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Original Research Article

Antimicrobial susceptibility pattern of newer beta lactam-beta lactamase inhibitor agents on the carbapenem resistant and sensitive strains of *Enterobacterales* and *Pseudomonas aeruginosa*

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ABSTRACT

Background: The rise of antimicrobial resistance has become a global threat in the recent years. With the rise in multidrug resistant organisms (MDRO), particularly the Carbapenem resistant organisms "difficult to treat" infections there is an urgent need for newer antibiotics. There are limited therapeutic options currently available, of which Ceftazidime avibactam (CZA) is a novel Beta lactam/ Beta lactamase inhibitor (BL/BLI) combination antibiotic. Avibactam is a non BL/BLI that binds reversibly to beta lactamase.
Aim: The study aims to find the susceptibility of the novel Beta lactam- Beta lactamase combination drugs in carbapenem resistant & carbapenem sensitive isolates.
Objectives: 1. To compare the susceptibility profile of CZA in Carbapenem resistant & carbapenem sensitive isolates of *Enterobacterales* & *P.aeruginosa*; 2. To compare the sensitivity of CZA with other group of antibiotics.
Materials and Methods: This is a retrospective observational study from January 2022 to November 2023 done in the Department of Microbiology, Medanta Hospital, Lucknow. All the bacterial culture samples received during this period were subjected to routine identification and antibiotic susceptibility test on Vitek2 compact automated system. *Enterobacterales* and *P.aeruginosa* isolates are included in the study group.
Results: Of the Carbapenem Resistant isolates, *E.coli*, *Klebsiella* spp., *Pseudomonas* spp. were 26.09% , 68.6% and 46.4% respectively. Amongst the carbapenem resistant(CR) isolates, CR *K.pnuemoniae* (18.6%) is most susceptible to CZA than 9% CR *P.aeruginosa* & 3.2% CR *E.coli*. Of the Carbapanem sensitive isolates, sensitivity to CZA in *E.coli* (90.5%), *K.pnuemoniae* (92.1%) & 87% in *P.aeruginosa* appeared to be much better than the other BL-BLI's agents.
Conclusion: The study suggests that CZA can be used as carbapenem sparing agent only in carbapenem sensitive pathogens. Also with the rise in resistance to the novel drug, it should be used judiciously and not as empiric therapy or an alternative to carbapenems. It may be useful in NDM carbapenemase producers if used synergistically with Aztreonam.

1. Introduction

Bacterial resistance to antibiotics is a critical public health problem worldwide. Currently the major threat of antibiotic resistant bacteria is from Multi Drug Resistant (MDR)

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Gram negative bacteria (GNB) particularly carbapenem resistant *Enterobacterales* (CRE) along with carbapenem resistant Acinetobacter baumannii (CRAB) and carbapenem resistant *Pseudomonas aeruginosa* (CRPA).[1] Beta lactam antibiotics are the most used antibacterial agents in the clinical management of infectious disease caused by Gram negative bacteria but the global rise in the antimicrobial resistance poses some questions about their future leading to its limitational use and prerequisite for the newer agents to combat antimicrobial resistance.[2] Among them, emergence of carbapenemases poses a significant threat to the management of MDR GNBs in critical patients as Carbapenem are considered as a last resort agent for suchcases.[3] Epidemiological studies have shown that production of carbapenemase is the main mechanism for carbapenem resistance with blaKPC and blaNDM being the most prevalent ones in the carbapenem resistant *Klebsiella* pneumonia (CRKP) and *E. coli* (CREC) respectively.[4] Carbapenem resistance is also mediated by ESBLs (extended spectrum beta lactamases) and AmpC cephalosporinases (AmpC) combined with structural mutation in GNB.[5] World Health Organisation(WHO) has listed CRE and CRPA in the critical priority list of pathogens to direct efforts for drug development.[6] Other drugs available to combat these infection such as Colistin, Tigecycline are limited in their efficacy and safety profile (known to cause nephrotoxicity), is an issue to worry. Thus to combat the emergence of resistance, newer novel beta lactam- beta lactamase inhibitor (BL-BLI) combination drugs has been developed e.g. Ceftazidime –Avibactam (CZA) which is considered as a drug of choice in CRE.[7] Avibactam is a non BL-BLI that protects ceftazidime from hydrolysis by carbapenemases like KPCs (class A), AmpC(class C) and Oxa-48(class D), but not Metallo Beta Lactamases(MBLs) such as NDM,VIM or IMP(Class B). However the rapid emergence of CZA resistance mediated by carbapenemase has posed a severe threat to healthcare after its clinical application.[3] MBLs are able to hydrolyze all beta lactams except Aztreonam and are not inhibited by the beta lactamase inhibitors.[8] Over the recent years, four new BL/BLI combinations were approved by Food and Drug Administration namely Ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam for the treatment of "difficult to treat" Gram negative bacteria.[9] There is lack of any recent data in this region limiting the understanding on its clinical utility.

The current study was undertaken to determine the susceptibility of CZA against the carbapenem resistant as well as carbapenem sensitive strains of *Enterobacterales* and *P.aeruginosa* in clinical specimens.

2. Materials and Methods

This is a retrospective observational study from January 2022 to November 2023 at a single centre, tertiary care multi-specialty hospital in Uttar Pradesh, India. Study has been reviewed and approved by the Ethical Committee of Medanta Hospital Lucknow. Here cultured isolates have been used in the study, the confidentiality and privacy of the data was maintained. As per our inclusion Criteria, Only *Enterobacterales* (*E.coli* and *Klebsiella* pneumoniae) and *Pseudomonas aeruginosa* which underwent Carbapenem and CZA susceptibility were included in the study. Repeat sample from same patient showing same isolate were excluded from the study.

Data was collected retrospectively from the Microbiology lab, Medanta Hospital, Lucknow. All the Gram negative bacterial isolates (*E.coli*, *K.pneumoniae* and *P.aeruginosa*) from all clinical specimens (Blood, Urine, CSF, swabs, Sputum, Endotracheal secretion, Transtracheal secretion, BAL, other body fluids, etc.) where Carbapenem drug sensitivity test along with CZA was performed, are included in the study. Of the total samples (77602) received during the study period, isolates tested for carbapenem & CZA susceptibility were 18.87% (6886) & 4.89% (3795) respectively. Isolates that were resistant to Imipenem or Meropenem or Ertapenem were considered as Carbapenem resistant.

In the Microbiology laboratory, Culture was performed as per the Standard Operating procedure (SOP) and laboratory's protocol. All the antibiotic sensitivity test was done on a fully automated machine Vitek2 compact (Biomerieux, India) with the AST cards 405 for *Enterobacterales*, 406 for *P.aeruginosa* and 407 for critical patients along with 405/406 cards, based on CLSI guidelines 2022 & 2023. (CLSI [M100 Performance standards for antimicrobial susceptibility testing, 32^{nd} & 33^{rd} ed.]. CLSI [Standards M02, M07, M11]).

3. Result

Overall, susceptibility of CZA was not found very high amongst carbapenem resistant organisms (**CRO**). Of the total carbapenem resistant isolates included in the study, maximum isolates were *Klebsiella* pneumoniae (61.7%) and *E.coli* (24.5%) followed by *P.aeruginosa*(13.7%) as shown in Table 1, whereas *E.coli* (61.2%) were maximum susceptible to carbapenem followed by *K.pneumoniae* (24.8%) and *P.aeruginosa* (14%).

In our study, it was found that CZA was more susceptible in carbapenem sensitive (**CS**) strains of GNB of which maximum susceptibility was seen amongst CS-*K.pneumoniae* (92.16%), followed by CS-*E.coli*(90.5%) and CS-*P.aeruginosa*(87.16%). The CZA susceptibility amongst carbapenem resistant (CR) was 13.90% but CZA has comparatively better response in CR-*Klebsiella*

Table 1: Carbapenem susceptibility of *Enterobacterales* (*E.coli* & klebsiella) and *P.aeruginosa* isolated in the study.

	Carbapenem resistant isolates (n/N %) (N=3257)	**Carbapenem sensitive isolates (n/N%) (N=3629)**
E.coli	24.5% (798/3257)	61.2% (2260/3629)
Klebsiella pneumoniae	61.7% (2010/3257)	24.8% (920/3629)
Pseudomonas aeruginosa	13.8% (449/3257)	14% (518/3629)
	100%	100%

(18.59%) , almost double that of CR-*P.aeruginosa*(9.8%). CR-*E.coli* showed poorest response 3.16% only to CZA as shown in Table 2 and Figure 1 .

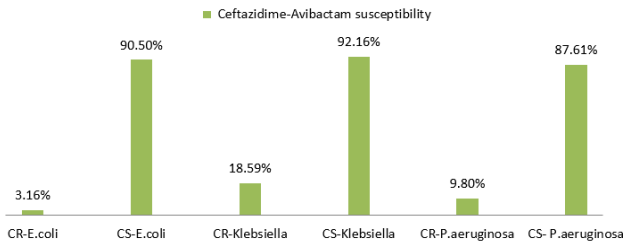

Figure 1: Susceptibility of Ceftazidime-Avibactam in carbapenem resistant and sensitive isolates.

Total susceptibility of CZA was found to be 30.43% (1155/3795) in combined Carbapenem resistant organisms (CRO) & Carbapenem sensitive organisms (CSO). The susceptibility of other BL-BLI combination agents like Amoxycillin- Clavulanate (Amc), Piperacillin -Tazobactam (Ptz), Cefoperazone -Sulbactam (Cfs) & Ceftolozone -Tazobactam (Ctz) in isolates susceptible to CZA were found comparatively poor whereas the organisms resistant to CZA 69.57% (2640/3795) showed only additional 0-2% susceptibility to other BL-BLI as shown in Figure 2 .

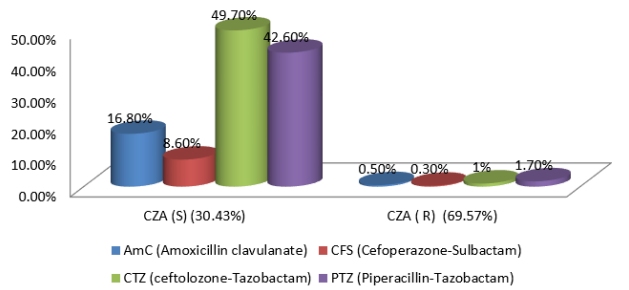

Figure 2: Susceptibility of other beta lactam- beta lactamase inhibitor agents compared to Ceftazidime-Avibactam (CZA)

The susceptibility of CZA was compared with other antimicrobials used as therapeutic drugs for carbapenem resistant as well as sensitive GNBs to find out their susceptibility pattern as a therapeutic option. Following antimicrobials were compared: PTZ (Piperacillin-Tazobactam), CFS(Cefoperazone-Sulbactam), CTZ (Ceftolozone-Tazobactam), AK (Amikacin), AMC (Amoxicillin-Clavulanate), AS (Ampicillin-Sulbactam), Colistin, Tigecycline. All these antimicrobials in contrast to CZA were poorly susceptible to CRO except in isolates of CR *P.aeruginosa* which showed comparatively better susceptibility to other antimicrobials as showed in Table 3 while aminoglycosides (Amikacin) were found comparable to and better than CZA in CRO (51.8%, 15%, 22.2% in CREC, CRKP & CRPA respectively). CZA and other antimicrobials showed better susceptibility in CSO than CRO but CZA was overall more susceptible in CSO. Tigecycline and colistin had much higher susceptibility in comparison to other drugs in in both CRO as well as CSO.

4. Discussion

This is a retrospective study of newer BL/BLI combination drug: Ceftazidime-Avibactam susceptibility against *E.coli, Klebsiella* and Pseudomonas in carbapenem resistant and carbapenem susceptibility strains to determine the CZA as a therapeutic option for MDROs (Multi drug resistant organisms). CRO are one major group of MDROs, resistant to many beta lactams including carbapenem.

WHO mentioned that CZA should be included as reserve drug/ last resort agent against MDROs susceptible to CZA with limited therapeutic options.[10] In our centre, maximum CRO causing difficult to treat infection belongs to *Enterobacterales* of which *K.pneumoniae* is the commonest organism followed by *E.coli* and *P.aeruginosa* which is similar toLeal et al.[11] which showed MDR K.pneumoniae (74.0%), *E.coli* (60.0%) and *P.aeruginosa* (8.3%).

In our study, Overall CZA susceptibility(30.43%) and CZA susceptibility amongst CSO (90.5%) was maximum found in CS-Enterbacterales isolates (*K.pneumoniae* and *E.coli* were almost equally susceptible) followed by CS-*P.aeruginosa* while amongst CRO, CZA susceptibility (13.90%) was found to be maximum in CRKP followed by CREC and CRPA which is similar to Priyadarshi et al.[12]showing total 33.5% sensitivity of CZA in CRKP followed by 3.2 % in CREC and 0% in CRPA and total 92.7 % CZA susceptibility in CSO while overall CZA susceptibility in CRO & CSO as 30.6%. but in contrast to Bakthavatchalam et al.[13] which had overall 87% & 72 % susceptible CZA in MDR *Klebsiella.pneumoniae* and *E.coli* respectively. The surveillance of CZA resistance and rationale therapeutic regimens is highly suggested for

Table 2: Susceptibility of Ceftazidime-Avibactam amongst Carbapenem resistant and carbapenem sensitive isolates.

	CZA susceptibility in carbapenem resistant isolates	**CZA susceptibility in carbapenem sensitive isolates**
E.coli	22/695 (3.16 %)	442/488 (90.5%)
Klebsiella pneumonia	356/1915 (18.59%)	200/217 (92.16%)
Pseudomonas aeruginosa	36/367 (9.8%)	99/113 (87.61%)
Total	414/2977 (13.90%)	741/818 (90.58 %)

Table 3: Comparison of other therapeutic drugs with Ceftazidime-Avibactam.

	CZA	**PTZ**	**CFS**	**CTZ**	**AK**	**AMC**	**AS**	**Tigecycline**	**Colistin**
Carbapenem resistant:									
CR-*E.coli*	3.16%	0.3%	1.3%	0.5%	51.8%	0.3%	0.5%	100%	100%
CR-*K.Pneumoniae*	18.59%	1.4%	1.5%	1%	15%	0.3%	0.3%	38.4%	92.5%
CR-*P.aeruginosa*	9.8%	10.1%	10.2%	8.9%	22.2%	—	—	—	95.3%
Carbapenem sensitive:									
CS-*E.coli*	90.5%	70.3%	81%	47.1%	99%	39%	13%	100%	100%
CS- *K.pneumoniae*	92.16%	79.4%	87%	50%	91.6%	69.7%	2%	88.9%	100%
CS-*P.aeruginosa*	87.61%	97.1%	84%	84.6%	95%	—	—	—	100%

clinicians to maximize the susceptibility of CZA.[14]

The CZA susceptibility in CRO when compared with other BL-BLI agents like PTZ, CFS, CTZ, AMC showed better sensitivity which is matching with Priyadarshi et al.[12] which had 21.6% CZA susceptible against 0.4% CFS, 0.4% PTZ, & 1.7% AMC in CRO. Aminoglycosides had better susceptibility than CZA in all CRO in our study,whereas other BL-BLI like PTZ, CFS, CTZ were more susceptible in CRPA only. Therefore PTZ, CFS, CTZ can be used as a therapeutic option in CRPA if used in a judicious manner. Ceftolozane-tazobactam is a treatment option mainly for carbapenem-resistant *P.aeruginosa* (non-carbapenemase producing), with some activity against ESBL-producing *Enterobacterales*.[8]

For CSO, CZA and other antimicrobials & BL-BLI were almost equally sensitive. This indicates that CZA and Amikacin can be used as a reserved drug for the treatment of CRO resistant to other BL-BLI. While amikacin was the most active antibiotic tested in the study, the excess nephrotoxicity associated with aminoglycoside-based regimens relative to newer β-lactam-β-lactamase inhibitor agents reduces the treatment utility against CRE infections other than catheter-related CRE bloodstream infections.[15] Polymyxins (colistin) and tigecycline are often used as a first-line treatment for CRE infections, owing to their susceptibility profiles against CRE. Overall, in the isolates included in our study, sensitivity of Polymyxins & Tigecycline was similar to internationally published data.[16] However, due to increased nephrotoxicity & neurotoxicity associated, avoidance of Polymyxins is suggested. In addition, tigecycline monotherapy is generally limited to treating intra-abdominal infections as there are limited urine concentrations and poor serum/lung concentrations are achieved.[15]

Our study showed CZA very far choice as therapeutic option for CRO due to very low susceptibility(13.90%) but CZA may be considered as better therapeutic option in CRKP than other CRE which is in contrast to various other studies which showed 63-68 % susceptible to CRE.[17,18] Also in our study, CRPA were 9.8% only susceptible to CZA, in contrast to other studies which shows resistance of CZA among CRPA varying between 14-33%.[16,19]

This low sensitivity of CZA in carbapenem resistant organisms may be due to high number of MBL(metallo beta lactamase), one of the most common and clinically significant gene producing carbapenem resistance (known to hydrolyze beta lactam drugs) which is approx 69% at our referral centre. MBL producing GNBs when tested for CZA synergistically with Aztreonam (ATM) showed 81.25% susceptibility. The combination of CZA and ATM is considered an effective therapeutic option particularly against *K.pneumoniae* and *E. coli* isolates producing more than one carbapenemase gene of MBLs and serine β-lactamases.[20] CZA+ATM demonstrated significant synergy in most ATM-resistant NDM-producing *Enterobacterales*.[21] This can be the reason for the decreased susceptibility of CZA in CRO study isolates in our tertiary care hospital.

Since this is a retrospective study, hence molecular detection of carbapenemases genes could not be included as one of the objectives. However, molecular characterization could have been beneficial for better understanding of susceptibility pattern of various therapeutic drugs. As this is a single centre study the results obtained may not be applicable for wider range of population. A further prospective study can be planned including more health centres of different parts of India to overcome these limitations.

CZA is a novel therapeutic option for carbapenem resistant organisms when used judiciously and not as empiric therapy or an alternative to carbapenem in carbapenem resistant organisms. Susceptibility testing should be routinely performed along with detection of carbapenemase production by phenotypic or genotypic method mostly in a tertiary referral centre where prevalence of MBL producing carbapenemase and MDROs is high. Our study suggests that CZA can be used as carbapenem sparing agent only in CSO.

5. Conclusion

It can be useful in MBL producing organisms, if used synergistically with Aztreonam. CZA is a novel drug combination which resistance can be a challenge for the treatment of "difficult to treat" MDROs especially in a limited resource countries like India. Better antimicrobial stewardship practices & rationale drug dosing regimens needs to be put in place to delay the emergence and spread of further resistance.

6. Source of Funding

None.

7. Conflict of Interest

None.

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