

Evaluation of Ceftazidime/Avibactam Administration in *Enterobacteriaceae* and *Pseudomonas aeruginosa* Bloodstream Infections by Monte Carlo Simulation

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Purpose: To evaluate the administration regimen of ceftazidime/avibactam (CZA) for bloodstream infections caused by *Enterobacteriaceae* and *Pseudomonas aeruginosa*.

Methods: The minimal inhibitory concentrations (MICs) of CZA against *Enterobacteriaceae* and *P. aeruginosa* isolated from blood cultures at member hospitals in BRICS (Blood Bacterial Resistant Investigation Collaborative System) in 2019 were determined by broth micro-dilution methodology. A 10,000-patient Monte Carlo simulation (MCS) was used to calculate the probability of target attainment (PTA) and cumulative fraction of response (CFR) for different CZA dosage regimens to evaluate their efficacies and optimize the best initial dosage regimen.

Results: Altogether, 6487 *Enterobacteriaceae* and *P. aeruginosa* strains were isolated from the blood cultures. The overall CZA resistance rate was 2.31%, of which the *Enterobacteriaceae* and *P. aeruginosa* rates were 1.57% and 14.29%, respectively. The MCS showed that the greater the MIC value, the worse the therapeutic effect. When the CZA MIC was ≤ 8 mg/L, the standard dose (2.5g iv q8h) achieved 90% PTA in the subset of patients with creatinine clearance (CrCl) values from 51 to 120 mL/min. Although the high-dose regimen (3.75g iv q8h) achieved 90% PTA in patients with CrCl values from 121 to 190 mL/min, implementing the low-dose regimen (1.25g iv q8h) was also effective for patients in the 51–89 mL/min CrCl range. Generally, the high-dose regimen (3.75g iv q8h) reached 90% CFR against all of the strains. Conversely, in patients with CrCl values of 121–190 mL/min, the standard dose (2.5g iv q8h) failed to reach 90% CFR against some *Enterobacteriaceae* members and *P. aeruginosa*. When the dose was reduced to the low-dose regimen (1.25g iv q8h), no patients reached 90% CFR against some *Enterobacteriaceae* members and *P. aeruginosa*.

Conclusion: CZA has good antibacterial activity against *Enterobacteriaceae* and *P. aeruginosa* in bloodstream infections. Clinicians could make individualized treatment regimens in accordance with the sensitivity of the strains and the level of renal function in their patients to best predict the drug-related clinical responses.

Keywords: Gram-negative bacteria, extended-spectrum β -lactamase, dosage regimens, pharmacokinetics, pharmacodynamics, minimum inhibitory concentration

Introduction

Gram-negative bacteria exist widely in natural environments and hospitals, and are the most common nosocomial infection-causing pathogens. In recent years, extensive

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antibiotics use and the ability of Gram-negative bacteria to readily obtain antibiotic resistance genes has created severe challenges in treating infections caused by these microbes.¹ Ceftazidime/avibactam (CZA), a new antibacterial agent, exhibits high bactericidal activity against multidrug-resistant Gram-negative bacteria (including extended-spectrum β -lactamase, AmpC enzyme- and serine carbapenemase-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*).²⁻⁴ CZA was approved by the United States Food and Drug Administration to treat complicated abdominal infections in adults, complicated urinary tract infections, hospital-acquired pneumonia, and ventilator-associated pneumonia. Indeed, CZA is a good choice for clinical treatment of carbapenem-resistant Gram-negative bacterial infections.

Monte Carlo simulation (MCS) is a probability analysis method that uses the pharmacokinetic parameters of antimicrobial agents in the human body, combined with the minimum inhibitory concentrations (MICs) obtained for large numbers of bacteria, and takes various pharmacokinetic (PK) and pharmacodynamic (PD) (pharmacokinetic/ pharmacodynamic, PK/PD) parameters as target values to predict and evaluate the antibacterial effect of antibacterial drugs and optimize their administration schemes.^{5,6} MCS is considered an accurate and rapid PD evaluation tool, and is widely used for comparison, optimization and evaluation of antimicrobial therapy. Based on the CZA resistance monitoring reports for *Enterobacteriaceae* and *P. aeruginosa* collected from BRICS in 2019, the probability of target attainment (PTA) and cumulative fraction of response (CFR) for the three different administration regimens were calculated by MCS with the objective of providing a reference for the clinical treatment of bloodstream infections (BSIs) caused by *Enterobacteriaceae* and *P. aeruginosa*.

Materials and Methods

Bacterial Isolates

Altogether, 6487 *Enterobacteriaceae* and *P. aeruginosa* bloodstream-sourced isolates were collected in the BRICS program during 2019. Repeat isolates from the same patient were excluded. Pathogens were isolated and identified in accordance with clinical microbiological

methods using the API20 system (bioMérieux, Durham, NC, USA). After the purified isolates were shipped to our laboratory, the pathogens were re-identified by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (VITEK[®] MS, bioMérieux, Nürtingen, Germany).

Antimicrobial Susceptibility Testing

The MICs of CZA (Pfizer, Zavicefta, Ringaskiddy, Ireland) were determined by the agar dilution method according to Clinical and Laboratory Standards Institute (CLSI) guidelines. CLSI criteria were used to interpret the results according to the interpretive standards for CZA (≤ 8 mg/L susceptible; ≥ 16 mg/L resistant).⁷ *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC BAA-1705, and *P. aeruginosa* ATCC 27853 were the quality control strains.

Pharmacokinetics (PKs)

A previously published one-compartment population-based PK model for CZA derived from 10 critically ill patients was used.⁸ The assay used different dosing regimens (3.75g iv q8h, 2.5g iv q8h and 1.25g iv q8h) to determine the drug serum concentrations, and an adequate PK analysis with appropriate parameters was performed, including the volume of distribution (Vd) in liters at steady state, the total body clearance (CL) in liters per hour, and the fraction (F) of unbound drug, as summarized in Table 1. In this model, the CL of each drug was parameterized as a linear function of CrCL: $CL = CL_s \times CrCL + CL_i$, where the slope term CL_s represents renal clearance and the intercept term CL_i represents nonrenal clearance.

Monte Carlo Simulation

CZA displays time-dependent PDs, and its bactericidal effect best correlates with %T>MIC. Multiple 10,000-patient Monte Carlo simulations (Crystal Ball, Oracle Corp.) were performed for the CZA dosing regimens based on CrCL. The PTA was assessed over a range of MICs between 0.03 and 256 mg/L in doubling dilutions. The PD index target for avibactam was a free concentration above

Table 1 The Pharmacokinetic Parameters Used in the Monte Carlo Simulations⁸

Drug	CL/(L/h)	Vd/L	CLs	CLi	F/%
CAZ	6.14 $\pm$ 3.80	34.78 $\pm$ 10.49	0.043 $\pm$ 0.016	1.15 $\pm$ 0.63	90
AVI	11.09 $\pm$ 6.78	50.84 $\pm$ 14.32	0.10 $\pm$ 0.03	0.89 $\pm$ 0.58	93

Abbreviations: Vd, volume of distribution; CLi, clearance intercept term; CLs, clearance slope terms; CL, total body clearance, where $CL = CL_i + (CL_s \times CrCL)$.

1 mg/L ($fT > 1$ mg/L) for 70% of the dosing interval, whereas that for ceftazidime was $\geq 70\% fT > \text{MIC}$.⁹ In all the simulations, the fraction of free ceftazidime was 90%, whereas the avibactam-free drug fraction was randomly sampled from a uniform distribution between 92% and 94%.¹⁰ Based on the PK index from the different dosage regimens and the MIC results, Monte Carlo simulation was used to simulate the PK/PD characteristics of the different dosage regimens to obtain the best one. The CFR was calculated to evaluate the efficacy of these regimens, and the $\%T > \text{MIC}$ results were calculated using the following equation: $f\% T > \text{MIC} = \ln(\text{Dose} \times f_u \times V_d^{-1} \times \text{MIC}^{-1}) \times V_d \times \text{CLT}^{-1} \times 100 \times \text{DI}^{-1}$, where Ln is the natural logarithm, dose is the intermittent dose in mg, MIC is the minimum inhibitory concentration in mg/L, and DI is the dosing interval in hours.

Results

MIC Determination

Altogether, 6487 bloodstream-sourced strains of *Enterobacteriaceae* and *P. aeruginosa* were isolated by the BRICS program in 2019, including *E. coli* (n=3,687), *K. pneumoniae* (n=1,656), *Salmonella* (n=117), *Enterobacter cloacae* (n=266), *Serratia* (n=83), *Proteus* (n=70) and other *Enterobacteriaceae* genera (n=160), *Klebsiella* genera (n=70), and *P. aeruginosa* (n=378). From these, 1881 and 624 were confirmed to be extended-spectrum- β -lactamase (ESBL)-producing *E. coli* and *K. pneumoniae*, respectively, by ESBL phenotype tests (Table 2). The ESBL rates for the BSIs caused by *E. coli* and *K. pneumoniae* were 51.02% and 37.68%, respectively. We analyzed the MIC data for CZA in these strains and established discrete MIC distributions for each

Table 2 Frequency Distributions of CZA MICs Against *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolated from BRICS

Species	Percentage of Isolates at Each MIC (mg/L)														MIC ₅₀	MIC ₉₀
	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256		
<i>E. coli</i> (ESBL+) (1881 strains)	0.1	7.9	7.4	23.3	34.8	14.2	5.2	3.0	2.3	0.2	1.5	0.0	0.0	0.0	0.5	2
<i>E. coli</i> (ESBL-) (1806 strains)	0.0	15.6	29.1	38.9	12.7	2.4	0.6	0.1	0.3	0.0	0.2	0.0	0.0	0.0	0.25	0.5
<i>Klebsiella pneumoniae</i> (ESBL+) (624 strains)	0.0	1.6	4.2	6.3	15.2	16.8	13.6	19.6	18.8	0.3	3.7	0.0	0.0	0.0	1	4
<i>Klebsiella pneumoniae</i> (ESBL-) (1032 strains)	0.0	14.3	17.2	39.2	20.4	3.9	1.9	1.3	1.6	0.1	0.1	0.0	0.0	0.0	0.25	0.5
<i>Salmonella</i> (117 strains)	0.0	0.0	6.8	30.8	56.4	3.4	1.7	0.0	0.9	0.0	0.0	0.0	0.0	0.0	0.5	0.5
<i>Enterobacter cloacae</i> (266 strains)	0.0	5.3	28.6	37.2	4.5	7.5	6.8	3.8	0.4	0.4	5.3	0.4	0.0	0.0	0.25	1
<i>Serratia</i> (83 strains)	0.0	15.7	36.1	43.4	1.2	1.2	1.2	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.125	0.25
<i>Proteus</i> (70 strains)	0.0	75.7	5.7	15.7	1.4	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.06	0.25
Other genera of <i>Enterobacteriaceae</i> (160 strains)	0.0	6.9	15.6	20.6	13.1	13.1	13.8	5.6	0.6	1.3	7.5	1.9	0.0	0.0	0.5	16
Other species of <i>Klebsiella</i> (70 strains)	0.0	17.1	31.4	24.3	11.4	4.3	2.9	2.9	5.7	0.0	0.0	0.0	0.0	0.0	0.25	1
<i>Pseudomonas aeruginosa</i> (378 strains)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	46.6	39.2	10.6	2.1	1.1	0.5	0.0	8	16

Abbreviations: *E. coli*, *Escherichia coli*; ESBL +, extended-spectrum beta-lactamase producing; ESBL -, not extended-spectrum beta-lactamase producing; MIC, minimum inhibitory concentration; MIC₅₀, 50% of the tested isolates were inhibited; MIC₉₀, 90% of the tested isolates were inhibited.

population based on the MIC frequencies. The overall CZA resistance rate was 2.31%, of which the Enterobacteriaceae and *P. aeruginosa* rates were 1.57% and 14.29%, respectively. MIC₅₀ and MIC₉₀ values for CZA against ESBL-producing *E. coli* and *K. pneumoniae* were 0.5 mg/L and 2 mg/L, and 1 mg/L and 4 mg/L, respectively; these values were slightly higher than those for non ESBL-producing strains. The MIC₅₀ (0.06 mg/L) and MIC₉₀ (0.25 mg/L) values for CZA against *Proteus* were the lowest. The MIC₅₀ (8 mg/L) and MIC₉₀ (16 mg/L) values for CZA in *P. aeruginosa* were the highest (Table 2).

Monte Carlo Simulation

In this study, an MCS with 10,000 subjects was performed to calculate PTA and CFR values based on the PK data for CZA from the different regimens. The PTA values for the three doses used for the patients with different renal functions are shown in Table 3 and Figure 1. The PTA values were close to 100% at low MIC values and decreased rapidly to 0 at high MICs. At the susceptibility breakpoint of 8 mg/L, the standard dose (2.5g iv q8h) achieved 90% PTA for the subset of patients with a CrCl range of 51–120 mL/min. For patients with a CrCl range of 121–190 mL/min, the high-dose regimen (3.75g iv q8h) achieved a PTA exceeding 90% at 8 mg/L, and although the PTA only increased from 51.67% to 80.93% at 16 mg/L there was no significantly increased benefit for other types of patient. When the dose was reduced to the low-dose regimen (1.25g iv q8h), it was effective for patients with a CrCL range of 51–89 mL/min. As shown in Table 4, the high-dose regimen (3.75g iv q8h) reached a 90% CFR against all the strains. For patients in whom the CrCl range was 121–190 mL/min, the standard dose (2.5g iv q8h) did not reach a CFR of 90% against some *Enterobacteriaceae* genera and *P. aeruginosa*. When the low-dose regimen (1.25g iv q8h) was used, none of the patients reached a CFR of 90% against some *Enterobacteriaceae* genera and *P. aeruginosa*.

Discussion

BSIs are commonly seen in hospitals,¹¹ but finding the most appropriate antimicrobial regimen for patients with suspected BSIs is not straightforward.¹² Gram-negative bacteria, particularly *Enterobacteriaceae* and *P. aeruginosa* have emerged as the predominant BSI-causing pathogens.¹³ The increasing rates of β-lactam-related antibiotic resistance, the spread of bacteria with

Table 3 PTA for Bactericidal Responses (70% of the Time Above the MIC) to CZA at Different Dosage Regimens

Dosage Regimens	eCrCL (mL/min)	PTA[MIC/(mg/L),%]													
		0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256
3.75g iv q8h	121–190	100.00	100.00	100.00	99.99	99.94	99.97	99.66	98.98	95.68	80.93	21.57	0.02	0.00	0.00
	90–120	100.00	100.00	100.00	100.00	100.00	100.00	99.97	99.95	99.42	96.61	54.32	0.51	0.00	0.00
	51–89	100.00	100.00	100.00	100.00	100.00	100.00	100.00	99.99	99.94	99.50	83.49	2.84	0.00	0.00
2.5g iv q8h	121–190	100.00	100.00	99.99	99.98	99.93	99.79	99.31	97.52	89.84	51.67	1.32	0.00	0.00	0.00
	90–120	100.00	100.00	100.00	100.00	100.00	99.98	99.93	99.74	98.73	82.99	7.37	0.00	0.00	0.00
	51–89	100.00	100.00	100.00	100.00	100.00	100.00	99.98	99.97	99.60	96.42	26.20	0.03	0.00	0.00
1.25g iv q8h	121–190	100.00	100.00	99.98	99.94	99.82	99.38	97.73	89.65	52.32	1.44	0.00	0.00	0.00	0.00
	90–120	100.00	100.00	100.00	100.00	100.00	99.96	99.77	98.73	82.72	7.57	0.00	0.00	0.00	0.00
	51–89	100.00	100.00	100.00	100.00	100.00	100.00	99.98	99.86	96.69	26.32	0.01	0.00	0.00	0.00

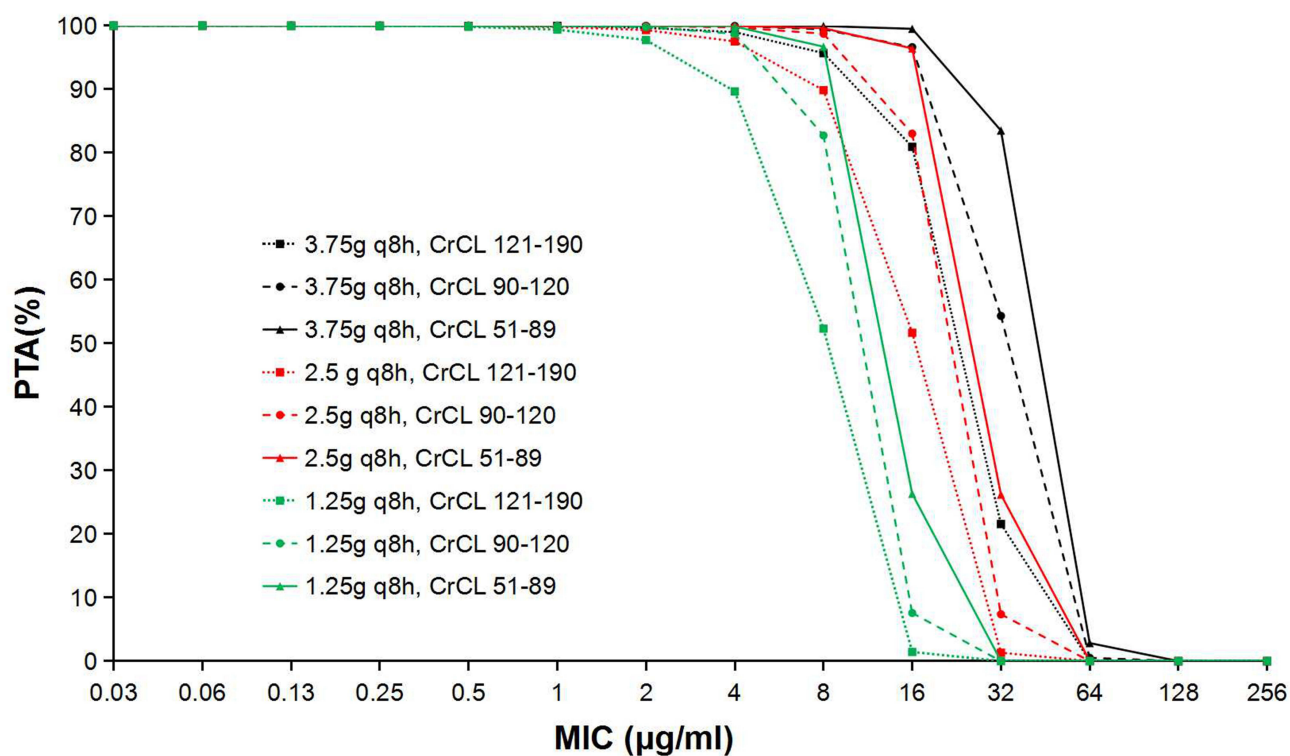


Figure 1 PTA at a pharmacodynamic target of 70% T>MIC for CZA.

ESBLs, and the emergence of carbapenem-resistant isolates, have made it particularly challenging to select appropriate antibiotic treatments. CZA, a new type of β -lactam/ β -lactamase inhibitor combination, can widely and effectively treat infections caused by carbapenem-resistant Gram-negative bacteria.¹⁴ Among them, ceftazidime is a third-generation cephalosporin, whereas avibactam, a new β -lactamase inhibitor type with a strong molecular

activity, can inhibit the activity of class A, class C and some class D Ambler enzymes but it is inactive against metallo- β -lactamases and OXA-type carbapenemases. Avibactam has no antibacterial activity per se, but it can restore or improve the antibacterial performance of ceftazidime. CZA can inhibit *Enterobacteriaceae* that produce ESBLs, *K. pneumoniae* carbapenemase, AmpC and OXA-48 enzyme types and carbapenem-resistant *P. aeruginosa*,

Table 4 CFR of the Different Dosage Regimens for CZA Against *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolated from BRICS

Species	CZA Dosage Regimens (CFR/%)								
	1.25g q8h			2.5g q8h			3.75g q8h		
eCrCL (mL/min)	121-190	90-120	51-89	121-190	90-120	51-89	121-190	90-120	51-89
<i>E.coli</i> (ESBL+)	96.54	97.72	98.18	97.96	98.47	98.82	98.43	99.42	99.74
<i>E.coli</i> (ESBL-)	99.57	99.77	99.68	99.76	99.76	99.89	99.8	99.87	99.95
<i>Klebsiella pneumoniae</i> (ESBL+)	84.66	92.38	95.6	93.14	96.06	97.43	96.08	98.42	99.34
<i>Klebsiella pneumoniae</i> (ESBL-)	98.89	99.66	99.77	99.59	99.78	99.9	99.81	99.94	99.96
<i>Salmonella</i>	99.4	99.87	99.94	99.91	99.99	99.99	99.92	100	100
<i>Enterobacter cloacae</i>	92.99	93.93	94.25	93.93	94.8	95.48	95.38	97.07	98.86
<i>Serratia</i>	99.8	99.97	99.98	99.91	100	100	99.97	100	100
<i>Proteus</i>	99.96	100	100	100	100	100	100	100	100
Other genera of <i>Enterobacteriaceae</i>	87.86	89.61	89.58	89.69	91.41	92.98	91.63	94.56	96.85
Other species of <i>Klebsiella</i>	96.69	99.06	99.82	99.4	99.96	99.97	99.72	99.97	100
<i>Pseudomonas aeruginosa</i>	62.41	79.45	87.18	85.54	93.82	96.33	92.71	96.51	97.92

but it has no effect on *Acinetobacter* and *Stenotrophomonas*,¹⁴ so they were excluded from this study.

Our results showed that CZA was highly active against *Enterobacteriaceae* isolated from BSIs. In fact, 98.43% of the *Enterobacteriaceae* isolates were susceptible to CZA, a finding similar to that reported previously.¹⁵ However, we also observed that the MIC_{90s} of some *Enterobacteriaceae* genera were high, and the MIC values were widely distributed among them, ranging from 0.06 mg/L to 64 mg/L, a finding possibly related to the inability of CZA to inhibit class B-metallo β -lactamase production. An in vitro study showed that the *P. aeruginosa* resistance rate to CZA was 3.4%, while that of extensively drug-resistant bacteria was 25.0%.¹⁵ In another study by Chinese researchers,¹⁶ the MIC₅₀ and MIC₉₀ values of CZA against the *P. aeruginosa* strains isolated from 30 medical centers in China in 2017 were 2 and 16 mg/L, respectively, but in our study the *P. aeruginosa* resistance rate to CZA was 14.29% and the MIC₅₀ and MIC₉₀ values were 8 and 16 mg/L, respectively. These results show that the susceptibility of *P. aeruginosa* to CZA decreased in 2019, and we speculate that this may be related to the rapid increase in multidrug-resistant *P. aeruginosa* strains occurring in BSIs in recent years. These data indicate that it may become more difficult to achieve the PK/PD target.

MCS, a statistical modeling approach, is based on PK parameters and microbiological susceptibility information. It can simulate the medication situation for thousands of virtual patients and therefore predict the probability of success of therapeutic targets using different treatment regimens.¹⁷ We calculated PTA and CFR values to explore the optimal breakpoints for different simulated dose regimens and to determine the appropriate dosage regimens with the highest success rates for treating pathogens. A high level of clinical efficacy is assured when the PTA is at least 90%. The MCS results predict that the standard regimen (2.5g iv q8h) will achieve the 90% PTA goal for CZA against organisms with MICs $\leq$ 8 mg/L, except for the subset of patients with a CrCl range of 121–190 mL/min. A similar finding was also reported for adult patients with cystic fibrosis and acute pulmonary exacerbation.¹⁸ Therefore, before empirical treatment, clinicians should be mindful of the bacterial culture and drug sensitivity tests and select the best treatment according to the MIC results. We found that the low-dose (1.25g iv q8h) CZA treatment against *E. coli* and ESBL-negative *K. pneumoniae*,

Salmonella, *Enterobacter cloacae*, *Serratia*, *Proteus* and other *Klebsiella* species isolated from BSIs exceeded a CFR of 90%, and the standard CZA regimen (2.5g iv q8h) against ESBL-positive *K. pneumoniae* and some other isolated *Enterobacteriaceae* and *P. aeruginosa* exceeded 90% of the CFR. Furthermore, the high-dose CZA regimen (3.75g iv q8h) only benefitted patients within the CrCl range of 121–190 mL/min whose CFRs ranged from 89.69% to 91.63% for some *Enterobacteriaceae* and from 85.54% to 92.71% for *P. aeruginosa*. The benefits for patients with other bacterial infections did not increase significantly.

There were some limitations to this study. First, the PK parameters for CZA were obtained from critically ill patients who had adequate renal function (CrCl=50–190 mL/min). These data may differ from the data from patients in daily clinical practice because of differences in race/ethnicity, obesity, renal impairment, illness severity, and other factors. Second, in clinical practice, infectious diseases are often mixed infections, and there may be infections in other body parts and/or other antibiotic-resistant strains occurring at the same time, and the CFR will also be variable. Third, we did not assess the activity of CZA against the different carbapenemase-producing strains.

Conclusions

CZA has a significant antibacterial activity against *Enterobacteriaceae* and *P. aeruginosa* isolates. Although the FDA set the CZA breakpoint at 8 mg/L, the wide MIC distribution for CZA in bacteria indicates that its clinical use can be more flexible. Clinicians can make individualized treatment regimens according to the sensitivity of strains and the level of renal function in patients to best predict their clinical drug-related responses.

Ethics Approval

Ethics approval was not required for this study, which used anonymized blood culture strains which were routinely collected from member hospitals.

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Author Contributions

All authors made significant contributions to the work reported, whether in the conception, study design,

execution, data acquisition, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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