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In vitro Synergistic Activity of Ceftazidime-Avibactam and Aztreonam Against Carbapenem-resistant *Enterobacterales*

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ABSTRACT

Introduction: Infections caused by multidrug-resistant Enterobacterales pose a significant global health challenge, thus necessitating novel therapeutic strategies. The increasing prevalence of carbapenem-resistant *Enterobacterales* has led to reliance on colistin and polymyxins as last-resort antibiotics. However, emerging colistin resistance and associated polymyxin toxicity have significantly limited their use. Aztreonam is effective against metallo-β-lactamase (MBL)-producing pathogens but requires protection from co-produced enzymes such as extended-spectrum β-lactamases (ESBLs), AmpC cephalosporinases, and other carbapenemases. Avibactam, a non-β-lactam β-lactamase inhibitor, inhibits ESBLs, *Klebsiella pneumoniae* carbapenemase (KPC), certain oxacillinase (OXA)-48-like enzymes, and AmpC cephalosporinases but is ineffective against metallo-β-lactamases. This study evaluated the *in vitro* synergy of ceftazidime-avibactam with aztreonam as a potential colistin-sparing strategy for carbapenem-resistant *Enterobacterales* infections. **Methods:** In a prospective cross-sectional study from July 2022 to June 2023, 97 carbapenem-resistant Gram-negative clinical isolates (prevalence: 97/8876 =1.09%) were obtained from 8876 samples tested for aerobic bacterial culture and antimicrobial susceptibility at a tertiary care hospital in Pune, India. For 69 *Enterobacterales* isolates resistant to ertapenem, imipenem, and meropenem, synergy between ceftazidime-avibactam and aztreonam was tested using disk diffusion and modified E-test/disk diffusion method, interpreted as per the guidelines of the Clinical and Laboratory Standards Institute (CLSI). **Results:** *Enterobacterales* comprised 69 (71.13%) of isolates, with 35 (50.73%) of these demonstrating synergy between ceftazidime-avibactam and aztreonam. *Klebsiella pneumoniae* (33/69; 47.83%) was the predominant species, followed by *Escherichia coli* (26/69; 37.68%) and *Citrobacter* species (10/69; 14.49%). **Conclusion:** *In vitro* synergy between ceftazidime-avibactam and aztreonam was observed in 50.73% of carbapenem-resistant *Enterobacterales* isolates, suggesting a possible colistin-sparing alternative for infections such as complicated urinary tract infections, intra-abdominal infections, and hospital-acquired pneumonia; however, further clinical studies are needed to validate its efficacy.

INTRODUCTION

Multidrug-resistant Gram-negative bacteria, particularly in healthcare settings, have emerged as a critical global health threat, contributing to increased morbidity, mortality, and rising healthcare costs [1, 2]. Carbapenem-resistant *Enterobacterales* (CRE) are significant contributors to morbidity and mortality in healthcare settings, particularly in critically ill patients and those with hospital-acquired infections [3, 4]. Carbapenemases are classified according to the Ambler system into classes A (*e.g.*, KPC and Guiana extended-spectrum β-lactamase GES enzymes), C (AmpC), and D (*e.g.*, OXA-48-like enzymes) being serine carbapenemases. Class B includes metallo-β-lactamases (MBLs; *e.g.*, New Delhi metallo-β-lactamase (NDM),

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Verona integron-encoded metallo-β-lactamase (VIM), and Imipenem-hydrolyzing metallo-β-lactamase (IMP) enzymes). CRE in Indian healthcare settings commonly produce New Delhi metallo-β-lactamase (NDM) and OXA-48-like carbapenemases (with KPC less common). Metallo-β-lactamase (MBL)-producing *Enterobacterales* are typically resistant to most β-lactams, including carbapenems and many β-lactam/β-lactamase inhibitor combinations [5, 6]. Limited therapeutic options—such as colistin, tigecycline, minocycline, and fosfomycin—are available for infections due to carbapenem-resistant organisms, but their use is restricted by toxicity or resistance. Newer β-lactam/β-lactamase inhibitor combinations, such as ceftazidime-avibactam, have been developed to inhibit the activity of carbapenemases and restore the efficacy of β-lactam antibiotics [3, 7].

Aztreonam is effective against MBLs-producing bacteria, but its clinical utility is often limited by co-production of ESBLs or AmpC β-lactamases, which hydrolyze aztreonam in MBL-producing bacteria. Avibactam, a β-lactamase inhibitor, counteracts class A β-lactamases (*e.g*., ESBLs, KPC) and AmpC producers, but it does not inhibit MBLs. Thus, combining ceftazidime-avibactam with aztreonam may protect aztreonam's activity against MBL-producing *Enterobacterales* [8].

Ceftazidime-avibactam may offer advantages in pharmacokinetic and pharmacodynamic properties compared to polymyxins, such as lower nephrotoxicity and enhanced lung penetration; this makes it a potential alternative for treating infections caused by serine carbapenemase-producing pathogens [5, 9].

Aztreonam is effective against MBL-producing bacteria but requires protection from other co-existing β-lactamases, such as ESBLs and class C β-lactamases, which are often produced by these MBL-producing strains. Avibactam effectively inhibits ESBLs and class C β-lactamases. Consequently, the clinical use of ceftazidime-avibactam in combination with aztreonam is primarily targeted to the treatment of infections caused by MBL-producing *Enterobacterales* [10, 11]. Given the challenges posed by infections caused by multidrug-resistant Enterobacterales, this study aimed to evaluate the *in vitro* synergistic activity of aztreonam and ceftazidime-avibactam against carbapenem-resistant *Enterobacterales.*

MATERIAL AND METHODS

Study setting. This prospective cross-sectional study was conducted in the Department of Microbiology, PCMC Postgraduate Institute and Yashwantrao Chavan Memorial Hospital, Pimpri-Chinchwad, Pune, India, from July 2022 to June 2023, following ethical approval from the Institutional Ethics Committee (IEC-PGI/OA-09/2022, dated August 29, 2022).

Sample collection and processing. Samples (blood, body fluids, pus, wound swabs, tissues, sputum, endotracheal secretions, and urine) from hospitalized patients with suspected bacterial infections were received in the Microbiology Laboratory. Samples were examined microscopically and cultured on blood agar and MacConkey agar; chocolate agar was used for respiratory samples, and cysteine lactose electrolyte-deficient (CLED) agar was used for urine samples. Plates were incubated aerobically at 37°C for 18–24 hours. Microbial identification was performed using standard biochemical tests. Antimicrobial susceptibility testing was done via a modified Kirby-Bauer disk diffusion method, with quality control strains *Escherichia coli* (*E. coli*) ATCC 25922 and *Klebsiella pneumoniae* (*K. pneumoniae*) ATCC 700603, as per the Clinical and Laboratory Standards Institute (CLSI) guideline [12]. A total of 97 Gram-negative bacterial isolates, all resistant to ertapenem, imipenem, and meropenem, were identified, with susceptibility breakpoints interpreted as per CLSI guideline [12].

Sample processing. For 69 *Enterobacterales* isolates resistant to ertapenem, imipenem, and meropenem, synergy between ceftazidime-avibactam and aztreonam was tested using disk diffusion and modified E-test/disk diffusion methods.

a) Disk diffusion synergy testing

A bacterial suspension of each test isolate was adjusted to a 0.5 McFarland turbidity standard, and a lawn culture was prepared on Mueller–Hinton agar. Synergy testing was performed using the double disk sandwich diffusion method, with *E. coli* ATCC 25922 as a quality control strain. A sandwich disk was prepared by placing the aztreonam disk (30 µg), moistened with sterile saline, over a ceftazidime-avibactam disk (30/20 µg; Oxoid, Thermo Fisher Scientific), and allowing it to dry before use. Disks of aztreonam, ceftazidime-avibactam, and the combination were placed 20 mm apart (centre-to-centre) on Mueller-Hinton agar plates and incubated at 37°C for 18–24 hours. The zone of inhibition diameter was measured in millimetres for *Enterobacterales*, as per CLSI guidelines [12]. Synergy was noted if the combination zone diameter exceeded that of ceftazidime-avibactam or aztreonam alone.

b) Modified E-test/disk diffusion synergy testing

A ceftazidime-avibactam E-strip (HiMedia Laboratories), with a fixed avibactam concentration (4 µg/mL) and graded ceftazidime concentrations (0.016–256 µg/mL), was placed on inoculated Mueller-Hinton agar. The aztreonam disk (30 µg) was positioned 15 mm from the E-strip, parallel to the susceptibility breakpoint for *Enterobacterales*. After incubation at 37°C for 18–24 hours, zones of inhibition were measured. Synergy was confirmed by an inverse D-shaped zone extension of aztreonam toward the ceftazidime-avibactam E-strip, or by an extension of the zone of inhibition around the aztreonam disk toward the elliptical zone of inhibition around the ceftazidime-avibactam E-strip (Figure 1).

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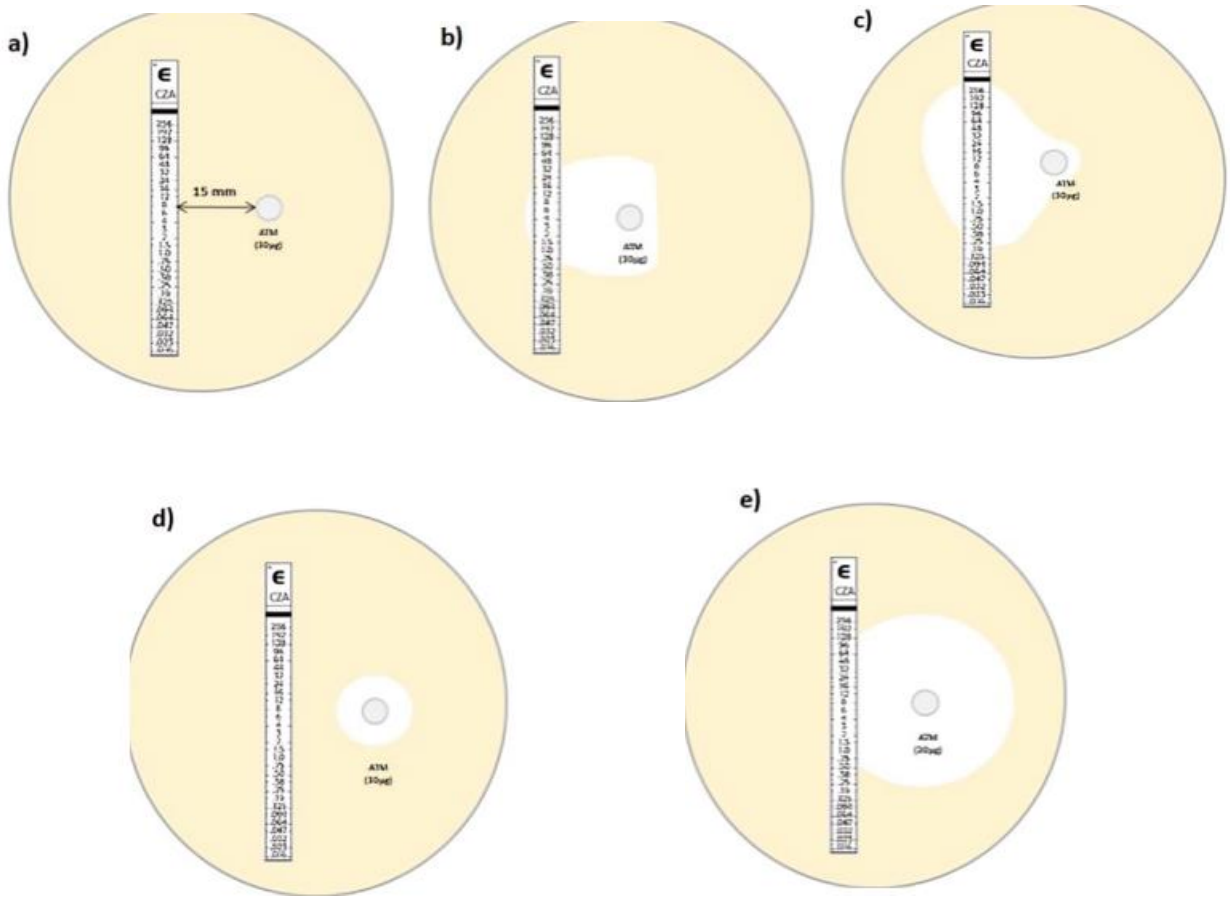

Fig. 1. Interpretation patterns for synergy testing of ceftazidime-avibactam with aztreonam using the modified E-test/disk diffusion method [13]. (a) Ceftazidime-avibactam E-strip and aztreonam disk were placed 15 mm apart; (b) positive synergy is shown by an inverse D-shaped zone; (c) positive synergy is shown by an extension of the zone of inhibition around the aztreonam disk toward the elliptical zone of inhibition around the E-strip; (d) no synergy, aztreonam-resistant isolate; (e) no synergy, aztreonam-susceptible isolate.

RESULTS

Patient demographics and clinical risk factors. From July 2022 to June 2023, 8876 samples were processed in the Microbiology Laboratory, yielding 97 Gram-negative isolates resistant to all three carbapenems: ertapenem, imipenem, and meropenem. The susceptibility breakpoints for carbapenems were interpreted according to CLSI guidelines.

Risk factor assessment revealed that 81/97 (83.5%) of the patients had undergone interventions, such as Foley's catheterization, dialysis cannulation, or other surgical interventions at least twice during their hospital stay (Figure 2). Comorbidities, including the co-occurrence of diabetes mellitus and hypertension, were present in 24/97 (24.74%) of patients, and chronic kidney disease was present in 15/97 (15.46%) of patients. Other risk factors, including cancer, history of transplant, and HIV infection, were present in 4.12%, 1.03%, and 1.03% of patients, respectively. In case of patients with CRE, infections with similar risk factors were observed including surgical intervention 31.88%, diabetes and hypertension 20.29%, Foley's catheterization 11.59%, CKD 10.15%, cancer 4.35% and Tuberculosis 2.9% (Figure 3). Among the 69 *Enterobacterales* isolates, 39 (56.5%) were from male patients, and 30 (43.5%) from female patients.

Distribution of clinical isolates. Sample-wise distribution of 97 isolates showed that 39.18% were recovered from urine samples, followed by 28.87% from pus samples (including frank pus, wound swabs, wound discharge, and tissues), 19.59% from respiratory samples, 9.28% from blood samples, and 3.09% from body fluids (Figure 4).

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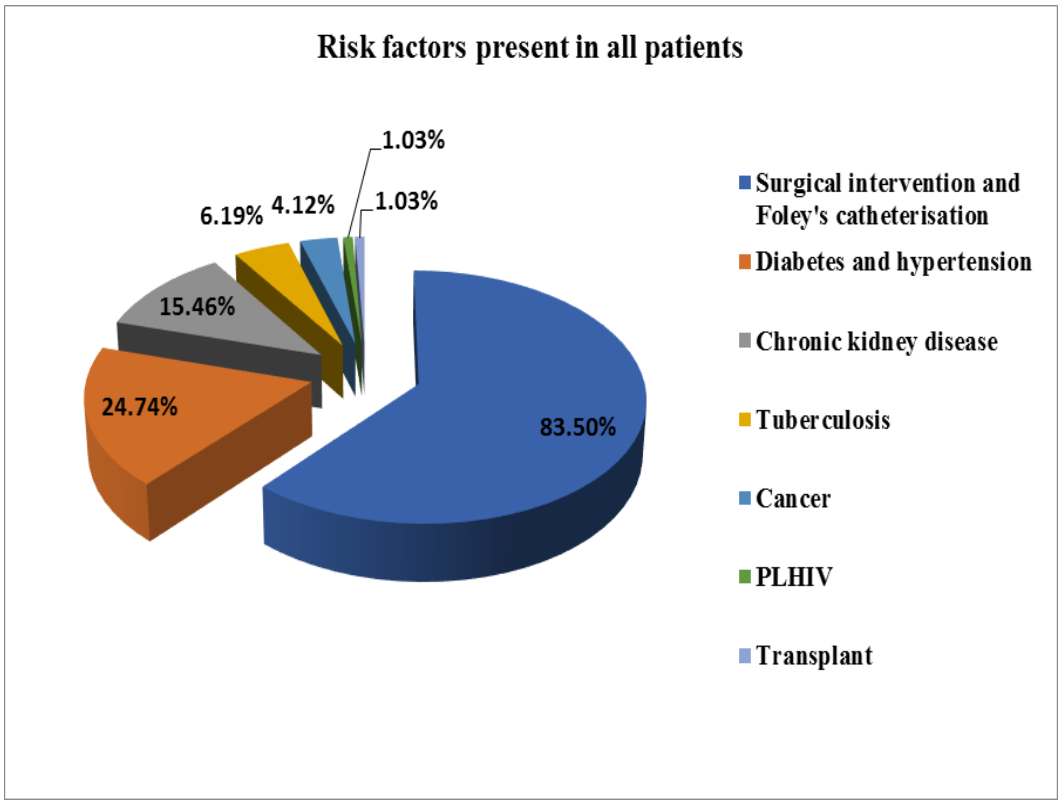

Fig. 2. Risk factors assessment among all patients (n = 97).

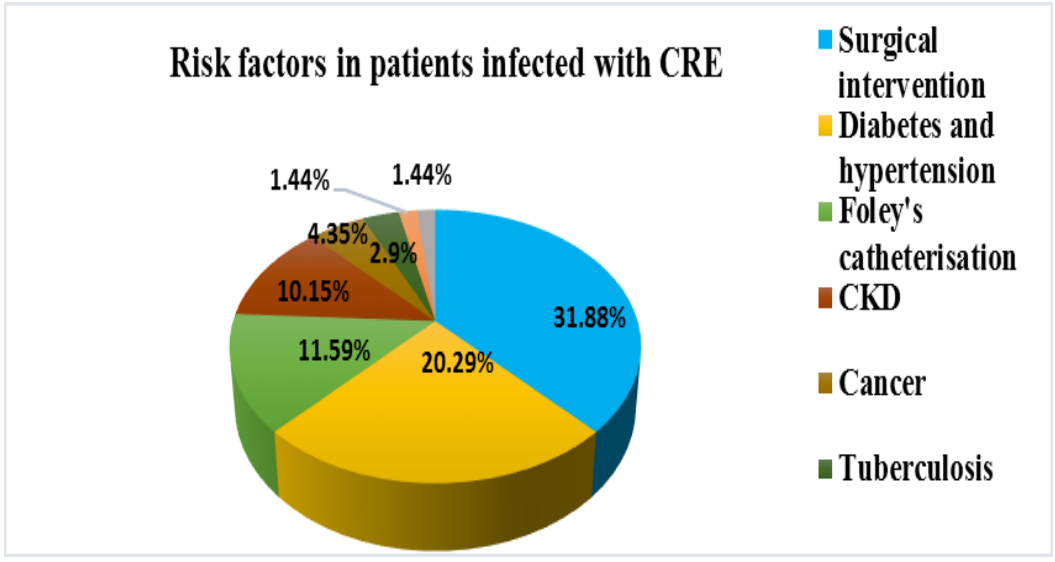

Fig. 3. Risk factors for infections in patients with CRE (n = 69)

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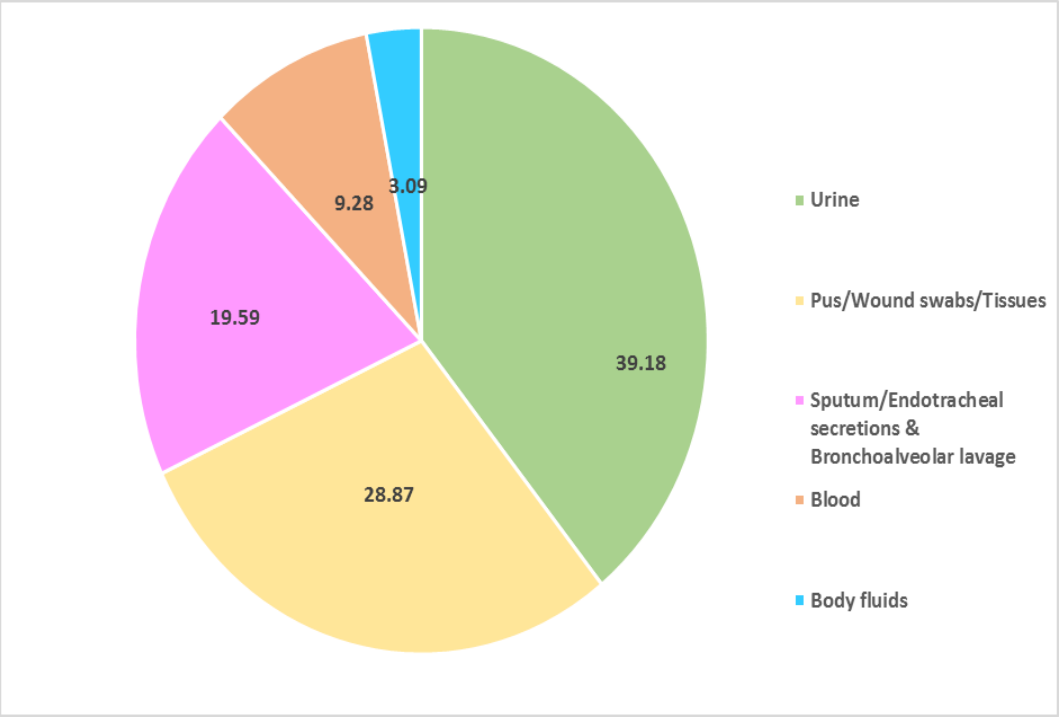

Fig. 4. Percentage distribution of 97 carbapenem-resistant Gram-negative isolates by sample type.

Among the 28 isolates from pus samples, 28.57% were *E. coli* and 17.86% each were *Klebsiella* and *Citrobacter* species, respectively. For respiratory samples, *Klebsiella* species comprised 47.37% of isolates, followed by *E. coli* (10.53%) and *Citrobacter* species (10.53%) (Figure 5). *Enterobacterales* were the predominant organisms associated with urinary tract infections, with *Klebsiella* species and *E. coli* comprising 42.11% and 39.47% of isolates, respectively.

Among the 97 isolates, 71.13% were from the order *Enterobacterales*, and 28.87% were non-fermenting Gram-negative bacilli. Among *Enterobacterales*, 47.83% of isolates were *K. pneumoniae*, 37.68% were *E. coli*, and 14.49% were *Citrobacter* species. Among non-fermenting Gram-negative bacilli, *Acinetobacter* species comprised 46.43%, followed by *Pseudomonas* species (25%), and other non-fermenters (28.57%). For the 28 non-fermenting Gram-negative bacilli, aztreonam use is challenging due to inactivation by efflux pumps [13]. Additionally, interpretation criteria for synergy between ceftazidime-avibactam and aztreonam are not available in CLSI or EUCAST guidelines for non-fermenting Gram-negative bacilli; hence, synergy was tested only for CRE.

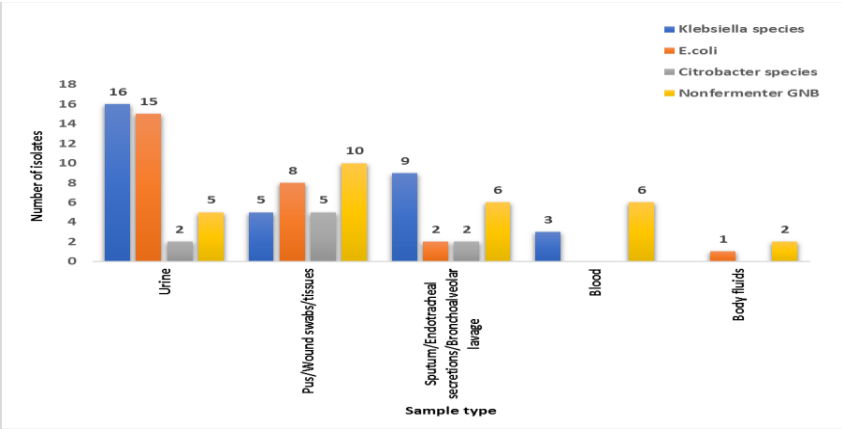

Fig. 5. Distribution of carbapenem-resistant Gram-negative isolates by sample type

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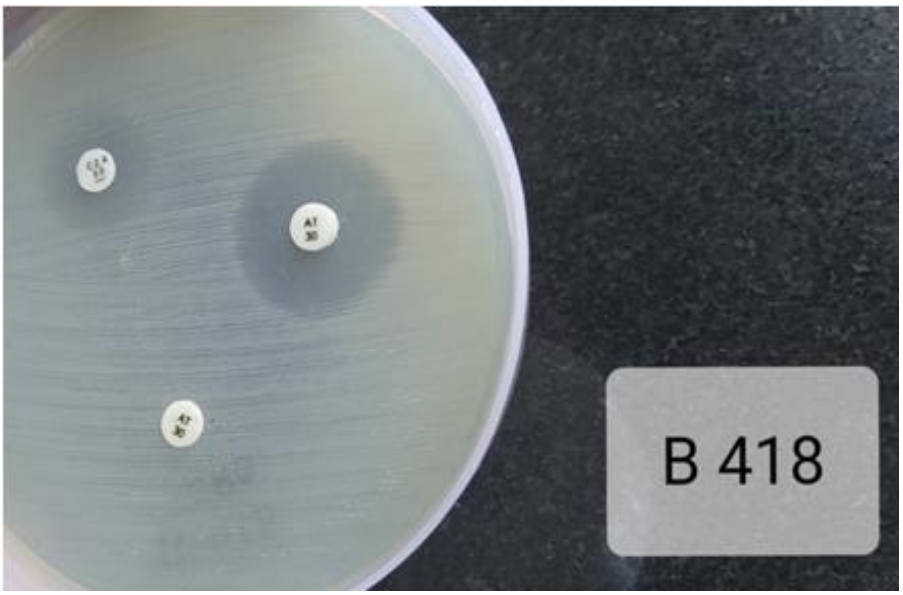

Fig. 6. An isolate of *K. pneumoniae* showing synergy by the disk diffusion method.

Synergy testing. Synergy between ceftazidime-avibactam and aztreonam was observed in 35/69 (50.73%) of *Enterobacterales* isolates; *E. coli* had the highest proportion of isolates (18/26 (69.23%)) exhibiting synergy, followed by *Klebsiella* species (16/33 (48.48%)).

All 69 *Enterobacterales* isolates were tested by both the disk diffusion and the modified E-test/disk diffusion methods to compare their performance (Table 1, Figure 6).

Table 1. Comparison of the disk diffusion method and the modified E-test/disk diffusion method for synergy testing in carbapenem-resistant *Enterobacterales.*

Serial No.	Species (n)	Synergy by disk diffusion method (n)	Synergy by modified E-test/disk diffusion method (n)	Percentage agreement between methods*
1	*Klebsiella species* (33)	16	14	93.9%
2	*E. coli* (26)	18	18	100%
3	*Citrobacter* species (10)	1	1	100%

*Agreement = isolates with identical result (both synergistic or both non-synergistic) / total × 100

DISCUSSION

Carbapenems are frequently used as last-resort antibiotics for multidrug-resistant *Enterobacterales* infections, but their efficacy is limited by the high prevalence of carbapenem-resistant isolates observed in this study (n = 97). Due to the increasing prevalence of CRE, treatment options remain restricted to polymyxins (polymyxin B and colistin). The detection of CRE in routine microbiology laboratories is beneficial for guiding precise treatment of these infections, as therapeutic options vary among different carbapenemase producers [13, 14].

In the present study, 97 isolates resistant to carbapenems (including *Enterobacterales* and non-fermenting Gram-negative bacilli) were obtained from various samples, including blood, body fluids, pus, wound swabs, tissues, sputum, endotracheal secretions, and urine, received in the laboratory.

Among CRE, *K. pneumoniae* was predominant (33/69 = 47.83%), followed by *E. coli* (26/69 = 37.68%). These findings align with studies by Prayag *et al*. [9], Taha *et al*. [14], and Yu *et al*. [15], which reported a similar predominance of *K. pneumoniae* and *E. coli* among CRE.

In the current study, 35/69 (50.73%) of *Enterobacterales* isolates demonstrated synergy between ceftazidime-avibactam and aztreonam. *E. coli* was the most common species, with 18/26 (69.23%) of isolates exhibiting synergy, followed by *Klebsiella* species (16/33, 48.48%). A study by Taha *et al*. (2023) reported synergy in 98.75% of *Klebsiella* species and 95% of *E. coli*, higher than the 50.73% synergy observed in this study [14]; this discrepancy may be due to differences in methods or isolate characteristics, warranting further investigation. In Taha *et al*. (2023), carbapenem resistance was detected by disk diffusion/broth dilution methods, and the Vitek-2 compact system for all three carbapenems: imipenem,

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ertapenem, and meropenem [14]. Synergy was demonstrated using the modified E-test method only, whereas in the present study, we isolated and reported carbapenem-resistant pathogens using conventional identification methods and manual susceptibility testing rather than automation. We also performed both the disk diffusion and modified E-test/disk diffusion methods to demonstrate synergy. The lower percentage of isolates showing synergy in this study might be attributed to the co-existence of multiple resistance mechanisms, such as other enzymes or non-metallo-β-lactamase mechanisms. This finding was supported by Prayag *et al*. (2023), who reported that several isolates in their study were multiple-enzyme producers, complicating patient management [9].

In Taha *et al*. (2023), the type of carbapenemase present in the isolates was determined phenotypically and genotypically through additional testing [14], whereas in the current study, we did not characterize the specific carbapenemases.

A study by Rawson *et al*. (2022) revealed that 53% of isolates demonstrated synergy [16]. In Rawson *et al*. (2022), synergy testing was performed on NDM-producing *Enterobacterales*, representing a selected subset of isolates. Synergy was tested using the modified E-test and broth microdilution methods, whereas in the current study, we included all carbapenem-resistant isolates for synergy testing due to the lack of genotypic or phenotypic carbapenemase characterization.

The disk diffusion method, when compared to methods such as broth microdilution and modified E-test, is inferior due to the potential for fluctuating diffusion of antimicrobial agents through the agar plate and human subjectivity in measuring zone diameters [17]. This could contribute to the lower percentage of isolates that demonstrated synergy in the current study. However, the disk diffusion method showed a higher synergy detection rate (Table 1) and may serve as a simpler alternative in resource-limited settings where ceftazidime-avibactam E-strips are unavailable.

The risk factor analysis (Fig. 2, Fig. 3) highlights the role of interventions and comorbidities in posing a threat to CRE infections. Interventions, including Foley's catheterization, dialysis cannulation, or other surgical procedures (81/97 = 83.51%), followed by comorbidities, such as diabetes mellitus and hypertension (24/97 = 24.74%), were the most common predisposing factors for infections associated with CRE in the present study. Similar risk factors, including ICU admission, central line insertion, immunosuppressive therapy, diabetes mellitus, chronic liver and kidney diseases, malignancies, and a history of transplant, were reported in a study by Prayag *et al*. (2023) [9]. In a study by Khattab *et al*. (2025), ICU hospitalization was identified as a significant risk factor for developing carbapenem-resistant *K. pneumoniae* [18]. In that study, 60% of isolates were carbapenem-resistant *K. pneumoniae*, of which 68.6% were metallo-β-lactamase producers. These metallo-β-lactamase producers were subjected to synergy testing, which revealed that 62.5% of isolates demonstrated positive synergy [18]. Based on the literature reviewed, the presence of risk factors predisposes patients to infections by these difficult-to-treat pathogens, requiring additional testing such as synergy testing or phenotypic and genotypic detection of enzymes responsible for resistance. Kalaivani *et al*. (2024) reported that 77.2% of isolates showed synergy between ceftazidime-avibactam and aztreonam by the modified E-test/disk diffusion method. They evaluated the clinical effectiveness of this combination, reporting a favorable clinical outcome in 4.5% of patients treated with ceftazidime-avibactam and aztreonam combination therapy for 7 days or more [19]. Guzek *et al.* (2024) assessed the clinical utility of the ceftazidime-avibactam and aztreonam combination in NDM-producing *K. pneumoniae*. They reported outcomes for 23 patients, primarily ICU-admitted, showing eradication of NDM-producing *K. pneumoniae* in all cases, with a 17.4% mortality rate. They also compared the clinical efficacy of the ceftazidime-avibactam and aztreonam combination versus treatment with colistin combined with fosfomycin and tigecycline, or tigecycline combined with aminoglycosides or fosfomycin, showing that the 30-day mortality rate for ceftazidime-avibactam with aztreonam was 19.2%, compared with approximately 44% for other antimicrobial combinations. The highest 30-day mortality rate of 59.3% was observed in patients receiving colistin-based regimens [20].

In the present study, we performed synergy testing using both the disk diffusion and the modified E-test/disk diffusion methods. Agreement between the methods was 100% in *E. coli* and *Citrobacter* species isolates, whereas it was reduced to 93.9% in *Klebsiella* species. A study by Rawson *et al*. (2022) showed that 74% and 53% of isolates exhibited synergy by broth microdilution and modified E-test/disk diffusion methods, respectively, with an 81% concordance between the results of these methods [16]. Given the higher synergy detection rate by disk diffusion in this study (Table 1), this method may be used as a practical alternative in resource-limited settings where ceftazidime-avibactam E-strips are unavailable, despite its limitations due to fluctuating diffusion and subjectivity [17].

Future studies incorporating genotypic and phenotypic characterization of carbapenemases are warranted to further elucidate the relationship between specific resistance mechanisms and their observed synergistic activity. In a study by Taha *et al*. (2023), the majority of *Klebsiella* isolates demonstrated the presence of OXA-48 and metallo-β-lactamase enzymes, whereas *E. coli* isolates showed the presence of metallo-β-lactamase and KPC enzymes [14]. Prayag *et al*. (2023) reported that the majority of isolates (66.3%) were OXA-48 producers, followed by 62.5% who were NDM producers [9].

In conclusion, *K. pneumoniae* was the predominant clinical isolate (47.83%). Among tested isolates, synergy

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was observed in 50.73% of isolates, with *Escherichia coli* showing the highest rate. The majority of these isolates were obtained from urine samples. Synergy testing of ceftazidime-avibactam and aztreonam was performed using both disk diffusion and modified E-test/disk diffusion methods to guide clinicians in selecting possible alternative antimicrobial agents for managing infections caused by carbapenem-resistant pathogens. Further clinical studies are needed to assess the efficacy of this combination. The newer β-lactam/β-lactamase inhibitor combination, ceftazidime-avibactam combined with aztreonam, shows promise as a therapeutic option and warrants further investigation as an alternative to polymyxins for serious Gram-negative bacterial infections.

The study included a limited dataset due to a low proportion of pediatric samples, potentially reducing generalizability to younger populations. Only clinical isolates from a single hospital were included in this study. Additionally, the lack of phenotypic or genotypic carbapenemase characterization has limited insights into specific resistance mechanisms. We could not assess the clinical effectiveness of the synergistic use of ceftazidime-avibactam combined with aztreonam, as most patients were lost to follow-up. The use of manual susceptibility testing methods may have introduced methodological variability compared to automated systems.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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AI DISCLOSURE

No assistance was used in the form of Artificial Intelligence (AI) for preparation of this manuscript.

DATA AVAILABILITY

This study was conducted in the Department of Microbiology, PCMC Postgraduate Institute and Yashwantrao Chavan Memorial Hospital, Pimpri, Pune, to perform synergy testing and identify therapeutic options for multidrug-resistant pathogens. All clinical isolates were obtained from patients undergoing culture and susceptibility testing. Synergy testing and routine susceptibility data are securely stored and available upon reasonable request, and are subject to ethical approval.

AUTHORS' CONTRIBUTIONS

CJ: Conceptualization; Methodology; Investigation; Formal Analysis; Writing – Original Draft. SM: Conceptualization; Methodology; Formal Analysis; Writing – Review & Editing. JP: Conceptualization; Methodology; Supervision; Project Administration; Writing – Review & Editing. SD: Formal Analysis; Writing – Review & Editing. KK: Investigation; Data Curation; Formal Analysis; Writing – Review & Editing.

ETHICS STATEMENT

The study protocol was reviewed and approved by the Institutional Ethics Committee of (Reference No. IEC-PGI/OA-09/2022, dated August 29, 2022).

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