by disk elution method. C: Control of control strain, AT: Aztreonam, CZA: Ceftazidime-avibactam, TC: Control of test strain

Table 4: Distribution of organisms producing MBLs and serine carbapenemases and positivity rate of CZA-AT synergy test among MBL producer isolates

Organisms	Total number of mCIM positive	No. of MBL producer isolates (eCIM +ve)	Percentage of MBL (%)	No. of serine carbapenemase producer isolates (eCIM -ve)	Percentage of Serine carbapenemase (%)	Percentage of CZA plus AT synergy positive isolates (%)
Escherichia coli	69	61	88.40	8	11.59	75
Klebsiella pneumoniae	36	34	94.44	2	5.56	78
Pseudomonas aeruginosa	5	4	80	1	20	72

CZA-AT: Ceftazidime-avibactam and aztreonam, MBLs: Metallo-beta-lactamases, mCIM: Modified carbapenem inactivation method, eCIM: EDTA-modified carbapenem inactivation method, CZA: Ceftazidime-avibactam, AT: Aztreonam

Table 5: Sample-wise distribution of MBL and their synergistic effect by the combination of ceftazidime avibactam plus aztreonam among mCIM-positive isolates

Sample type	Total number of samples	No. of mCIM +ve isolates	No. of eCIM +ve isolates (MBL)	No. of CZA-AT synergy-positive isolates (%)
Urine	85	45	43	33 (76.74)
Pus	40	19	15	11 (73.33)
Blood	38	20	20	16 (80)
Wound swab	22	8	7	5 (71.42)
Sputum	21	9	6	4 (66.67)
ET tube	11	9	8	6 (75)

MBLs: Metallo-beta-lactamases, mCIM: Modified carbapenem inactivation method, eCIM: EDTA-modified carbapenem inactivation method, CZA-AT: Ceftazidime-avibactum and aztreonam, ET tube: Endotracheal tube

Table 6: Different risk factors among patients infected with CRE and CR-PA isolates according to our study

Risk factors	Percentage of patients infected with CRE and CR-PA
Prolonged hospital stays	14
Intake of broad-spectrum antibiotic	68
Prior hospital admission in last 30 days	5
Chronic kidney disease on hemodialysis	8
Long-term insertion of any medical devices	30
Diabetes mellitus	10

CRE: Carbapenem-resistant *Enterobacterales*, CR-PA: Carbapenem-resistant *Pseudomonas aeruginosa*

in *K. pneumoniae* followed by *E. coli*. Similar results were found in a study by Taha et al.[17] In the present study, the percentages of isolates showing CZA-AT synergy positivity in different samples were urine (76.74%), pus (73.33%), blood (80%), wound swab (71.42%), sputum (66.67%), and ET tube (75%). Similar results were seen in a study by Khan et al.[9] The different risk factors seen in our study were prolonged hospital stay (14%), intake of broad spectrum antibiotics (68%), prior hospital admission in the past 30 days (5%), chronic kidney disease (8%), insertion of medical devices (30%), and diabetes mellitus (10%). Somewhat discrepancies in percentages of risk factors were seen in other studies by Pérez-Galera et al., and Liu et al.[18,19] These discrepancies may be due to differences in demographic patterns, geographical distributions as well as lifestyle variations.

Strength and limitations of the study

It was an extensive study. We have done the phenotypic detection of carbapenemases in CRE and *Pseudomonas aerugimosa* by mCIM method, and also, eCIM method was performed to determine which is MBLs. Furthermore, synergy test was performed between CZA+AT in MBL-producing isolates. Although it was an extensive study, the molecular methods for gene detection in carbapenem resistant isolates could not be done due to the lack of facility.

CONCLUSION

Understanding the mechanisms causing emergence of carbapenem resistance in Enterobacterales and *Pseudomonas aeruginosa* has important clinical implications and may help in taking better infection control measures. Also associated testing for CZA+AT synergy in MBLs-producing isolates will help in appropriate antibiotic stewardship.

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PC- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, editing; **SG**- Concept, design, clinical protocol, manuscript preparation, editing and manuscript revision; **SB**- Design of study, manuscript revision, editing, and submission of article; **SC**- Manuscript revision and editing.

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