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Original Article

Microbiology Section

Efficacy of Ceftazidime-avibactam against Multidrug-resistant Gram-negative Pathogens in ICU Patients: A Cross-sectional Study from a Subhimalayan Tertiary Care Hospital

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ABSTRACT

Introduction: Antimicrobial Resistance (AMR) is a pressing global health issue, posing challenges in clinical management, increasing morbidity and mortality rates, and burdening healthcare systems economically. The present study assesses the in-vitro efficacy of Ceftazidime-Avibactam (CZA) against Multidrug-Resistant (MDR) Gram-negative isolates from Intensive Care Unit (ICU) patients, comparing it to other beta-lactam/beta-lactamase inhibitors, with a focus on Carbapenem-Resistant Enterobacterales (CRE), Extended-Spectrum Beta-Lactamase (ESBL)- producing Enterobacterales, and MDR Pseudomonas aeruginosa.

Aim: To determine the sensitivity pattern of CZA against various MDR Gram-negative isolates from ICU patient samples and compare its efficacy with other second-line drugs.

Materials and Methods: The present cross-sectional observational study was conducted over a six-month period from January to June 2021 on 94 MDR bacterial isolates obtained from Intensive Care ICU patients at the Himalayan Institute of Medical Sciences (HIMS), Swami Rama Himalayan University (SRHU) Dehradun, Uttrakhand, India. All clinical samples received from ICU patients with clinically suspected sepsis were included in the study. These samples were routinely processed in the bacteriology laboratory following Standard Operating Procedures (SOPs). Bacterial identification and Antimicrobial Susceptibility Testing (AST) were performed using the VITEK-2 automated system from bacterial colonies isolated after overnight incubation. Demographic characteristics of the patients were systematically recorded and analysed. E-test strips for CZA were only applied to those bacterial isolates identified as MDR *Enterobacteriaceae* and *Pseudomonas spp.* Statistical analyses were conducted to determine antimicrobial susceptibility rates, with statistical significance set at $p<0.05$.

Results: Among the 94 MDR Gram-negative isolates, *Klebsiella pneumoniae* and *Escherichia coli* were the most prevalent pathogens, comprising 34 (36.2%) and 32 (34.0%) of samples, respectively. CZA demonstrated a sensitivity rate of 35 (37.2%) across 94 samples, with limited efficacy against 46 CRE isolates i.e., 10(21.7%) and 15 MDR *Pseudomonas aeruginosa* i.e., 4 (26.6%), and no efficacy against *Acinetobacter baumannii* 0 (0%). Notably, CZA outperformed amoxicillin-clavulanic acid and piperacillin-tazobactam in-vitro activity against ESBL-producing *Enterobacteriaceae* but showed reduced efficacy against 61 carbapenem resistant isolates when compared to last-resort antibiotics like colistin 39 (63.9%).

Conclusion: The findings indicate CZA's moderate efficacy against ESBL-producing Gram-negative bacteria but limited effectiveness against CRE and MDR *P. aeruginosa* in ICU settings. These results suggest a need for careful evaluation of CZA use in ICU settings and highlight the importance of ongoing antimicrobial surveillance and the potential for combination therapy to address rising MDR infections.

Keywords: Antimicrobial resistance, Bacterial identification, Beta-lactamase, Intensive care unit

INTRODUCTION

The AMR is recognised as a significant public health challenge due to its impact on morbidity, mortality, hospitalisation rates, and the economic burden it places on healthcare systems. A recent study on the global burden of bacterial AMR reported that AMR caused 1.27 million deaths in 2019 [1]. Projections suggest that by 2050, AMR could lead to approximately 10 million deaths annually [2]. The situation is further aggravated by the limited number of new antimicrobial molecules being developed, with only a small fraction of those in preclinical testing expected to proceed to Phase 1 clinical trials [3]. Gram-negative bacilli, particularly *Pseudomonas aeruginosa* and Enterobacterales such as *Escherichia coli, Klebsiella pneumoniae, and Enterobacter spp.*, are responsible for a large proportion of AMR-associated fatalities [4].

In response, new antimicrobials have been developed, either by modifying existing molecules or combining them with new compounds. CAZ-AVI is one of the newer antimicrobials used to treat infections caused by CRE, ESBL-producing Enterobacterales, and MDR *P. aeruginosa* [5]. The combination is currently approved for the treatment of complicated Urinary Tract Infections (cUTI), Complicated Intra-Abdominal Infections (cIAI), and Hospital-Acquired Pneumonia (HAP) in both the European Union and the United States. Additionally, in Europe, CAZ-AVI is approved for the treatment of Gram-negative bacterial infections in adults with limited treatment options [6]. CAZ-AVI has demonstrated strong in-vitro efficacy against MDR Enterobacterales and *P. aeruginosa*. Additionally, CAZ-AVI has exhibited significant in-vitro activity against MDR *P. aeruginosa* and carbapenem-resistant strains of *P. aeruginosa* [7]. The rationale for this study stems from the increasing burden of AMR, particularly among MDR Gram-negative bacteria in ICU settings, where treatment options are limited. The novelty of this research lies in its assessment of CZA against a spectrum of MDR pathogens, providing real-world in-vitro susceptibility data from a

tertiary care center. Unlike previous studies, which have primarily focused on broad resistance trends, this study uniquely compares CZA's efficacy against other second-line antimicrobials, highlighting its limitations against CRE and *Pseudomonas aeruginosa* while demonstrating its relative effectiveness against ESBL-producing strains. By contributing regional microbiological insights, The present study adds to the existing literature by reinforcing the need for alternative or combination therapies for MDR pathogens, particularly in ICU settings. The hypothesis of the study is that while CZA exhibits moderate activity against ESBL-producing *Enterobacteriaceae*, its efficacy against CRE and MDR *Pseudomonas aeruginosa* is limited, necessitating a cautious approach in its clinical application. The aim of the present study to find the sensitivity pattern of CZA against various gram-negative isolates obtained from ICU patient's sample. To compare the in-vitro efficacy of CZA with other drugs (Carbapenems and other 2nd line drugs) against MDR pathogens.

MATERIALS AND METHODS

The present cross-sectional observational study was conducted in the Bacteriology section, Department of Microbiology, Himalayan Institute of Medical Sciences (HIMS), Swami Rama Himalayan University (SRHU) Dehradun, Uttrakhand, India. over a period of six months, from January to June 2021. The study was approved by the Institutional Ethics Committee (ECR/1741/Inst/UK/2022), with approval number (HIMS/RC/2021/15). Written informed consent was obtained from all patients or their legal guardians before their inclusion in the study.

Inclusion criteria: Clinical samples (urine, lower respiratory tract samples, blood, pus, body fluids) from ICU admitted patients. Isolates identified as MDR *Enterobacteriaceae* (ESBL or CRE) and MDR *Pseudomonas aeruginosa* by the VITEK automated system.

Exclusion criteria: Samples from outpatients, duplicate isolates from the same patient, insufficient or contaminated samples.

Sample size calculation: The sample size was determined based on consecutive convenient sampling method. As this was a time-bound study, all eligible consecutive clinical isolates obtained during the study period were included. A total of 94 MDR isolates were analysed.

Study Procedure

Consecutive clinical samples (urine, lower respiratory samples, blood, pus, body fluids, CSF, drain, bed sore swabs) obtained from ICU admitted patients during the study period were processed using standard microbiological techniques. Identification and AST were performed using the VITEK system (bioMérieux, France). ESBL-producing *Enterobacteriaceae* were identified by resistance to third-generation cephalosporins and confirmed by ≥8-fold MIC reduction with clavulanic acid, as per CLSI guidelines [8]. CRE were defined by MIC ≥4 µg/mL to at least one carbapenem (imipenem, meropenem, or ertapenem). MDR *Pseudomonas aeruginosa* were those resistant to ≥1 agent in ≥3 antimicrobial classes, per international consensus [9]. Isolates confirmed as ESBL or CRE-producing *Enterobacteriaceae* and MDR *Pseudomonas aeruginosa* were further subjected to AST using the E-strip method for CZA. The Minimum Inhibitory Concentration (MIC) values were interpreted according to the manufacturer's instructions [10]. Colistin susceptibility testing was performed using the VITEK-2 system (bioMerieux, France), acknowledging its limitations, as broth microdilution remains the gold standard.

STATISTICAL ANALYSIS

Descriptive statistics were used for data analysis. Categorical variables were expressed as percentages (%). Statistical significance was determined using appropriate tests i.e., Chi-square test and Fisher-exact test (where number are less than 5), and a p-value of <0.05 was considered statistically significant.

RESULTS

The distribution of 94 MDR Gram-negative bacteria across various clinical samples (34 urine, 14 Endotracheal Aspirate (ET), 13 blood, 13 pus, 6 Tracheal Tube (TT), 3 Bronchoalveolar Lavage (BAL), three fluid, two tissue, two sputum, and one each from Cerebrospinal Fluid (CSF), Catheter Tip (C.TIP), drain, and bed sore samples) from ICU patients during the study period reveals that *Klebsiella pneumoniae* was the most frequently isolated pathogen, accounting for 34 isolates (36.2%), followed closely by *Escherichia coli* with 32 isolates (34.0%). *Klebsiella pneumoniae* was predominantly found in 10 (76.9%) blood samples, while *Escherichia coli* was most commonly isolated from 21 (61.7%) urine samples. *Pseudomonas* species were found in 18 (19.1%) samples overall, with a notable presence in Tracheostomy tube (TT) secretions samples 5 (27.8%). Other bacteria were less frequently isolated, including *Serratia marcescens* 2 (2.1%), *Klebsiella oxytoca* 1 (1.1%), *Citrobacter braakii* 1 (1.1%), *Proteus mirabilis* 1 (1.1%), and *Acinetobacter baumannii* 4 (4.3%), mostly from single or few samples. Urine was the most common source of isolates 34 (36.2%), followed by ET 14 (14.8%), blood 13 (13.8%) and pus 13 (13.8%) [Table/Fig-1].

The in-vitro activity of CZA against commonly isolated organisms showed that 32 *E. coli* isolates and 34 *Klebsiella pneumoniae* iolates exhibited similar sensitivity rates, with 14 (43.7%) and 14 (41.2%) isolates sensitive to the drug, respectively. The p-value of 0.150 indicates no statistically significant difference between sensitive and resistant strains. *Pseudomonas aeruginosa* (n=15) demonstrated a lower sensitivity rate, with 4 (26.7%) isolates sensitive and 10 (66.7%) resistant. *Acinetobacter baumannii* (n=4) exhibited complete resistance, with 0 (0.0%) isolates sensitive and 4 (100%) resistant. These findings highlight the varied effectiveness of CZA, particularly

Bacteria	Blood	CSF	Urine	Fluid	Pus	Sputum	ET secretions	C.TIP	TT secretions	Tissue	BAL fluid	Drain	Bed sore	Total
Escherichia coli	1	1	21	2	5	0	1	0	0	1	0	0	0	32
Klebsiella pneumoniae	10	0	9	1	2	0	7	1	1	0	1	1	1	34
Serratia marcescens	0	0	0	0	0	0	0	0	0	1	1	0	0	2
Pseudomonas species[a]	1	0	2	0	3	2	4	0	5	0	1	0	0	18
Klebsiella oxytoca	0	0	1	0	0	0	0	0	0	0	0	0	0	1
Citrobacter BRAAKII	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Proteus mirabilis	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Acinetobacter baumannii	0	0	1	0	1	0	2	0	0	0	0	0	0	4
Enterobacter cloacae	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Total	13	1	34	3	13	2	14	1	6	2	3	1	1	94

[Table/Fig-1]: Distribution of MDR gram-negative bacteria isolated from different samples received from ICU patients (n-94).
CSF: Cerebrospinal fluid; ET: Endotracheal; CT: Catheter tip; TT: Tracheostomy tube
[a]includes *Pseudomonas aeruginosa* (15) and *Pseudomoas sutzeri* (3)

its limited efficacy against *Pseudomonas aeruginosa* and complete ineffectiveness against *Acinetobacter baumannii* [Table/Fig-2].

MDR isolates	Sensitive (S%)	Resistant (R%)	p-value
E.coli (n=32)	14 (43.7%)	14 (43.7%)	0.150
Klebseilla pneumonia (n=34)	14 (41.2%)	14 (41.2%)	
Pseudomonas aeruginosa (n=15)	4 (26.7%)	10 (66.7%)	

[Table/Fig-2]: In-vitro activity of Ceftazidime avibactam against commonly MDR isolated organisms (n=94).
MDR: Multidrug resistant; Chi-square test used to calculate p-value; *Totals of S and R do not equal n, as remaining isolates showed intermediate susceptibility.

In-vitro activity of CZA against gram-negative strains isolated from various clinical samples. Among the different sample types, urine (n=34) had a sensitivity rate of 15 (44.1%) and an equal resistance rate of 15 (44.1%), with a p-value of 0.41, indicating no statistically significant difference. Blood samples (n=14) showed a lower sensitivity rate of 4 (28.6%) and a higher resistance rate of 8 (57.1%). Pus samples (n=13) had 6 (46.1%) sensitivity and an equal resistance rate. ET samples (n=13) exhibited the lowest sensitivity at 2 (15.4%) and the highest resistance at 7 (53.8%). Overall, across all samples (n=94), CZA demonstrated a sensitivity rate of 35 (37.2%) and a resistance rate of 47 (50%), highlighting a concerning level of resistance among the gram-negative strains tested, particularly in blood and ET samples [Table/Fig-3].

	Sensitive (%)	Resistance (%)	p-value[b]
Urine (n=34)	15 (44.1%)	15 (44.1%)	0.41
Blood (n=14)	4 (28.6%)	8 (57.1%)	
Pus (n=13)	6 (46.1%)	6 (46.1%)	
ET secretion (n=13)	2 (15.4%)	7 (53.8%)	
Overall sample (n=94)[a]	35 (37.2%)	47 (50%)	

[Table/Fig-3]: In-vitro activity of Ceftazidime-Avibactam (CZA) activity against MDR gram negative strains isolated from different clinical samples (n=94).
[a]overall samples includes 20 other samples too apart from urine, blood, pus and Endotracheal (ET) as mentioned in the tables; [b]Chi-square test used to calculate p-value; *Totals of S and R do not equal n, as remaining isolates showed intermediate susceptibility

For ESBL-producing *Enterobacteriaceae* (n=51), CZA showed a sensitivity rate of 12 (23.5%), significantly higher than the other drugs, as indicated by a p-value of 0.0002. In CRE (n=46), CZA had a low sensitivity of 10 (21.7%), with significant difference (p=0.0011) to the other antibiotics. For MDR *Pseudomonas aeruginosa* (n=15), CZA demonstrated a sensitivity of 4 (26.6%), which was not statistically significant compared to the other drugs, reflected by a p-value of 0.3171. These findings suggest that CZA is more effective than the other tested antibiotics against ESBL-producing *Enterobacteriaceae* and MDR *Pseudomonas aeruginosa*, but it shows limited effectiveness against CRE [Table/Fig-4].

Drugs name	ESBL producing *Enterobacteriaceae* (n=51)		Carbapenem Resistant Enterobacterales (CRE) (n=46)		MDR *pseudomonas aeruginosa* (n=15)	
	Klebseilla pneumoniae (30) *Escherichae coli* (19) *Enterobacter cloacae* (1) *Serratia marcescenes* (1)		*Klebseilla pneumoniae* (29) *Escherichae coli* (15) *Enterobacter cloacae* (1) *Serratia marcescenes* (1)			
	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)
Ceftazidime-Avibactam (CZA)	12 (23.5%)	29 (56.8%)	10 (21.7%)	26 (56.5%)	4 (26.6%)	10 (66.6%)
Amoxicillin-clavulanic acid	4 (7.8%)	42 (82.3%)	2 (4.3%)	42 (91.3%)	1 (6.6%)	10 (66.6%)
Piperacillin-tazobactum	3 (5.8%)	47 (92.1%)	0 (0%)	45 (97.8%)	1 (6.6%)	10 (66.6%)
Cefoperazone-sulbactum	2 (3.9%)	47 (92.1%)	1 (2.1%)	44 (95.6%)	2 (13.3%)	13 (86.6%)
p-value	0.0002		0.0011		0.3171	

[Table/Fig-4]: In-vitro activity of Ceftazidime-Avibactam (CZA) in comparison with other Betalactam- betalactam inhibitors drugs against ESBL producing *Enterobacteriaceae*, Carbapenem Resistant Enterobacterales (CRE) and MDR pseudomonas aeruginosa.
*Totals of S and R do not equal n, as remaining isolates showed intermediate susceptibility; Fisher-exact test used to calculate p-value; S: Sensitive; R: Resistant; ESBL: Extended spectrum beta-lactamases; CRE: Carbapenem resistant enterobacterales; MDR: Multidrug resistant

On comparing the in-vitro activity of CZA with Tigecycline, Colistin, and Amikacin against 61 Carbapenem-resistant isolates, CZA showed the lowest sensitivity at 6 (9.8%), while Colistin had the highest sensitivity at 39 (63.9%). Tigecycline and Amikacin exhibited intermediate sensitivity rates of 27 (44.3%) and 16 (26.2%), respectively. The key finding is that Colistin is the most effective among the drugs tested against CR isolates, with CZA showing significantly lower effectiveness [Table/Fig-5].

Carbapenem resistant isolates (n=61)	Ceftazidime-Avibactam	Tigecycline	Colistin	Amikacin
Sensitive (S%)	6 (9.8%)	27 (44.3%)	39 (63.9%)	16 (26.2%)

[Table/Fig-5]: In-vitro activity of Ceftazidime-Avibactam (CZA) in comparison with other class drugs against Carbapenem resistant (CR) isolates (n=61).

DISCUSSION

The distribution of MDR Gram-negative bacteria observed in our study highlights significant trends in the prevalence of pathogens among ICU patients. The findings reveal that *Klebsiella pneumoniae* accounted for 36.2% of isolates, while *Escherichia coli* represented 34.0%. This aligns with global trends, as reported by Kaye KS and Pogue JM who noted that *K. pneumoniae and E. coli* are among the most frequently isolated pathogens in ICU settings, particularly in bloodstream infections [11]. The predominance of *K. pneumoniae* in bloodstream infections is particularly concerning, with Tumbarello M et al., documenting a 44.8% prevalence of carbapenem-resistant strains, contributing to increased mortality rates [12].

In The present study, the high frequency of *E. coli* in urine isolates (65.6%) reflects ongoing challenges in managing UTIs in hospital settings. Gupta K et al., reported that *E. coli* is responsible for approximately 80% of community-acquired UTIs, with increasing resistance to fluoroquinolones and trimethoprim-sulfamethoxazole, complicating treatment options [13]. Furthermore, the moderate sensitivity of *E. coli* to CZA (43.7%) is consistent with findings from a study by Shields RK et al., which documented a sensitivity range of 40–50% for CZA against ESBL-producing *E. coli* isolates [14]. This regional variability is highlighted by Torres-Castillo LC et al., in Chile, where the efficacy rate of CZA against ESBL-producing Enterobacterales was notably higher at 99.34% [15].

The in-vitro sensitivity of MDR *K. pneumoniae* to CZA (41.2%) observed in our study is comparable to results from AIIMS Patna study, which found CZA to be effective in approximately 37.3% of MDR *K. pneumoniae* infections [16]. However, rising rates of resistance among Carbapenem-resistant *Klebsiella Pneumoniae* (CRKP) isolates necessitate alternative strategies. For instance, Ran X et al., reported resistance rates of 74.7% to CZA in certain paediatric cohorts, emphasising the urgent need for continuous surveillance and the development of novel treatment options [17]. In contrast, Karlowsky JA et al., (2021) reported significantly higher CZA efficacy rates (96.8%) against CRE in the Middle East and Africa, highlighting the regional disparities in resistance patterns [18].

The low sensitivity of *Pseudomonas aeruginosa* to CZA (26.7%) is concerning and mirrors findings by Bonomo RA et al., who documented resistance rates exceeding 70% for this organism against beta-lactam antibiotics, including CZA [19]. This underscores the complexity of treating infections caused by *P. aeruginosa*,

particularly in ventilator-associated pneumonia cases, where biofilm formation and intrinsic resistance mechanisms complicate therapeutic approaches [20]. Regional studies indicate varied efficacy, with Carvalho TN et al., reporting an 87.2% efficacy rate of CZA against carbapenem-resistant *P. aeruginosa* in Brazil [21], while a study in Poland recorded a lower efficacy rate of 65.9% against MDR P. aeruginosa [22].

Acinetobacter baumannii showed complete resistance (100%) to CZA in The present study, which is consistent with observations made by Savov E et al., who noted that CZA has limited activity against MDR *Acinetobacter* isolates and recommended the use of combination therapy for effective management of infections caused by this pathogen [23]. The resilience of *A. baumannii* to multiple antibiotics, including CZA, underscores the necessity for alternative treatment modalities, particularly in critical care settings.

The comparative efficacy of CZA against other beta-lactam/beta-lactamase inhibitor combinations is notable. In The present study findings, CZA demonstrated a sensitivity rate of 23.5% against ESBL-producing *Enterobacteriaceae*, significantly higher than that of amoxicillin-clavulanic acid (7.8%) and piperacillin-tazobactam (5.8%), seems higher resistance data pattern from other study like Castanheira et al., who reported CZA sensitivity rates of 40–50% against ESBL producers [24]. However, the low efficacy against CRE observed in our study (21.7%) aligns with global reports that indicate limited effectiveness of CZA against CRE strains, which can exhibit resistance due to various mechanisms [25]. Interestingly, Wise MG et al., documented an exceptionally high CZA efficacy rate of 96.2% against CRE in Sub-Saharan Africa [26], while Yang Y et al., reported a 90.1% efficacy rate against KPC-producing Enterobacterales in China, further emphasising the regional variability in resistance patterns [27].

In the context of last-resort antibiotic therapy for carbapenem-resistant infections, our study found that colistin exhibited the highest sensitivity (63.9%), followed by tigecycline (44.3%) and amikacin (26.2%). These findings align with the work of Karaiskos I and Giamarellou H who noted that colistin remains one of the few active agents against carbapenem-resistant infections, despite the associated nephrotoxicity risks [28]. The moderate sensitivity of tigecycline supports its use in combination therapy for treating resistant infections [29]. Meanwhile, in the US, Sader HS et al., documented a significantly higher CZA efficacy rate (99.2%) against MDR Enterobacterales, indicating a stark contrast with our findings and reinforcing the importance of local resistance surveillance [30].

Clinical implication of the study are the high prevalence of MDR *Klebsiella pneumoniae* and *Escherichia coli* in ICU patients, along with their reduced susceptibility to CZA and carbapenems, underscores the urgent need for robust antimicrobial stewardship programs. The complete resistance of *Acinetobacter baumannii* to CZA highlights the growing challenge of treating these infections, necessitating alternative therapeutic strategies such as combination therapy. Additionally, the limited efficacy of CZA against *Pseudomonas aeruginosa* suggests the need for novel treatment approaches, including biofilm-targeting agents. Strengthening local resistance surveillance and implementing rapid diagnostic techniques are crucial for optimising empirical antibiotic therapy and improving patient outcomes.

Future research should focus on unraveling the molecular mechanisms of resistance in MDR Gram-negative bacteria to facilitate the development of targeted therapies. Investigating novel antimicrobial agents, such as next-generation β-lactam/β-lactamase inhibitors, phage therapy, and immunotherapeutic approaches, may offer alternative treatment options.

Limitation(s)

The present study has several limitations, including its single-center design and small sample size, which may limit the generalisability of the findings. The six-month duration may not fully capture long-term resistance trends. The use of the VITEK-2 system for colistin susceptibility testing is a limitation, as broth microdilution is the gold standard for accurate MIC determination. The exclusion of molecular mechanism analysis and clinical outcome data restricts a deeper understanding of resistance patterns and the efficacy of CAZ-AVI in actual patient settings. Additionally, the focus on a limited range of pathogens and reliance on E-strip testing may have influenced susceptibility results. Further large-scale, multicenter studies are needed to validate these findings.

CONCLUSION(S)

The study highlights that while CZA shows moderate efficacy against ESBL-producing *Enterobacteriaceae* (40% sensitivity), it has limited activity against CRE (20%) and MDR *Pseudomonas aeruginosa* (26.6%), with complete resistance observed in *Acinetobacter baumannii*. Although CZA remains a viable option compared to other beta-lactam/beta-lactamase inhibitors, its role against highly resistant pathogens is restricted, especially when compared to agents like colistin. These findings underscore the necessity for careful use of CZA, continuous surveillance, and the development of new therapeutic strategies in ICU settings.

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