

Evaluation of the sensitivity pattern of ceftazidime-avibactam against multidrug-resistant gram-negative Isolates of *Enterobacterales*

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ABSTRACT

Objectives: Surveillance of antimicrobial susceptibility patterns is essential for guiding effective therapy. This study aimed to evaluate the in vitro activity of ceftazidime-avibactam against *Enterobacterales* stratified by resistance phenotype.

Material and Methods: This retrospective, laboratory-based surveillance study was conducted from 1st February to 30th November 2023 at the National Institute of Cardiovascular Diseases, a tertiary care cardiac centre in Karachi, Pakistan. We analysed 236 non-duplicate *Enterobacterales* isolates obtained from 98 blood and 138 respiratory specimens. Antimicrobial susceptibility testing was performed according to Clinical and Laboratory Standards Institute guidelines. Associations between resistance phenotype and ceftazidime-avibactam susceptibility were assessed using the Chi-square test, Cramér's V, linear-by-linear association, and odds ratios with 95% confidence intervals.

Results: Overall, 179/236 (75.8%; 95% CI: 70.0–80.9) isolates were susceptible, and 57/236 (24.2%; 95% CI: 19.1–30.0) were resistant to ceftazidime-avibactam. Among blood isolates, susceptibility declined from 95.0% in non-Multidrug resistant organisms (non-MDRO) to 30.3% in carbapenem-resistant *Enterobacterales* (CRE) isolates ($\chi^2 = 32.08$, $p < 0.001$). Respiratory isolates showed a similar decrease from 97.1% to 34.5% ($\chi^2 = 55.83$, $p < 0.001$). Significant linear trends of decreasing susceptibility across resistance phenotypes were observed in both specimen groups. CRE isolates had significantly higher odds of resistance than ESBL producers.

Conclusion: Ceftazidime-avibactam demonstrated high activity against non-MDRO and ESBL-producing *Enterobacterales* but reduced efficacy against CRE isolates, with susceptibility declining progressively across resistance phenotypes in both blood and respiratory specimens.

Keywords: Beta-lactamase inhibitors, Carbapenem-resistant Enterobacteriaceae, Ceftazidime, Drug resistance, Microbial, Sensitivity test.

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INTRODUCTION

The rapid emergence and global spread of multidrug-resistant (MDR) Gram-negative bacteria, particularly *Enterobacterales*, represent a major threat to public health and clinical practice. Infections caused by Extended-spectrum β -lactamase (ESBL)-producing and Carbapenem-resistant *Enterobacterales* (CRE) are associated with increased morbidity, mortality, prolonged hospital stay, and limited therapeutic options [1-3]. The burden is particularly high in low- and middle-income countries, including South Asia, where the prevalence of carbapenem resistance and metallo- β -lactamases (MBLs) such as New Delhi metallo- β -lactamase (NDM) is increasing [4, 5].

Ceftazidime-avibactam has emerged over the past decade as an important therapeutic option for the management of infections caused by MDR Gram-negative organisms. It is a combination of a third-generation cephalosporin (ceftazidime) and a novel non- β -lactam β -lactamase inhibitor (avibactam), which effectively inhibits class A (including KPC), class C (AmpC), and some class D β -lactamases [6, 7]. Recent global surveillance studies, including the ATLAS and INFORM programs, have demonstrated sustained high activity of ceftazidime-avibactam against ESBL-producing *Enterobacterales*, with susceptibility rates often exceeding 90% [8, 9]. However, the clinical utility of ceftazidime-avibactam in CRE infections remains variable. While it is effective against KPC-producing organisms, its activity is limited against MBL-producing isolates, which are increasingly prevalent in many regions [3,8].

Recent studies have reported declining susceptibility rates of different antibiotics like Colistin, Tigecycline, Amikacin etc. among CRE isolates and the emergence of resistance during therapy, raising

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concerns about its long-term effectiveness [10]. Furthermore, clinical outcomes in critically ill patients remain heterogeneous, influenced by factors such as infection severity, comorbidities, and appropriateness of antimicrobial therapy [11, 12].

Although several clinical and surveillance studies have evaluated the efficacy of ceftazidime-avibactam, there remains a paucity of region-specific data correlating in vitro susceptibility patterns with resistance phenotypes, particularly in high-burden settings. In Pakistan, several studies have reported susceptibility patterns of ceftazidime-avibactam; however, most are limited to descriptive analyses from lab settings or general hospital populations and lack stratification by resistance phenotype or specimen type [13-17]. Furthermore, data from specialized high-risk settings, such as cardiac care centers, remain scarce. Patients admitted to cardiac intensive care units represent a particularly vulnerable population due to invasive procedures, mechanical ventilation, prolonged hospital stay, and extensive exposure to broad-spectrum antibiotics, all of which contribute to the emergence and selection of MDR organisms.

Therefore, the present study aimed to evaluate the in vitro susceptibility of *Enterobacterales* isolates to ceftazidime-avibactam obtained from blood and respiratory specimens in a tertiary care cardiac centre. By focusing on a predominantly critically ill cardiac population and demonstrating a biologically meaningful gradient in susceptibility across resistance categories, this study offers clinically relevant insights beyond conventional descriptive surveillance.

MATERIAL AND METHODS

This retrospective lab-based surveillance study was conducted at the Section of Microbiology, Department of Pathology & Laboratory Services at the National Institute of Cardiovascular Diseases from 1st February 2023 to 30th November 2023. A total of 236 non-duplicate *Enterobacterales* isolates were included, comprising 98 blood and 138 respiratory specimens. Respiratory specimens comprised of 100 tracheal aspirate samples and 38 bronchoalveolar lavage samples. The sample size was calculated using the formula [18]:

$$n = \frac{Z^2 \times p \times (1 - p)}{d^2}$$

where Sensitivity prevalence (p) was taken as 1% [19], confidence level (Z=1.96) was 95%, and margin of error (d) was 5%. Gram-negative rods belonging to

Enterobacterales in Blood and respiratory specimens obtained from patients admitted to critical care units, including cardiac and surgical intensive care units were included in the study. Duplicate isolates, Gram-negative rods other than *Enterobacterales* and specimens other than blood and respiratory sources were excluded. Ethical exemption was obtained from the Institutional Review Board of NICVD (Ref no: IRB-37/2025 dated 8th May 2025).

Blood Cultures were processed in BACT/ALERT® 3D (bioMerieux) blood culture system. Respiratory specimens were processed using standard microbiological quantitative techniques. After gram staining, identification of isolates were performed using conventional biochemical methods, including oxidase, Triple Sugar Iron agar, Sulfide Indole Motility testing, urease detection and citrate utilization testing. Routine antimicrobial susceptibility testing and further susceptibility to ceftazidime-avibactam was carried out using the Kirby–Bauer disk diffusion method in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines. CLSI 2023 breakpoints have been used for detecting resistance in Gram-negative isolates of *Enterobacterales*

The minimum inhibitory concentration (MIC) of colistin was determined using the broth microdilution method. Briefly, serial, two-fold dilutions of the antimicrobial agents were prepared in a sterile, multiwall microtiter plate and inoculated with a standardized bacterial suspension. The inoculated plates were incubated overnight at 35 ± 2°C under appropriate conditions. Following incubation, the MIC was defined as the lowest concentration of the antimicrobial agent that completely inhibited visible bacterial growth. The resulting MIC values were interpreted as susceptible, intermediate, or resistant according to the breakpoints and interpretive criteria established by the Clinical and Laboratory Standards Institute [20]. The breakpoint of <2 has been used for colistin resistance detection.

Isolates were categorized into non-MDR organisms, ESBL-producing, and CRE based on phenotypic resistance patterns. Non-multidrug-resistant *Enterobacterales* (Non-MDRO) were defined as isolates susceptible to at least four groups of antibiotics especially 3rd generation cephalosporins and carbapenems. ESBL-producing isolates were defined as *Enterobacterales* demonstrating phenotypic evidence of extended-spectrum β-lactamase production, as indicated by resistance to extended-spectrum cephalosporins. Specifically, isolates with a ceftriaxone zone diameter of ≤19 mm

using a 30- μ g ceftriaxone disk in the Kirby–Bauer disk diffusion method were classified as resistant according to the CLSI M100 interpretive criteria. Carbapenem-resistant *Enterobacterales* (CRE) were operationally defined as *Enterobacterales* isolates exhibiting a meropenem zone diameter of ≤ 19 mm when tested with a 10- μ g meropenem disk using the Kirby–Bauer disk diffusion method, consistent with the resistant-category interpretive criteria specified in the CLSI M100 guidelines.

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics version 28. The primary outcome variable was Ceftazidime–Avibactam susceptibility status (sensitive/resistant). The main independent variable was resistance phenotype category (non-MDRO, ESBL-producing, and CRE isolates). Additional categorical variables included specimen type (blood and respiratory specimens). Categorical variables were summarized as frequencies and percentages. Corresponding 95% confidence intervals (CIs) for proportions were calculated using the Wilson score method. Associations between resistance phenotype and Ceftazidime–Avibactam susceptibility were evaluated using the Chi-square test or Fisher's exact test, where appropriate. The strength of association was assessed using Cramér's V effect size measure. A Chi-square test for trend (linear-by-linear association) was applied to assess ordered changes in susceptibility across resistance categories (non-MDRO, ESBL, and CRE). Odds ratios (ORs) with 95% confidence intervals were calculated using binary logistic regression to quantify the likelihood of resistance among different phenotypic groups. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

A total of 236 *Enterobacterales* isolates were analyzed, including 98 blood and 138 respiratory specimens. Overall, 179 (75.8%; 95% CI: 70.0 – 80.9) isolates were sensitive and 57 (24.2%; 95% CI: 19.1 – 30.0) were resistant to ceftazidime-avibactam.

Among blood isolates, 66 (67.3%; 95% CI: 57.3–76.1) were sensitive, and 32 (32.7%; 95% CI: 23.9–42.7) were resistant (Table-I). Susceptibility varied significantly across resistance phenotypes (Table-II). In the non-MDRO group, 19 (95.0%; 95% CI: 75.1–99.9) isolates were sensitive, compared to 37 (82.2%; 95% CI: 68.0–91.4) among ESBL producers and 10 (30.3%; 95% CI: 16.7–48.1) among CRE isolates. Resistance was correspondingly higher in CRE isolates (69.7%; 95% CI: 51.9–83.3). A statistically significant association was observed between resistance phenotype and ceftazidime-avibactam susceptibility ($\chi^2 = 32.08$, df = 2, $p < 0.001$), with a strong effect size (Cramér's V = 0.57). As shown in Figure-I, a significant linear trend, with decreasing susceptibility from non-MDRO to ESBL to CRE isolates, was also identified (χ^2 for trend = 27.67, df = 1, $p < 0.001$).

Among respiratory isolates, 113 (81.9%; 95% CI: 74.6–87.5) were sensitive, and 25 (18.1%; 95% CI: 12.5–25.4) were resistant (Table-I). Susceptibility remained high among non-MDRO 33 (97.1%; 95% CI: 84.7–99.5) and ESBL isolates 70 (93.3%; 95% CI: 85.4–97.2) but was markedly reduced among CRE isolates 10 (34.5%; 95% CI: 19.2–53.2), with resistance reaching 65.5% (95% CI: 46.8–80.8) (Table-II). A statistically significant association was observed ($\chi^2 = 55.83$, df = 2, $p < 0.001$), with a strong effect size (Cramér's V = 0.64). A significant linear trend of increasing resistance across resistance phenotypes was observed in both blood and respiratory isolates (Figure-I). Comparative analysis showed that CRE isolates had significantly higher odds of resistance compared to ESBL producers in both blood (OR = 10.6; 95% CI: 3.7–30.9) and respiratory specimens (OR = 26.6; 95% CI: 8.1–87.2) (Table-III). All isolates exhibited intermediate susceptibility to Colistin in our study and did not have any significant association with ceftazidime-avibactam susceptibility.

Table-I: Overall susceptibility of *Enterobacterales* to ceftazidime-avibactam.

Outcome	n (%)	95% CI
Total Isolates n= 236		
Sensitive	179 (75.8)	70.0 – 80.9
Resistant	57 (24.2)	19.1 – 30.0
Blood Isolates n= 98		
Sensitive	66 (67.3%)	57.3–76.1
Resistant	32 (32.7%)	23.9–42.7
Respiratory Isolates n= 138		
Sensitive	113 (81.9%)	74.6–87.5
Resistant	25 (18.1%)	12.5–25.4

Values are presented as n (%) with 95% confidence intervals (CI). Abbreviations: CI, confidence interval.

Table-II: Susceptibility pattern of ceftazidime-avibactam by resistance phenotype in blood and respiratory isolates.

Specimen	Resistance Category	Sensitive n (%)	Resistant n (%)	p-value	Cramér's V
Blood (n=98)	Non-MDRO	19 (95.0)	1 (5.0)	<0.001	0.57
	ESBL	37 (82.2)	8 (17.8)		
	CRE	10 (30.3)	23 (69.7)		
Respiratory (n=138)	Non-MDRO	33 (97.1)	1 (2.9)	<0.001	0.64
	ESBL	70 (93.3)	5 (6.7)		
	CRE	10 (34.5)	19 (65.5)		

Values are presented as n (%). p-values correspond to overall comparison across resistance categories within each specimen type and were derived using the Pearson Chi-square test. Effect size was assessed using Cramér's V. Abbreviations: MDRO, multidrug-resistant organisms; ESBL, extended-spectrum β -lactamase; CRE, carbapenem-resistant *Enterobacterales*.

Table-III: Comparative risk of resistance (CRE vs. ESBL).

Specimen Type	Odds Ratio (OR)	95% CI	p-value
Blood	10.6	3.7 – 30.9	<0.001
Respiratory	26.6	8.1 – 87.2	<0.001

Odds ratios represent the likelihood of resistance in CRE isolates compared with ESBL-producing isolates within each specimen type. P-values were derived using the Chi-square test.

Abbreviations: OR, odds ratio; CI, confidence interval; ESBL, extended-spectrum β -lactamase; CRE, carbapenem-resistant *Enterobacterales*.

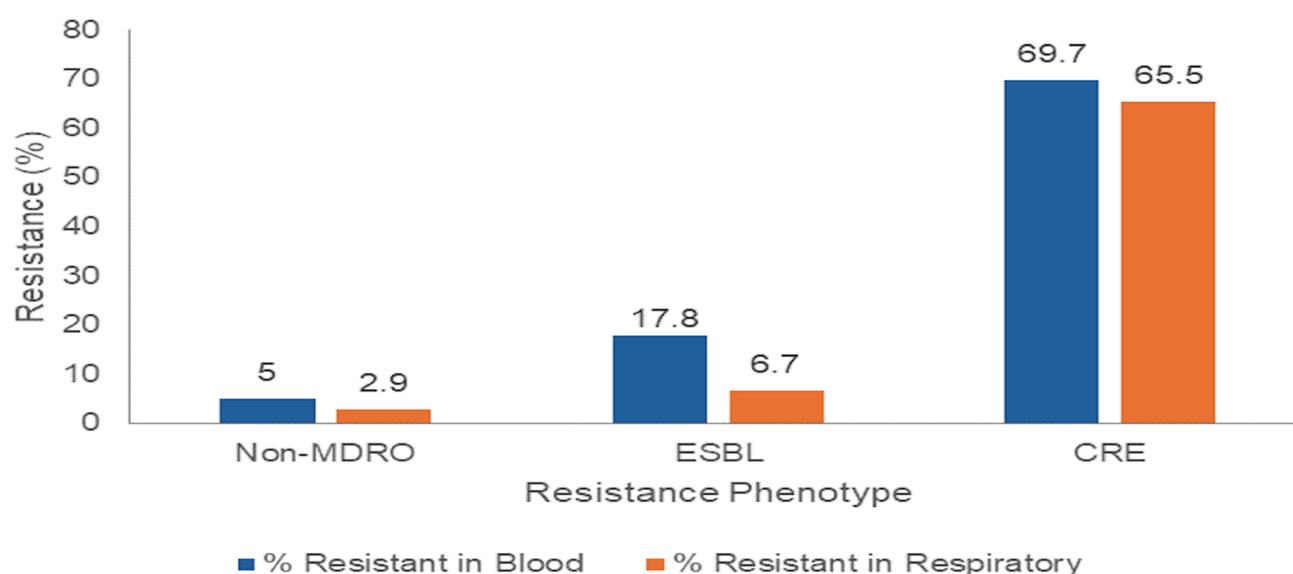


Figure-I: Percentage resistance to ceftazidime-avibactam across resistance phenotypes (Non-MDRO, ESBL, CRE) in blood and respiratory isolates, demonstrating a progressive increase in resistance across categories (p for trend < 0.001).

DISCUSSION

This study demonstrated that ceftazidime-avibactam retains high activity against non-MDRO and ESBL-producing *Enterobacterales*, with a marked reduction in susceptibility among CRE isolates. The statistically significant gradient observed across resistance categories highlights a strong biological relationship between resistance burden and antimicrobial efficacy. To our knowledge, this is among the first studies from Pakistan to demonstrate such a biologically meaningful gradient in ceftazidime-avibactam susceptibility across resistance phenotypes within a predominantly cardiac critical care population.

The susceptibility we observed among ESBL-producing isolates (82.2% in blood and 93.3% in respiratory specimens) is broadly consistent with contemporary global surveillance data reported by El

Kettani *et al.* and Wang *et al.*, which report sustained efficacy of ceftazidime-avibactam against these organisms, often exceeding 90% susceptibility across multiple regions [21, 22]. Large-scale surveillance programmes such as ATLAS and INFORM, reported by Wise *et al.* and Gales *et al.*, have consistently demonstrated preserved activity against ESBL-producing *Enterobacterales* over recent years, supporting its role as a key therapeutic option [8, 21, 23]. Our overall resistance rate of 24.2% is nonetheless substantially higher than the 6.1% (95% CI 4.9–7.4) pooled resistance proportion reported for *Enterobacterales* in the global meta-analysis by Wang *et al.*, which also documented a rise in ceftazidime-avibactam resistance across Gram-negative bacteria from 5.6% in 2015–2020 to 13.2% in 2021–2024 [22]. This divergence is most plausibly explained by the enrichment of CRE within our

cardiac critical care population and by the regional predominance of metallo- β -lactamase-producing organisms. In this context, the reduced activity observed against CRE isolates aligns with emerging global trends indicating increasing resistance to ceftazidime-avibactam. Recent studies have reported declining susceptibility rates among CRE isolates, particularly in regions with a high prevalence of metallo- β -lactamases (MBLs), including New Delhi metallo- β -lactamase (NDM) [24-26]. This is biologically plausible, as avibactam lacks inhibitory activity against MBL enzymes, which, as reported by Ain *et al.*, are increasingly prevalent in South Asia and other endemic regions; in their series of 338 carbapenem-resistant clinical isolates from Lahore, Pakistan, 53.25% harbored bla_{NDM}, and 52.36% were extensively drug-resistant while 47.63% were multidrug-resistant [24].

The significantly higher odds of resistance among CRE isolates observed in this study underscore the clinical challenges associated with carbapenem resistance. These findings are consistent with recent global studies demonstrating that CRE isolates exhibit substantially higher resistance rates to newer β -lactam/ β -lactamase inhibitor combinations compared to ESBL-producing organisms [27, 28]. Locally, Mehdi *et al.* reported a resistance rate of 70.5% (153/217) to ceftazidime-avibactam among carbapenem-resistant Gram-negative organisms at a paediatric tertiary care center in Lahore, closely mirroring the 69.7% and 65.5% resistance recorded among our CRE isolates from blood and respiratory specimens, respectively [13]. This concordance across two very different Pakistani patient populations suggests that the loss of ceftazidime-avibactam activity in carbapenem-resistant isolates is a national rather than a centre-specific phenomenon. The growing prevalence of multidrug-resistant and extensively drug-resistant phenotypes further complicates treatment strategies and limits available therapeutic options [29, 30].

The higher resistance burden observed here than in most previously published Pakistani series is likely attributable to differences in case mix. Most of our isolates were recovered from patients in cardiac intensive care undergoing complex interventions and requiring prolonged mechanical ventilation and invasive monitoring. This population is heavily exposed to broad-spectrum antimicrobials, creating selective pressure for resistant organisms. Boattini *et al.* similarly reported reduced ceftazidime-avibactam activity and high mortality among KPC-producing

Klebsiella pneumoniae bloodstream infections in critical care populations [31]. Compared with previously published Pakistani data [16, 17], which largely represent mixed hospital populations, this study provides more targeted insights into antimicrobial susceptibility in cardiac critical care, where timely and appropriate therapy is crucial for reducing morbidity and mortality.

Bloodstream infections and respiratory tract infections, particularly ventilator-associated pneumonia, are among the most serious complications in critically ill patients [32]. Site-stratified surveillance data provide a useful comparator, although peer-reviewed reports that separate specimen types remain limited. Analyzing respiratory isolates from the ATLAS programme, Piérard and Stone found that at least 94.4% of respiratory *Enterobacterales* were susceptible to ceftazidime-avibactam in every region surveyed, including 93.6% of ESBL-positive and 98.9% of carbapenemase-positive but MBL-negative isolates, whereas fewer than 42.7% of MBL-positive isolates were susceptible to any agent tested other than colistin [33]. Our respiratory ESBL susceptibility (93.3%) is almost identical to their ESBL figure, whereas our overall respiratory rate (81.9%) and respiratory CRE rate (34.5%) are considerably lower, consistent with a greater proportion of MBL-producing isolates in this setting. Our CRE susceptibility is likewise well below the 68.9% reported by Lim *et al.* among 858 carbapenem-resistant *Enterobacterales* isolates from Singapore, at 30.3% in blood and 34.5% in respiratory specimens, a regional difference again attributable to the predominance of NDM in South Asia [1]. Taken together, these comparisons suggest that the specimen-type differences we observed reflect the differing proportion of CRE within each specimen group rather than an independent effect of infection site, although prior antimicrobial exposure may also influence resistance patterns, highlighting the importance of specimen-specific interpretation of susceptibility data in guiding empirical therapy.

The significant linear trend of decreasing susceptibility across resistance categories reinforces the progressive loss of antimicrobial effectiveness with increasing resistance burden. Similar biological gradients have been reported by Golli *et al.* in a recent analysis of Gram-negative pathogens in intensive care, emphasizing the importance of stratified antibiograms based on resistance pattern [34]. From a laboratory perspective, these findings

support integrating resistance-phenotype stratification into routine susceptibility reporting, which may enhance clinical decision-making in high-risk settings. From a clinical perspective, these findings support the continued use of ceftazidime-avibactam in infections caused by ESBL-producing *Enterobacterales* while highlighting its limited utility in CRE infections. The 2024 Infectious Diseases Society of America guidance by Tamma *et al.* suggests that alternative strategies, including combination therapy or newer agents such as aztreonam-avibactam, may be required in such scenarios [35]. Taken together, these findings support prescribing ceftazidime-avibactam based on a confirmed resistance phenotype rather than empirically, and they underline the need for continuous surveillance, active antimicrobial stewardship and access to molecular diagnostics in high-risk critical care settings.

This study has several limitations. The overall sample of 236 isolates was relatively small, and the number of isolates within some resistance-phenotype and specimen subgroups was smaller still, yielding wide confidence intervals around those estimates. The study was retrospective and confined to a single unit within one tertiary cardiac center, so the findings cannot be generalized to other hospitals, patient populations or geographical settings in Pakistan. Resistance mechanisms were not characterized molecularly, so the contribution of metallo- β -lactamases, serine carbapenemases and porin loss to the observed resistance could not be determined; this also restricts direct comparison with surveillance programmes such as ATLAS, which report susceptibility by β -lactamase genotype. Ceftazidime-avibactam susceptibility was determined by disk diffusion rather than by minimum inhibitory concentration testing, limiting comparability with international studies that use broth microdilution. Finally, clinical outcome data, including treatment received and mortality, were unavailable, so the clinical significance of these in vitro findings could not be assessed. Future multicenter studies incorporating genotypic characterization of carbapenemases, minimum inhibitory concentration-based testing and linked clinical outcomes would permit more direct comparison with local and international data.

CONCLUSION

Ceftazidime-avibactam was active against 75.8% of *Enterobacterales* isolates overall, with susceptibility declining progressively from non-

MDRO to ESBL-producing to CRE isolates in both blood and respiratory specimens. It is therefore a dependable carbapenem-sparing option for ESBL-producing infections in critically ill cardiac patients, but with about two-thirds of CRE isolates resistant it should not be used as empirical monotherapy where carbapenem resistance is suspected; in such cases treatment must be guided by the individual susceptibility report, with alternative or combination regimens for resistant isolates.

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CONFLICT OF INTEREST

None

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Declared none

AUTHORS CONTRIBUTION

Faiza Rezwan: Concept, literature search, data collection, data analysis, data interpretation, drafting, final approval, responsible for every aspect of the research

Noreen Sherazi: Literature search, data collection, drafting, final approval, responsible for every aspect of the research

Tazeen Fatima: Literature search, data interpretation, drafting, review, final approval, responsible for every aspect of the research

Farheen Ali: Data Collection, final approval, responsible for every aspect of the research

Muhammad Nadeem: Drafting, final approval, responsible for every aspect of the research

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