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RESEARCH ARTICLE

In Vitro Activity of Ceftazidime-Avibactam Against Carbapenem-Resistant Enterobacterales: A Prospective Study from a Tertiary Care Centre in Patna, India

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ABSTRACT

Background: Carbapenem-resistant Enterobacterales (CRE) represent a critical therapeutic challenge with limited treatment options. Ceftazidime-avibactam (CZA), a novel β-lactam/β-lactamase inhibitor combination, has shown promising in vitro activity against CRE. This study aimed to evaluate the in vitro susceptibility of CZA against CRE isolates at a tertiary care hospital in eastern India.

Methods: In this prospective cross-sectional study conducted at the Department of Microbiology, IGIMS, Patna, 450 non-duplicate CRE isolates were collected from various clinical samples over nine months. Species identification was performed by conventional biochemical methods and MALDI-TOF MS. Carbapenem resistance was confirmed by Kirby-Bauer disc diffusion (KBDD) and VITEK-2. CZA susceptibility was tested by KBDD and E-test and interpreted per CLSI 2024 guidelines.

Results: Of 450 clinical isolates, 180 (40%) were CRE. Klebsiella pneumoniae (49.4%) was the predominant species, followed by Escherichia coli (25.6%) and Enterobacter cloacae (12.8%). The ICU contributed the highest proportion of CRE (30.6%). By disc diffusion, 63.3% of CRE isolates were susceptible to CZA. E-test MIC analysis confirmed susceptibility in 65.0% of isolates (MIC90 = 8 mg/L). Overall categorical agreement between the two methods was 92.2%. Among K. pneumoniae isolates, CZA susceptibility was 58.4%, while E. coli showed the highest susceptibility (69.6%).

Conclusion: CZA demonstrated clinically significant in vitro activity against CRE isolates, with susceptibility rates exceeding 60%. These findings support CZA as a viable therapeutic option for CRE infections in the Indian clinical setting. Routine susceptibility testing of CZA is recommended for CRE isolates to guide optimal treatment decisions.

Keywords: Carbapenem-resistant Enterobacterales, Ceftazidime-avibactam, in vitro susceptibility, MALDI-TOF MS, E-test, IGIMS, Kirby-Bauer disc diffusion, β-lactamase.

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INTRODUCTION

AMR has become one of the greatest public health challenges of the 21st Century. AMR has been identified as one of the ten major public health challenges to humankind by the World Health Organization (WHO) [1]. Both the burden of morbidity and mortality from AMR and the burden of morbidity and mortality from Gram-negative bacterial infections are disproportionately high globally.

In clinical practice, carbapenems (meropenem, imipenem, ertapenem), class of antibiotics that have been used as a last resort for treating Gram-negative infections that are multidrug resistant (MDR), have been used traditionally for treating these infections [2]. Yet, the global emergence and spread of carbapenem-resistant Enterobacterales (CRE) has seriously weakened this cornerstone of therapy. Patients with CRE infections are likely to have prolonged hospitalizations, increased health care costs, and alarmingly high mortality rates that can be up to 40-50% in bloodstream infections [5].

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The carbapenemase enzymes are most clinically important of the mechanisms involved in carbapenem resistance. These enzymes are classified by the Ambler molecular classification into three major classes: Class A, KPC (Klebsiella pneumoniae carbapenemase); Class B, metallo-β-lactamases (MBLs) (e.g., NDM, VIM, IMP); and Class D, oxacillinases (OXA) (e.g., OXA-48 and variants) [9,10]. In addition to carbapenemases, resistance can also be via synergistic mechanisms with extended-spectrum β-lactamases (ESBLs), AmpC enzymes, over-expression of efflux pumps and loss of outer membrane porins [7].

Traditionally, antibiotics have been used for the treatment of CRE infections and these have considerable limitations. Polymyxins (colistin/polymyxin B) and tigecycline are regarded as 'last resort' agents, but suffer from nephrotoxicity, suboptimal pharmacokinetic/pharmacodynamic (PK/PD) profiles and inadequate microbiological cover [4,6]. Moreover, CRE is often resistant to other classes of antibiotics, such as fluoroquinolones, aminoglycosides and tetracyclines, which further limit treatment options [7].

CZA is a new β-lactam/β-lactamase inhibitor (BLBI) combination that was FDA-approved in 2015 for the treatment of complicated intra-abdominal and urinary tract infections (cIAI/UTI) [3]. Avibactam is a non-β-lactam β-lactamase inhibitor that is potent and reversible inhibitor of Ambler class A (including KPC), class C (AmpC), and some class D (OXA-48-type) β-lactamases, which restores the ability of ceftazidime to inhibit otherwise resistant organisms [13]. CZA therapy has been shown to be more effective than available alternatives in multiple in vitro and clinical studies with better clinical and survival outcomes in cases of KPC-producing CRE infection [3,4,14,15].

The epidemiology of CRE varies greatly in the Indian subcontinent, where New Delhi Metallo-β-lactamase (NDM) is the major enzyme, in contrast to those common in Western countries. CZA is not active against metallo-β-lactamases (MBLs); however, CZA can be used as a combination with aztreonam that was demonstrated synergistic effect against NDM-producing organisms [1]. Though there is an increasing therapeutic importance of CZA, data from tertiary care hospitals in eastern region of India such as Bihar are still limited to the surveillance. Understanding local susceptibility patterns is essential to rationally guide empirical and targeted antibiotic therapy in this region.

Keeping these in view, this prospective study was conducted at the Indira Gandhi Institute of Medical Sciences (IGIMS), Patna, a premier tertiary care hospital of eastern India to evaluate in vitro susceptibility to ceftazidime-avibactam of the CRE isolates collected from various clinical samples, to estimate the concordance between the disc diffusion and E-test methods and to study the epidemiology of CRE species-wise and department-wise.

AIMS AND OBJECTIVES

Aim

To evaluate the in vitro susceptibility of Ceftazidime-Avibactam (CZA) against Carbapenem-Resistant Enterobacterales (CRE) isolated from clinical samples at IGIMS, Patna.

Objectives

- To determine the prevalence of CRE among clinical isolates from admitted patients at a tertiary care hospital.
- To evaluate in vitro CZA susceptibility among CRE isolates by Kirby-Bauer disc diffusion (KBDD) and E-test methodology.
- To assess species-wise and department-wise distribution of CRE isolates and their CZA susceptibility patterns.
- To compare the concordance between disc diffusion and E-test results for CZA susceptibility testing.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, hospital-based cross-sectional study conducted in the Department of Microbiology, Indira Gandhi Institute of Medical Sciences (IGIMS), Patna, Bihar, India. IGIMS is a premier government-run tertiary care teaching hospital providing specialized healthcare services to the population of Bihar and neighbouring states.

Study Period

Samples were collected and analyzed over a period of nine months. Data analysis and result interpretation were performed subsequently.

Study Population and Sampling

Non-duplicate CRE isolates obtained from clinical samples of admitted patients across all departments were included. Approximately 4,000 samples per month were processed; an estimated 450 CRE isolates were targeted for the study duration based on prior laboratory records.

Inclusion Criteria

Non-duplicate clinical isolates of CRE isolated from samples including urine, blood, pus/wound swabs, pleural fluid, ascitic fluid, sputum, bronchoalveolar lavage (BAL),

and endotracheal (ET) aspirates received from admitted patients of all departments.

Exclusion Criteria

Samples collected by inappropriate or non-sterile technique, samples from outpatient department (OPD) attendees, and stool specimens were excluded from the study.

Identification of Isolates

All clinical samples were processed as per standard microbiological protocols. Primary identification was based on Gram staining and colony morphology on standard bacteriological media. Speciation was confirmed using conventional biochemical reactions (triple sugar iron agar, indole, urease, citrate, motility, etc.) supplemented by Matrix-Assisted Laser Desorption/Ionization–Time of Flight Mass Spectrometry (MALDI-TOF MS) for rapid and accurate species identification.

Carbapenem Susceptibility Testing

Carbapenem susceptibility was assessed for meropenem, imipenem, and ertapenem by: (a) Kirby-Bauer disc diffusion (KBDD) on Mueller-Hinton Agar (MHA) and (b) automated VITEK-2 system (bioMérieux, France). Escherichia coli ATCC 25922 was used as the quality control strain. Results were interpreted as per the Clinical and Laboratory Standards Institute (CLSI) 2024 guidelines.

Ceftazidime-Avibactam (CZA) Susceptibility Testing

CZA susceptibility was tested using two methods: (a) Kirby-Bauer Disc Diffusion with CAZ-AVI (30/20 µg) disc and (b) E-test (Epsilometer test) strips for minimum inhibitory concentration (MIC) determination. A 0.5 McFarland standard inoculum was prepared using spectrophotometry and lawn-cultured on cation-adjusted Mueller-Hinton Agar (CAMHA). CAZ-AVI antibiotic disc was placed on one lawn culture plate and CAZ-AVI E-test strip on a second plate. Plates were incubated overnight at 37°C. Zone of inhibition diameters and MIC values were recorded and interpreted per CLSI 2024 breakpoints (Susceptible: MIC ≤8 mg/L; Resistant: MIC >8 mg/L for CZA).

Classification of Drug Resistance

Isolates were categorized as multidrug-resistant (MDR), extensively drug-resistant (XDR), or pan-drug-resistant (PDR) per internationally agreed upon criteria. MDR was defined as resistance to at least one agent in three or more antimicrobial classes; XDR as resistance to all but two or fewer antimicrobial classes; PDR as resistance to all agents in all classes tested [4].

Table 1: Distribution of CRE Isolates by Clinical Sample Type

Sample Type	*Total Isolates (n=450)*	*CRE Isolates (n)*	*CRE (%)*
Urine	180	72	16.0
Blood	95	38	8.4
Pus/Wound swab	85	34	7.6
Sputum/ BAL/ET aspirate	55	22	4.9
Pleural/ Ascitic fluid	20	8	1.8
Other	15	6	1.3
Total	450	180	40.0

DD = Disc Diffusion; BAL = Bronchoalveolar lavage; ET = Endotracheal

Statistical Analysis

Data were entered and managed in Microsoft Excel. Statistical analysis was performed using SPSS version 25.0. Categorical variables were expressed as frequencies and percentages. Concordance between disc diffusion and E-test was calculated as percentage agreement.

Ethical Approval

The study was approved by the Institutional Ethics Committee (IEC) of IGIMS, Patna. Patient identifiers were anonymized; routine clinical samples were used and no additional interventions were performed.

Table 2: Species Distr ibution Among CRE Isolates (n=180)

Organism	*Number of Isolates*	*Percentage (%)*
Klebsiella pneumoniae	89	49.4
Escherichia coli	46	25.6
Enterobacter cloacae	23	12.8
Klebsiella oxytoca	12	6.7
Proteus mirabilis	6	3.3
Citrobacter freundii	4	2.2
Others	0	0
Total	180	100

* Others include Proteus mirabilis, Citrobacter freundii, and Morganella morganii.

RESULTS

Overall Prevalence of CRE

Over the study period, a total of 450 non-duplicate Enterobacterales isolates from admitted patients were included. Of these, 180 (40.0%) were identified as carbapenem-resistant Enterobacterales (CRE) based on disc diffusion and VITEK-2 confirmation. The distribution of CRE by sample type is summarized in Table 1.

Urine samples yielded the highest number of CRE isolates (72/180; 40.0%), followed by blood (38/180; 21.1%) and pus/wound swab (34/180; 18.9%). Respiratory samples (sputum, BAL, ET aspirate) collectively accounted for 22 isolates (12.2%). Body fluid samples (pleural/ascitic) contributed 8 (4.4%) isolates.

Species Distribution

Speciation by MALDI-TOF MS and conventional biochemical tests revealed Klebsiella pneumoniae as the predominant CRE species (Table 2).

Klebsiella pneumoniae was the most common CRE (89/180; 49.4%), followed by *Escherichia coli* (46/180; 25.6%), *Enterobacter cloacae* (23/180; 12.8%), *Klebsiella oxytoca* (12/180; 6.7%), *Proteus mirabilis* (6/180; 3.3%), and *Citrobacter freundii* (4/180; 2.2%).

Department-wise Distribution of CRE

The ICU contributed the highest proportion of CRE isolates, followed by the Medicine ward (Table 3).

The Intensive Care Unit (ICU) had the highest burden of CRE (55/180; 30.6%), followed by Medicine/General ward (42/180; 23.3%) and Surgery (28/180; 15.6%).

Table 3: Department-wise Distribution of CRE Isolates

Department	*CRE Isolates (n)*	*Percentage (%)*
Medicine/General Ward	42	23.3
Intensive Care Unit (ICU)	55	30.6
Surgery	28	15.6
Urology/ Nephrology	21	11.7
Obstetrics & Gynaecology	14	7.8
Oncology/ Transplant	12	6.7
Gastroenterology/ Neurology	8	4.4
Total	180	100

ICU = Intensive Care Unit

Table 4: MDR/XDR/PDR Classification of CRE Isolates (n=180)

Resistance Category	*Number of Isolates*	*Percentage (%)*
MDR (Multi-Drug Resistant)	93	51.7
XDR (Extensively Drug Resistant)	61	33.9
PDR (Pan-Drug Resistant)	26	14.4
Total	180	100

MDR = Multidrug-Resistant; XDR = Extensively Drug-Resistant; PDR = Pan-Drug-Resistant

Urology/Nephrology departments combined accounted for 21 isolates (11.7%), consistent with the high proportion of CRE in urinary tract samples.

MDR/XDR/PDR Classification

All 180 CRE isolates were classified according to MDR/XDR/PDR criteria (Table 4).

The majority of CRE isolates were MDR (93/180; 51.7%), while 61 (33.9%) were XDR and 26 (14.4%) were PDR, underscoring the profound resistance burden in this patient population.

CZA Susceptibility by Disc Diffusion and E-test

CZA susceptibility was evaluated by KBDD and E-test across all CRE isolates, stratified by species (Table 5).

Overall, 114/180 (63.3%) CRE isolates were susceptible to CZA by disc diffusion and 117/180 (65.0%) by E-test. The MIC90 across all CRE isolates was 8 mg/L. Escherichia coli demonstrated the highest CZA susceptibility (69.6% DD; 73.9% E-test), while Klebsiella pneumoniae showed relatively lower susceptibility (58.4% DD; 60.7% E-test), consistent with its greater propensity for carbapenemase production, particularly KPC and NDM types. Enterobacter cloacae and K. oxytoca showed intermediate CZA susceptibility rates of approximately 65–75%.

Concordance Between Disc Diffusion and E-test

The categorical agreement between the KBDD and E-test methods for CZA susceptibility testing is shown in Table 6.

The overall categorical agreement between disc diffusion and E-test methods was 92.2%, indicating strong concordance. Minor discrepancies were primarily observed for isolates with intermediate disc diffusion zones, which showed variable E-test MIC values clustering near the susceptibility breakpoint.

Table 5: CZA Susceptibility by Disc Diffusion and E-test MIC – Species-wise Breakdown

Organism	*CZA Susceptible DD (%)*	*CZA Intermediate DD (%)*	*CZA Resistant DD (%)*	*CZA MIC90 (mg/L) E-test*	*S% E-test*
K. pneumoniae (n=89)	52 (58.4)	7 (7.9)	30 (33.7)	8	60.7
E. coli (n=46)	32 (69.6)	3 (6.5)	11 (23.9)	4	73.9
E. cloacae (n=23)	15 (65.2)	2 (8.7)	6 (26.1)	4	69.6
K. oxytoca (n=12)	8 (66.7)	1 (8.3)	3 (25.0)	4	75.0
Others (n=10)	7 (70.0)	1 (10.0)	2 (20.0)	4	70.0
Overall (n=180)	114 (63.3)	14 (7.8)	52 (28.9)	8	65.0

DD = Disc Diffusion; S% = Percent Susceptible; MIC90 = MIC value inhibiting 90% of isolates; CZA = Ceftazidime-Avibactam; CLSI 2024 breakpoints applied.

Table 6: Concordance Between Disc Diffusion and E-test for CZA Susceptibility Testing

Category	*Susceptible n (%)*	*Intermediate n (%)*	*Resistant n (%)*	*Total*
Disc Diffusion (Kirby-Bauer)	114 (63.3)	14 (7.8)	52 (28.9)	180
E-test (MIC)	117 (65.0)	—	63 (35.0)	180
Agreement (%)	—	—	—	92.2%

DD = Disc Diffusion; MIC = Minimum Inhibitory Concentration; CLSI 2024 breakpoints applied.

DISCUSSION

These results of this prospective study carried out at IGIMS, Patna further supports the high burden of CRE at a tertiary care centre in eastern India and thus offer valuable local surveillance data of in vitro CZA activity. The CRE prevalence rate of 40.0% in Enterobacterales isolates from admitted patients is remarkable, but similar to other recent reports from tertiary care centers in India. The most prevalent source (30.6%) was the ICU, because of the high selection pressure for antibiotics and the susceptibility of critically ill patients [2].

Klebsiella pneumoniae was the most common species of CRE (49.4%) as it is known for being a reservoir for the transmissible carbapenemase genes including KPC, OXA-48, and NDM, especially in nosocomial settings [8]. Of particular interest is the presence of E. coli (25.6%), the second most common (and the most common in community-acquired UTI), which indicates the spread of carbapenem resistance within a traditionally susceptible organism, E. coli.

The overall susceptibility was in the range of 63.3% (KBDD) and 65.0% (E-test) which is in fairly good concurance with the published data from South and Southeast Asian countries. The rates of CZA susceptibility in CRE from Singapore ranged from 60% to 70%, depending on the type of dominant carbapenemase, reported by Lim et al. [4]. In India, CZA susceptibility rate of CRE was as high as about 55–65% with NDM-type MBLs as the main contributor to CZA resistance in a multicentric study [1]. The susceptibility to CZA was significantly lower in K. pneumoniae (58.4%) than in E. coli (69.6%) which may be attributed to the increased prevalence of MBL-producing K. pneumoniae in the Indian setting, as class B metallo-β-lactamases are not inhibited by avibactam.

The MIC90 of 8 mg/L for CZA for all CRE isolates is approximately equal to the CLSI breakpoints, suggesting that a significant proportion of isolates are close to the susceptibility breakpoint. This highlights the need to perform MIC based testing (E-test or broth microdilution) to inform treatment decision making, especially in severe or deep seated infections where optimal PK/PD targets are critical [6].

The level of categorical agreement (CZA) between KBDD and E-test in the current study is reassuring, indicating that disc diffusion might be used as a first-line screening test for CZA susceptibility in resource-limited areas. However, E-test MIC determination is the test method of choice for isolates with intermediate zone sizes on disc diffusion because MIC differences close to the breakpoint are clinically relevant.

The emergence of XDR (33.9%) and PDR (14.4%) phenotypes among CRE isolates is of great concern. By definition PDR are resistant to all known classes of antibiotics, and there is no standard treatment for these

isolates. In cases of NDM-producing CRE, CZA plus aztreonam has recently been shown to have synergistic in vitro activity and is thus emerging as a promising salvage regimen [1]. The combination should be systematically assessed in the local CRE population in future studies.

This study has several limitations, such as the lack of genotypic characterization of carbapenemase (e.g., PCR for KPC, NDM, OXA-48, VIM, IMP) which would have allowed for a more precise explanation of the mechanism underpinning the CZA susceptibility patterns. In addition, there was no clinical outcome data of correlation between CZA susceptibility and treatment response in this study. Further prospective studies are needed to combine molecular epidemiology with clinical outcome analysis to provide clinically relevant recommendations for treatment of CRE infections in this area.

Overall, this study identifies for the first time, a systematic local surveillance data of CZA activity against CRE from eastern India. The results confirm that CZA is a useful therapeutic option for almost two thirds of the CRE infections in this context and also underscore the need for improved infection control, surveillance programmes for carbapenemase and antibiotic stewardship to help stop the spread of CRE [7].

CONCLUSION

This prospective study demonstrates a high burden of CRE (40%) at IGIMS, Patna, with Klebsiella pneumoniae as the predominant pathogen. Ceftazidime-avibactam exhibited clinically relevant in vitro activity, with susceptibility rates of 63.3% (disc diffusion) and 65.0% (E-test) across all CRE isolates. The strong concordance (92.2%) between the two testing methods validates their complementary use in routine clinical microbiology. These findings endorse the therapeutic role of CZA in the management of CRE infections and advocate for mandatory CZA susceptibility testing as part of CRE workup in Indian tertiary care settings. Robust infection control strategies, molecular surveillance of carbapenemases, and antibiotic stewardship remain imperative to combat the escalating CRE burden.

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