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ORIGINAL RESEARCH

Adequacy of the Dosing and Infusion Time of Ceftazidime/Avibactam for the Treatment of Gram-Negative Bacterial Infections: A PK/PD Simulation Study

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Introduction: Recent studies suggested the potential benefits of extended infusion times to optimize the treatment efficacy of ceftazidime/avibactam, which indicated that the current pharmacokinetic/pharmacodynamic (PK/PD) target may not be sufficient, especially for severe infections. The purpose of this study is to assess the adequacy of dosing strategies and infusion durations of ceftazidime/avibactam when applying higher PK/PD targets.

Methods: This study utilized published PK parameters to conduct Monte Carlo simulations. Different dosages including the recommended regimen based on renal function were simulated and evaluated by the probability of target attainment (PTA) and cumulative fraction of response (CFR). Different PK/PD targets were set for ceftazidime and avibactam. MIC distributions from various sources were used to calculate the CFR.

Results: Multiple PK/PD targets have been set in this study, All recommended dosage could easily achieve the target of 50%$fT \geq$ MIC (ceftazidime) and 50%$fT \geq C_{T=1.0\ mg/L}$ (avibactam). However, for severe infection patients with normal renal function and augmented renal clearance at the recommended dosage (2000 mg/500 mg, every 8 hours), the infusion duration needs to be extended to 3 hours and 4 hours to achieve the targets of 100%$fT \geq$ MIC and 100%$fT \geq C_{T=1.0\ mg/L}$. Only continuous infusion at higher dosages achieved 100%$fT \geq 4\times$MIC and 100%$fT \geq C_{T=4.0\ mg/L}$ targets to all currently recommended regimens. According to the varying MIC distributions, higher concentrations are needed for *Pseudomonas aeruginosa*, with the attainment rates vary across different regions.

Conclusion: The current recommended dosing regimen of ceftazidime/avibactam is insufficient for severe infection patients, and continuous infusion is suggested.

Keywords: ceftazidime, avibactam, pharmacokinetic/pharmacodynamic, probability of target attainment

Introduction

The increasing prevalence of multidrug-resistant (MDR) gram negative bacteria (GNB) worldwide poses a great threat to anti-infection treatment.[1,2] The vast majority of MDR-GNB production is caused by β-lactamases, which prevents antibiotics from exerting their effects.[3–6] Avibactam has inhibitory effects on the vast majority of β-lactamases and carbapenemases, especially KPC.[7–9] Ceftazidime/avibactam has been used to treat complex abdominal infections, hospital acquired pneumonia, ventilator-associated pneumonia, and infections caused by carbapenem resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* in adult patients with limited treatment options.[10,11] It has

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demonstrated good clinical efficacy and yielded favorable results in non-inferiority studies, confirming its value in clinical practice.[12–14]

The recommended dosage of ceftazidime/avibactam is 2.5 g (2.0 g of ceftazidime and 0.5 g of avibactam) administered every 8 hours (q8h) by intravenous infusion.[15,16] The label emphasized that ceftazidime/avibactam should be infused over 2 hours. This is because ceftazidime exhibits a time-dependent bacterial-killing profile and prolonged infusion time enhances the antibacterial effect.[17–20] The pharmacokinetic/pharmacodynamic (PK/PD) index, which is related to the bacterial-killing effect of ceftazidime, is the time fraction of free drug above the MIC (%fT≥MIC). The PK/PD index of avibactam is similar to that of ceftazidime, that is the time fraction of free drug above a threshold concentration (%fT $\geq$ C_T).[21] However, there is limited evidence in clinical to support the vitro PK/PD target for ceftazidime/avibactam. The recommended dose is established based on PK/PD targets of 50%fT $\geq$ MIC for ceftazidime and 50%fT $\geq$ $C_{T=1.0\ mg/L}$ for avibactam.[22–24] Recent studies have indicated the benefits of prolonging the infusion of antibiotics.[25] Furthermore, a study demonstrated that prolonging the infusion time of ceftazidime/avibactam for more than three hours is beneficial for patient survival.[26,27] This finding reinforced the notion of extending the infusion duration to optimize antibiotic therapy and indicated the current therapeutic PK/PD target may be insufficient. A higher PK/PD target is needed for ceftazidime/avibactam, especially for those who are severely infected and critically ill to provide assurance for infection control.[28–30] The most frequently used PK/PD target is 50% fT $\geq$ MIC for ceftazidime and 50% fT$\geq$ $C_{T=1.0\ mg/L}$ for avibactam.[22–24] For susceptible *Enterobacteriaceae*, 50% fT $\geq$ MIC for ceftazidime and 50% fT $\geq$ $C_{T=0.5\ mg/L}$ for avibactam were also selected.[18] More stringent targets, such as 70% fT $\geq$ MIC, 100% fT $\geq$ MIC, 50% fT $\geq$ 4×MIC for ceftazidime and 100%fT $\geq$ $C_{T=4.0\ mg/L}$ for avibactam, have also been established based on existing studies.[18,23,31] The probability of target attainment (PTA) of the current ceftazidime/avibactam dosage regimen is uncertain when implying a higher PK/PD target. Moreover, patients who require ceftazidime/avibactam for the treatment of drug-resistant bacterial infections are usually critically ill.[11,32] The special physiological and pathological conditions of critical patients could have a significant impact on drug concentrations, resulting in the effectiveness of the drug.[33–35] Differences in drug concentrations would lead to underexposure or overexposure to patients, even induce drug resistance.[6,36]

This study focused on the adequacy of the dosing and infusion time of ceftazidime/avibactam in treating severe gram-negative bacterial infections when implying a higher PK/PD target. By employing Monte Carlo simulation as the primary method, this study aimed to ascertain the efficacy of various recommended regimens and diverse extended infusion durations, by evaluating their predetermined therapeutic objectives. Additionally, this investigation also aimed to probe the feasibility of achieving these targets across varying distributions of MICs.

Methods

PPK Model Selection and PK Parameters

The PK parameters of ceftazidime/avibactam for non-severely infected patients were derived from a Phase I clinical study involving 43 healthy volunteers by Dimelow et al in the UK.[37] The PK parameters for severe infection patients with different renal functions were derived from Li et al's population pharmacokinetic model, which included more than 1000 adult patients with various indications and characteristics (the type of infection includes complicated intra-abdominal infection [cIAI], complicated urinary tract infection [cUTI], hospital-acquired pneumonia [HAP] and ventilator-associated pneumonia [VAP]; the races included Caucasian, black, Asian and Indian patients).[38] The detailed parameters of those models are listed in the Tables S1 and S2).[37,38]

Monte Carlo Simulation

Monte Carlo simulation is widely used to optimize the antibiotic treatment regimens by combining PK and PD data.[31,38–40] MCS with 1000 replicates for each condition was performed using NONMEM (ICON Development Solution, USA, version 7.5.0) and Python (version 3.10.9) for data processing. For Li et al's critically infected population model, we fixed several parameters before simulation: the population type was fixed to severe patients with an APACHE II score $\geq$ 10; the covariate of infection type was fixed to cIAI (the reason for fixing to cIAI is that

the Li's model provides a relatively complete set of covariate parameters affecting both CL and V for this patient group, including population effect, race effect, and clinical trial phase); and the race type was fixed to people other than non-Japanese and non-Chinese Asians. The MCS results were represented by the PTA and the cumulative fraction of response (CFR).

PK/PD Targets and PTAs

The recommended dosages of ceftazidime/avibactam for different renal functions were as follows: augmented renal clearance (CrCL ≥ 130 mL/min): 2000 mg/500mg, every 8 hours; normal renal function: 2000 mg/500 mg, every 8 hours; CrCL between 30 to 50 mL/min: 1000 mg/250 mg, every 8 hours; CrCL between 15 to 30 mL/min: 750 mg/187.5 mg, every 12 hours.

For non-severe infection patients, the PK/PD target for ceftazidime was set as 50%$fT \geq$ MIC, and that for avibactam was set as 50%$fT \geq C_{T=1.0\ mg/L}$.[21] For patients with severe infection, the PK/PD target for ceftazidime was set as 100%$fT \geq$ MIC, and that for avibactam was set as 100%$fT \geq C_{T=1.0\ mg/L}$.[17–20] The results of the targets of 50%$fT \geq$ MIC / 50%$fT \geq C_{T=0.5\ mg/L}$ and 100%$fT \geq$ MIC / 100%$fT \geq C_{T=0.5\ mg/L}$ were also calculated for susceptible *Enterobacteriaceae*, but the results with this target are displayed in the Supplementary Tables S4, S6, S9 and S11 only.[18] According to MacGowan et al's and Marta et al's research, when avibactam is equal to or greater than 4 mg/L, ceftazidime could achieve the susceptive threshold of less than MIC = 8 mg/L.[36,41,42] Therefore, we also set an aggressive PK/PD target: 100%$fT \geq 4\times$MIC for ceftazidime and 100%$fT \geq C_{T=4.0\ mg/L}$ for avibactam.

The target of β-lactam and β-lactamase inhibitor is the joint PTA, which is calculated as follows,

$$jointPTA(MIC) = PTA\ (ceftazidime) \times PTA\ (avibactam) \quad (1)$$

MIC Distributions and CFR

According to new definitions of S, I and R by EUCAST in 2019, the microorganisms with MICs≤8 mg/L are defined as ceftazidime/avibactam-susceptible. The MIC distributions of ceftazidime/avibactam for susceptible *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were obtained from EUCAST (assessed on 2023–12-01). The MIC distributions of susceptive *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in China (CHINET 2022 data) were also listed. In addition to the above two sources, other MIC distributions of *Pseudomonas aeruginosa* (from 2012 to 2015) of the International Network for Optimal Resistance Monitoring Program in the United States (INFORM)) and *Klebsiella pneumoniae* (isolated from patients in three hospitals in northern China from April 2015 to October 2015) were obtained in Kang's study.[22,23] The MIC distributions are listed in Table S3.

The CFR is calculated based on joint PTA and MIC distributions as follows,

$$CFR = \sum_{i=1}^{n} jointPTA(MICi) \times p(MICi) \quad (2)$$

PTA: probability of target attainment; *MIC*: minimum inhibitory concentration; *CFR*: cumulative fraction of response; *i*: the i-th MIC; *p*: probability distribution.

A dosage regimen with joint PTA and CFR ≥ 90% was considered adequate.

Results

Simulations for Non-Severe Infection Patients

The targets for non-severely infected patients were 50%$fT \geq$ MIC for ceftazidime and 50%$fT \geq C_{T=1.0\ mg/L}$ for avibactam. Through the model simulations of patients with non-severe infection, at a MIC=8 mg/L, joint PTA could achieve ≥ 99.8% at all recommended doses, even with a short infusion duration of 0.5 hours. The joint PTAs of other PK/PD targets were similar, as shown in Tables S4–S7.

Through all simulated infusion times at the recommended doses, the goal of CRF ≥ 90% could be easily achieved for all micro-organisms even when infusion length was only half an hour (Table S8).

Joint PTA for Severe Infection Patients

The joint PTAs of recommended dosages under different infusion times for patients with various renal functions are shown in Figure 1 (detailed data in Tables S9–S13). When the PK/PD target for ceftazidime was set as 100%$fT \geq$ MIC and for avibactam was set as 100%$fT \geq C_{T=1.0\ mg/L}$, the 2-hour infusion time only enabled PTA to reach 63.25% and 33.27% for patients with normal renal function and augmented renal clearance, respectively, at a MIC=8 mg/L. The PTA increased as infusion time prolonged, and continuous infusion of the recommended dose could achieve a PTA ≥ 90%. For patients with impaired renal function, a PTA ≥ 90% could be achieved at any infusion length for pathogens with MICs ≤ 8 mg/L. The effect of prolonged infusion time was weak in these populations. When the PK/PD target was set as 100%$fT \geq 4\times$MIC and 100%$fT \geq C_{T=4.0\ mg/L}$, only continuous infusion with 3000 mg/750 mg every 6 hours could achieve PTA ≥ 90% at an MIC = 8 mg/L.

CFR for Severe Infection Patients

The CFR Results (based on EUCAST) of the different targets for severe infection patients are shown in Table 1. For severe infection patients with augmented renal clearance, prolonged infusion of the recommended dosage for more than 4 hours

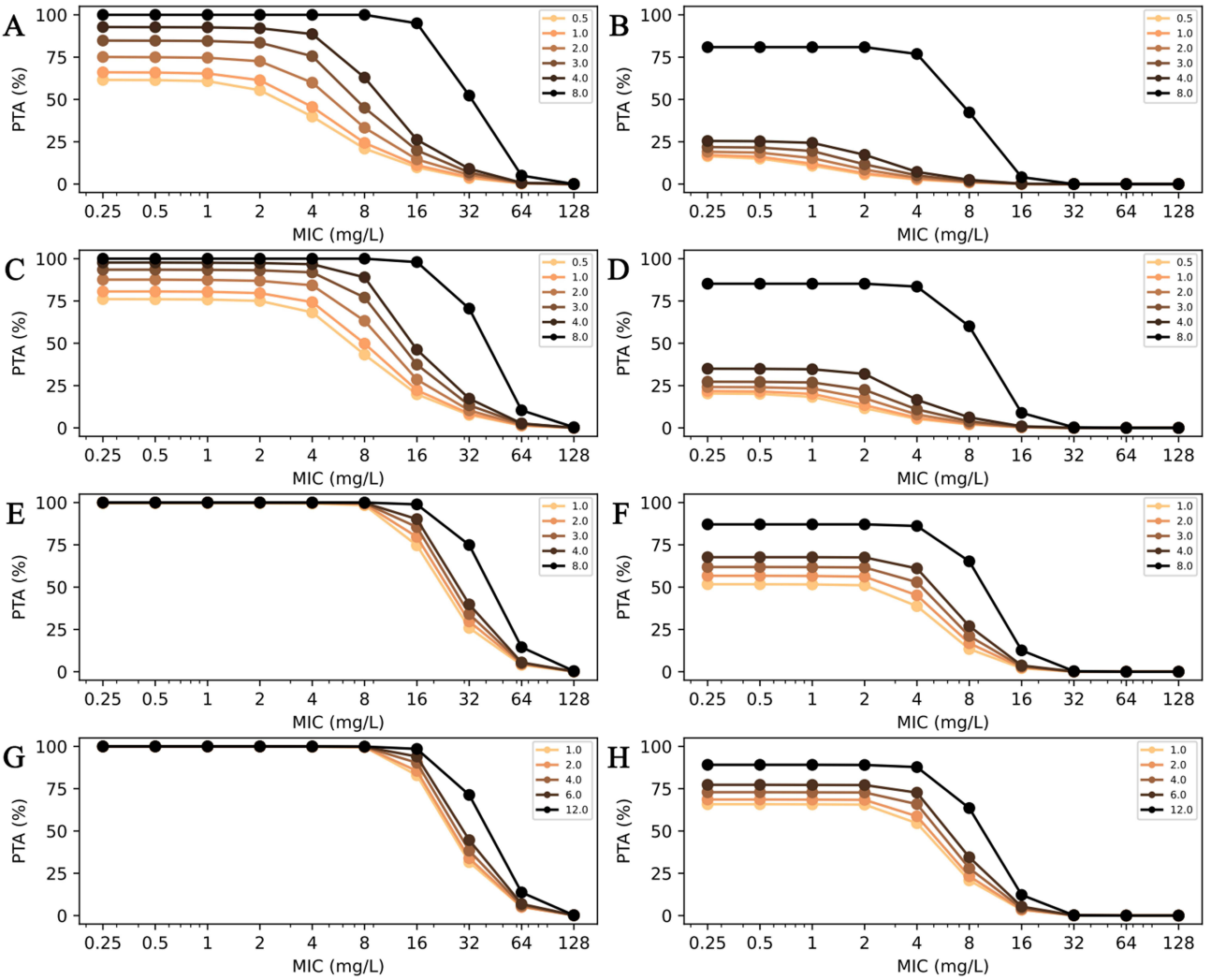

Figure 1 Probability of target attainment of the different ceftazidime-avibactam dosing regimens for patients with severe infection. Each line represents different infusion length. (**A**) CrCL = 130 mg/L, 2000 mg/500 mg, q8h, PTA of 100%$fT \geq$ MIC × PTA of 100%$fT \geq C_{T=1.0\ mg/L}$; (**B**) CrCL = 130 mg/L, 2000 mg/500 mg, q8h, PTA of 100%$fT \geq$ 4×MIC × PTA of 100%$fT \geq C_{T=4.0\ mg/L}$; (**C**) CrCL = 85 mg/L, 2000 mg/500 mg, q8h, PTA of 100%$fT \geq$ MIC × PTA of 100%$fT \geq C_{T=1.0\ mg/L}$; (**D**) CrCL = 85 mg/L, 2000 mg/500 mg, q8h, PTA of 100%$fT \geq$ 4×MIC × PTA of 100%$fT \geq C_{T=4.0\ mg/L}$; (**E**) CrCL = 40 mg/L, 1000 mg/250 mg, q8h, PTA of 100%$fT \geq$ MIC × PTA of 100%$fT \geq C_{T=1.0\ mg/L}$; (**F**) CrCL = 40 mg/L, 1000 mg/250 mg, q8h, PTA of 100%$fT \geq$ 4×MIC × PTA of 100%$fT \geq C_{T=4.0\ mg/L}$; (**G**) CrCL = 20 mg/L, 750 mg/187.5 mg, q12h, PTA of 100%$fT \geq$ MIC × PTA of 100%$fT \geq C_{T=1.0\ mg/L}$; (**H**) CrCL = 20 mg/L, 750 mg/187.5 mg, q12h, PTA of 100%$fT \geq$ 4×MIC × PTA of 100%$fT \geq C_{T=4.0\ mg/L}$.

Table 1 CFR for Severe Infection Patients

Dose (mg)	Interval	Duration (h)	CrCL (mL/min)	100%*f*T ≥ MIC 100%*f*T ≥ $C_{T= 1.0\ mg/L}$			100%*f*T ≥ 4*MIC 100%*f*T ≥ $C_{T= 4.0\ mg/L}$		
				PA	E. coli	KP	PA	E. coli	KP
2000/500	q8h	1	130	57.26%	62.51%	61.30%	8.09%	13.47%	12.14%
2000/500	q8h	2	130	67.94%	72.27%	71.17%	10.25%	15.50%	14.28%
2000/500	q8h	3	130	79.24%	82.65%	81.68%	13.21%	18.33%	17.23%
2000/500	q8h	4	130	89.12%	**91.40%**	**90.69%**	17.43%	22.18%	21.21%
2000/500	q8h	CI	130	**100.00%**	**100.00%**	**100.00%**	76.77%	79.36%	78.50%
2000/500	q8h	1	85	76.45%	79.01%	78.27%	14.21%	18.69%	17.74%
2000/500	q8h	2	85	84.58%	86.46%	85.87%	17.16%	21.31%	20.46%
2000/500	q8h	3	85	**91.60%**	**92.79%**	**92.40%**	20.87%	24.67%	23.89%
2000/500	q8h	4	85	**96.63%**	**97.30%**	**97.08%**	28.37%	32.29%	31.47%
2000/500	q8h	CI	85	**100.00%**	**100.00%**	**100.00%**	82.65%	84.26%	83.71%
1000/250	q8h	1	40	**99.46%**	**99.55%**	**99.52%**	45.99%	49.46%	48.56%
1000/250	q8h	2	40	**99.89%**	**99.96%**	**99.94%**	51.09%	54.52%	53.59%
1000/250	q8h	3	40	**99.95%**	**99.98%**	**99.97%**	56.71%	59.90%	58.98%
1000/250	q8h	4	40	**99.98%**	**99.99%**	**99.99%**	62.93%	65.89%	64.98%
1000/250	q8h	CI	40	**100.00%**	**100.00%**	**100.00%**	84.96%	86.32%	85.84%
750/187.5	q12h	1	20	**99.86%**	**99.88%**	**99.88%**	59.90%	63.52%	62.50%
750/187.5	q12h	2	20	**99.86%**	**99.88%**	**99.88%**	62.86%	66.40%	65.37%
750/187.5	q12h	4	20	**99.87%**	**99.89%**	**99.88%**	67.67%	70.92%	69.91%
750/187.5	q12h	6	20	**99.97%**	**99.99%**	**99.98%**	72.61%	75.55%	74.59%
750/187.5	q12h	CI	20	**99.99%**	**100.00%**	**99.99%**	86.54%	88.16%	87.59%

Note: Boldface text: ≥ 90%.

Abbreviations: CrCL: Creatinine clearance; CI, Continuous infusion; qxh, Administer every x hours; MIC: Minimum inhibitory concentration; %*f*T ≥ C_T: Time fraction of free drug above a threshold concentration; PA, *Pseudomonas aeruginosa*; E. coli, *Escherichia coli*; KP, *Klebsiella pneumoniae*.

could meet a CFR ≥ 90% at the target of 100%*f*T ≥ MIC and 100%*f*T ≥ $C_{T=1.0\ mg/L}$ to *Escherichia coli* and *Klebsiella pneumoniae* but failed to achieve the target for *Pseudomonas aeruginosa*.

For severe infection patients with normal renal function, extending infusion for more than 3 hours could meet a CFR ≥ 90% at the target of 100%*f*T ≥ MIC and 100%*f*T ≥ $C_{T=1.0\ mg/L}$ to *Pseudomonas aeruginosa, Escherichia coli* and *Klebsiella pneumoniae* at the recommended dosage.

For severe infection patients with CrCL between 30 and 50 mL/min at recommended dosage and the CrCL between 15 and 30 mL/min at recommended dosage, a CFR ≥ 90% at 100%*f*T ≥ MIC and 100%*f*T ≥ $C_{T=1.0\ mg/L}$ could be achieved for *Pseudomonas aeruginosa, Escherichia coli* and *Klebsiella pneumoniae* at any infusion time.

According to the results of a PTA of 100%*f*T ≥ 4×MIC and PTA of 100%*f*T ≥ $C_{T=4.0\ mg/L}$, only continuous infusion of partial dosing regimens could achieve this goal.

The CFRs for different MIC distributions of recommended doses are shown in Figure 2. Higher dose or longer infusion time is need for *Pseudomonas aeruginosa* infection, when comparing to *Klebsiella pneumoniae* infection. The detailed results are shown in Tables S14–S16. The MIC distributions of *Pseudomonas aeruginosa* in CHINET and INFORM were less susceptible than those in EUCAST. Thus, the regional difference should be taken into consideration when dosing ceftazidime/avibactam.

Discussion

In this study, we successfully simulated various scenarios with different dosages, infusion times, renal function, and MIC distributions of ceftazidime/avibactam. For severely infected patients with normal renal function, the infusion time needs to be extended to over three hours to obtain a satisfactory concentration when using the recommended doses. For patients

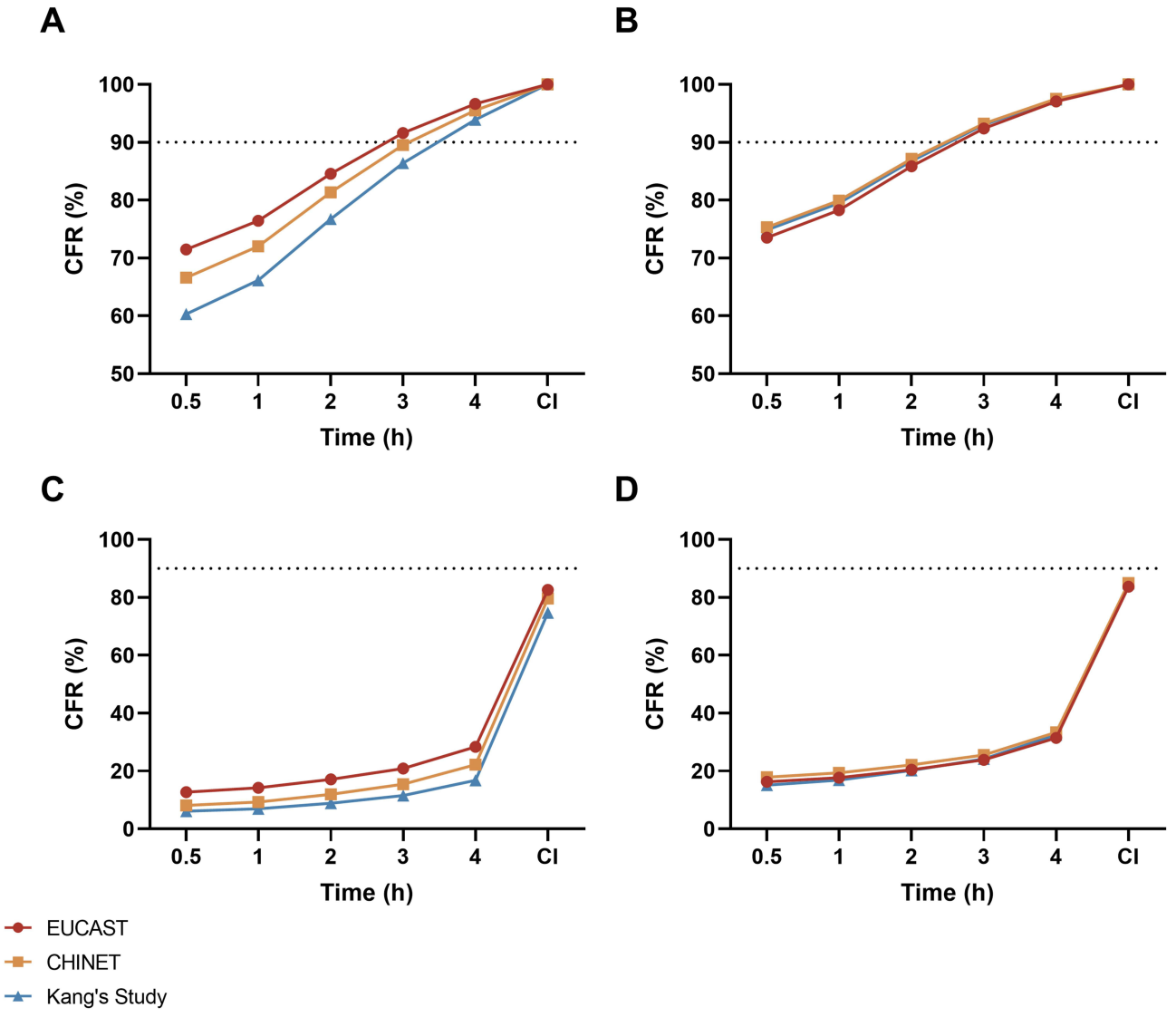

Figure 2 The trends in CFR based on different MIC distributions. (**A**) PA, target: 100%*f*T ≥ MIC and 100%*f*T ≥ $C_{T= 1.0\ mg/L}$ (**B**) KP, target: 100%*f*T ≥ MIC and 100%*f*T ≥ $C_{T= 1.0\ mg/L}$ (**C**) PA, target: 100%*f*T ≥ 4×MIC and 100%*f*T ≥ $C_{T= 4.0\ mg/L}$ (**D**) KP, target: 100%*f*T ≥ 4×MIC and 100%*f*T ≥ $C_{T= 4.0\ mg/L}$.
Abbreviations: PA, Pseudomonas aeruginosa; KP, Klebsiella pneumoniae; CI, Continuous infusion.

with augmented renal clearance, a higher dose is required with a prolonged infusion time. It is difficult to achieve the aggressive target with all the recommended regimens. From the CFR calculated by different MIC distributions, it could be inferred that higher concentration is required for *Pseudomonas aeruginosa*. Therefore, the current dosing regimen of ceftazidime/avibactam is insufficient for severe infection patients, and continuous infusion is needed.

We selected three PK/PD targets in this simulation: 50%*f*T ≥ MIC with 50%*f*T ≥ $C_{T=1.0\ mg/L}$, 100%*f*T ≥ MIC with 100%*f*T ≥ $C_{T=1.0\ mg/L}$ and 100%*f*T ≥ 4×MIC with 100%*f*T ≥ $C_{T=4.0\ mg/L}$. Currently, there are some in vitro pharmacological studies on the efficacy of ceftazidime/avibactam against a variety of bacterial strains, and C_T values significantly impact its effectiveness. According to current studies, the chosen C_T = 1 mg/L is reasonable. Berkhout et al's study revealed this phenomenon. Avibactam remained above the threshold concentration of 1 mg/L (%*f*T ≥ $C_{T=1.0\ mg/L}$) inhibited ceftazidime-resistant *Pseudomonas aeruginosa*.[41] A study by Sy et al simulated bacterial responses and revealed that the activity of avibactam against multidrug-resistant *Pseudomonas aeruginosa* was correlated with the C_T, and a C_T of 1 mg/L achieved at least a 2-log kill for a clinical dose of 500 mg q8h avibactam with a 2-hour infusion.[17] Additionally, for *Enterobacteriaceae* sensitive to ceftazidime/avibactam, the required concentration is generally well below 1 mg/L.[43] Therefore, %*f*T ≥ $C_{T=1.0\ mg/L}$ could be chosen as a standard. Moreover, some studies have

proposed that a higher threshold concentration is also needed. MacGowan et al's study showed that at a maximal concentration of 1–2 mg/L, avibactam could eradicate *Escherichia coli* and *Enterobacter cloacae* strains, but 4 mg/L was required for a maximum reduction in the bacterial load of *Klebsiella pneumoniae* strains in its concentration-MIC curve.[42] In another recent study, Marta et al reported that 8 mg/L avibactam maintained the ceftazidime MIC above the clinical breakpoint in the majority of CAZ-AVI-resistant KPC-Kp isolates. An even higher concentration of avibactam (64 mg/L) was needed for ceftazidime to exhibit bactericidal activity against CAZ-AVI-resistant KPC-Kp isolates.[36] These two results suggested that the current threshold concentration of avibactam may be inadequate, and high concentrations of avibactam are necessary in vivo for ceftazidime to effectively combat resistant bacteria. Therefore, there is a rationale for increasing the target concentration to $C_{T=4.0\ mg/L}$. In our study, achieving the challenging $C_{T=4.0\ mg/L}$ target necessitates switching to continuous infusion. Meanwhile, achieving high targets may increase the likelihood of patient overdosing, which is particularly concerning given the associated severe adverse effects on the central nervous system (CNS).[44–46] High concentrations of ceftazidime/avibactam, have been linked to CNS toxicity, manifesting as seizures, encephalopathy, and other neurotoxic effects.[47] These risks necessitate a careful balance between maximizing therapeutic efficacy and minimizing potential harm to patients. Therefore, setting an excessively high C_T at 8 mg/L or 64 mg/L is challenging or unfeasible.

To date, there have been some simulation and clinical studies on the dosing adequacy of ceftazidime/avibactam. Han et al investigated various novel β-Lactam/β-lactamase inhibitors, including ceftazidime/avibactam, and simulated them at different doses and infusion times. It was recommended that the infusion of ceftazidime/avibactam be extended to 4 hours for *Escherichia coli* at a standard dose of 2000 mg/500 mg/q8h. For *Pseudomonas aeruginosa*, it was recommended to use a dosage of 3500 mg/875 mg/q6h for extended infusion for 4 hours or 4000 mg/1000 mg/q6h for continuous infusion. The highest dosage regimen (4000 mg/1000 mg/q6h) for *Klebsiella pneumoniae* could not meet the target.[31] The reasons for the difference in the results are the PK/PD targets and the calculation method used of the CFR. The targets of ceftazidime were 50%$fT \geq$ MIC, 70%$fT \geq$ MIC, 100%$fT \geq$ MIC, but the target of avibactam was 50%$fT \geq C_T$ (C_T=1 mg/L). However, in Han's study, resistant microorganisms were also used for CFR calculations, which was inappropriate because ceftazidime/avibactam should not be used for infections caused by those pathogens. Worapong et al's simulation employed the following targets: 50%$fT \geq$ MIC with 50%$fT \geq C_{T=0.5\ mg/L}$, 100%$fT \geq$ MIC with 100% $fT \geq C_{T=0.5\ mg/L}$ for *Klebsiella pneumoniae* producing OXA-48 enzymes or New Delhi metallo-beta-lactamase (NDM) enzymes. At the recommended dose (2000 mg/500 mg, q8h), when the target was set to 50%$fT \geq$ MIC with 50%$fT \geq C_{T=0.5\ mg/L}$, the probability of target attainment (PTA) was consistently ≥ 90%; however, when the target was set to 100% $fT \geq$ MIC with 100%$fT \geq C_{T=0.5\ mg/L}$, continuous infusion of at least 2 hours was required to achieve PTA ≥ 90%. The PTA for *Klebsiella pneumoniae* producing NDM enzymes was consistently less than 10%.[18] This study selected a lower C_T target for ceftazidime/avibactam-susceptible *Klebsiella pneumoniae* and obtained the same results as our study (blue text of Table S14), which also indicated that it was not a suitable option for producing NDM enzymes. A clinical study of patients with *Klebsiella pneumoniae* infection included 577 patients, 246 of whom received a medication regimen with an extended infusion time. The results showed that the mortality rate of patients who extended the infusion time by more than 3 hours was significantly lower than that of patients who extended the infusion time by 2 hours as recommended (P = 0.006).[26] This clinical study aligns with our findings, indicating that for patients with normal renal function, continuous infusion for more than 3 hours could better achieve PK/PD targets, thus leading to improved treatment outcomes.

For the delineated MIC distributions by EUCAST and CHINET, it was revealed a higher demand for elevated concentrations of ceftazidime/avibactam for *Pseudomonas aeruginosa*, and the regional distribution disparities of different microorganisms was explored.[22] Resistance in *Pseudomonas aeruginosa* has proven to be more complex, and may involve multiple mechanisms.[48] The mechanisms of resistance could be caused by the interplay between different resistance mechanisms including ESBL carriage, increased efflux, loss of permeability and depression of the intrinsic *ampC* gene.[49] Kang et al proposed a two-step medication treatment strategy involving CZA for patients infected with *Pseudomonas aeruginosa*. The recommended dosing regimen was a rapid infusion of 1.25 g (0.5 h infusion) in the first step and a continuation of the remaining 1.25 g (2 h infusion) in the second step.[22] But in practice, one-time administration and only changing the infusion time have more practical significance in clinical practice. Additionally, the results also indicated significant differences in the regional distribution of these microorganisms, indicating that

geographical location had a crucial relationship with the prevalence and resistance levels of different bacteria. Such regional disparities in microbial resistance underscore the necessity for tailored antibiotic strategies and dosages according to local resistance patterns.

Simulation research may also have certain limitations. Although the target could be achieved for patients with renal insufficiency, the upper limit of the ceftazidime/avibactam concentration was not considered during the simulation process, which may cause adverse drug events during implementation. Therefore, although using shorter dosing intervals at the same dose could significantly improve the PTA and CFR, further research is needed on the potential hazards associated with excessively high concentrations. Patients who received dialysis or renal replacement therapy were not considered. The existing models are mainly based on plasma concentrations, which indeed simplify the complexities of drug distribution at different infection sites. Future research should incorporate site-specific data to provide more tailored treatment recommendations, addressing the unique challenges associated with drug concentration and penetration at different infection sites. Moreover, large-scale and high-quality clinical studies are needed in the future to verify the effectiveness and safety of different infusion durations for severe infections caused by drug-resistant bacteria.

Conclusion

Recent studies have indicated that the current recommended regimen is insufficient. This study evaluated the adequacy of dosage regimens by Monte Carlo simulation. For non-severely infected patients, the current recommended dosage regimen could easily achieve the target PTA and CFR for susceptible microorganisms, even with a short infusion length. For severe infection patients, prolonging the infusion time could be adopted to achieve the target of PTA and CFR. When the target is 100%$fT \geq$ MIC and 100%$fT \geq C_{T= 1.0\ mg/L}$, patients with normal renal function need to extend the infusion time to more than 3 hours to achieve a CFR $\geq$ 90% at the recommended dose. For patients with augmented renal clearance, infusion might be extended for more than 4 hours to reach a CFR $\geq$ 90%, and patients with *Pseudomonas aeruginosa* infection require a longer infusion time. For the aggressive target (100%$fT \geq 4\times$MIC and 100%$fT \geq C_{T= 4.0\ mg/L}$), it is difficult for all the recommended regimens to achieve this goal apart from continuous infusion. We conclude that the recommended dose is insufficient for severe infection. In the future, further large-scale and high-quality clinical studies are needed to identify the PK/PD target of ceftazidime/avibactam in severe infection and to suggest a reasonable dose.

Data Sharing Statement

All data are within the manuscript.

Ethic Approval and Informed Consent

Ethic approval is not required as only published materials are involved.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Thomsen J, Menezes GA, Abdulrazzaq NM, Moubareck CA, Senok A, Everett DB. Evolving trends among Pseudomonas aeruginosa: a 12-year retrospective study from the United Arab Emirates. *Front Public Health*. 2023;11:1243973. doi:10.3389/fpubh.2023.1243973
2. Govindaraj VA, Vanitha A. WHO global priority pathogens list on antibiotic resistance: an urgent need for action to integrate One Health data. *Perspect Public Health*. 2018;138(2):87–88. doi:10.1177/1757913917743881
3. El-Sayed AM, Zhong LL, Shen C, Yang Y, Doi Y, Tian GB. Colistin and its role in the Era of antibiotic resistance: an extended review (2000-2019). *Emerg Microbes Infect*. 2020;9(1):868–885.

4. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18(3):318–327. doi:10.1016/S1473-3099(17)30753-3
5. Sholeh M, Krutova M, Forouzesh M, et al. Antimicrobial resistance in Clostridioides (Clostridium) difficile derived from humans: a systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2020;9(1):158. doi:10.1186/s13756-020-00815-5
6. Shields RK, McCreary EK, Marini RV, et al. Early experience with meropenem-vaborbactam for treatment of carbapenem-resistant Enterobacteriaceae infections. *Clin Infect Dis*. 2020;71(3):667–671. doi:10.1093/cid/ciz1131
7. Shirley M. Ceftazidime-avibactam: a review in the treatment of serious gram-negative bacterial infections. *Drugs*. 2018;78(6):675–692. doi:10.1007/s40265-018-0902-x
8. Davies DT, Everett M. Designing inhibitors of β-Lactamase enzymes to overcome carbapenem resistance in gram-negative bacteria. *Acc Chem Res*. 2021;54(9):2055–2064. doi:10.1021/acs.accounts.0c00863
9. Yahav D, Giske CG, Gramatniece A, Abodakpi H, Tam VH, Leibovici L. New beta-Lactam-beta-Lactamase Inhibitor Combinations. *Clin Microbiol Rev*. 2020;34(1). doi:10.1128/CMR.00115-20
10. Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, Phase 3 non-inferiority trial. *Lancet Infect Dis*. 2018;18(3):285–295. doi:10.1016/S1473-3099(17)30747-8
11. Liu C, Chen K, Wu Y, et al. Epidemiological and genetic characteristics of clinical carbapenem-resistant Acinetobacter baumannii strains collected countrywide from hospital intensive care units (ICUs) in China. *Emerg Microbes Infect*. 2022;11(1):1730–1741. doi:10.1080/22221751.2022.2093134
12. Che H, Wang R, Wang J, Cai Y. Ceftazidime/avibactam versus carbapenems for the treatment of infections caused by Enterobacteriaceae: a meta-analysis of randomised controlled trials. *Int J Antimicrob Agent*. 2019;54(6):809–813. doi:10.1016/j.ijantimicag.2019.09.007
13. Zhang Y, Tao LN, Qu XY, Niu JQ, Ding YH, Zhang SX. Efficacy and safety of ceftazidime-avibactam in the treatment of complicated intra-abdominal infections (CIAIs) and complicated urinary tract infections (CUTIs): a meta-analysis of randomized controlled trials. *Rev Assoc Med Bras*. 2018;64(3):253–263. doi:10.1590/1806-9282.64.03.253
14. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis*. 2016;16(6):661–673. doi:10.1016/S1473-3099(16)30004-4
15. Levasseur P, Girard AM, Claudon M, et al. In vitro antibacterial activity of the ceftazidime-avibactam (NXL104) combination against Pseudomonas aeruginosa clinical isolates. *Antimicrob Agent Chemoth*. 2012;56(3):1606–1608. doi:10.1128/AAC.06064-11
16. Levasseur P, Girard AM, Miossec C, Pace J, Coleman K. In vitro antibacterial activity of the ceftazidime-avibactam combination against Enterobacteriaceae, including strains with well-characterized beta-lactamases. *Antimicrob Agent Chemoth*. 2015;59(4):1931–1934. doi:10.1128/AAC.04218-14
17. Sy SK, Zhuang L, Sy S, Derendorf H. Clinical pharmacokinetics and pharmacodynamics of ceftazidime–avibactam combination: a model-informed strategy for its clinical development. *Clin Pharmacokinet*. 2019;58(5):545–564. doi:10.1007/s40262-018-0705-y
18. Nasomsong W, Nulsopapon P, Changpradub D, et al. The potential use of ceftazidime-avibactam against carbapenem resistant Klebsiella pneumoniae clinical isolates harboring different carbapenemase types in a Thai university hospital. *Drug Des Devel Ther*. 2021;15:3095–3104. doi:10.2147/DDDT.S321147
19. Muller AE, Punt N, Mouton JW. Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. *J Antimicrob Chemoth*. 2013;68(4):900–906. doi:10.1093/jac/dks468
20. MacVane SH, Kuti JL, Nicolau DP. Clinical pharmacodynamics of antipseudomonal cephalosporins in patients with ventilator-associated pneumonia. *Antimicrob Agent Chemoth*. 2014;58(3):1359–1364. doi:10.1128/AAC.01463-13
21. Sy S, Zhuang L, Xia H, Schuck VJ, Nichols WW, Derendorf H. A model-based analysis of pharmacokinetic-pharmacodynamic (PK/PD) indices of avibactam against Pseudomonas aeruginosa. *Clin Microbiol Infect*. 2019;25(7):904–909. doi:10.1016/j.cmi.2018.10.014
22. Kang Y, Cui J. Evaluation of the efficacy of optimized two-step-administration therapy with ceftazidime/avibactam for treating extensively drug-resistant Pseudomonas aeruginosa pulmonary infections: a pharmacokinetic/pharmacodynamic analysis. *Jpn J Infect Dis*. 2023;76(1):1–6. doi:10.7883/yoken.JJID.2022.289
23. Kang Y, Zhou Q, Cui J. Pharmacokinetic/pharmacodynamic modelling to evaluate the efficacy of various dosing regimens of ceftazidime/avibactam in patients with pneumonia caused by Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae: a multicentre study in northern China. *J Glob Antimicrob Re*. 2021;27:67–71.
24. Franzese RC, McFadyen L, Watson KJ, et al. Population pharmacokinetic modeling and probability of pharmacodynamic target attainment for ceftazidime-avibactam in pediatric patients aged 3 months and older. *Clin Pharmacol Ther*. 2022;111(3):635–645. doi:10.1002/cpt.2460
25. Qin X, Tran BG, Kim MJ, et al. A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. *Int J Antimicrob Agents*. 2017;49(5):579–588. doi:10.1016/j.ijantimicag.2017.01.010
26. Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-avibactam use for Klebsiella pneumoniae carbapenemase–producing K. pneumoniae infections: a retrospective observational multicenter study. *Clin Infect Dis*. 2021;73(9):1664–1676. doi:10.1093/cid/ciab176
27. Gatti M, Pea F. Continuous versus intermittent infusion of antibiotics in Gram-negative multidrug-resistant infections. *Curr Opin Infect Dis*. 2021;34(6):737–747. doi:10.1097/QCO.0000000000000755
28. Zavrelova A, Sima M, Malakova J, et al. Superiority of ceftazidime off-label high-dose regimen in PK/PD target attainment during treatment of extensively drug-resistant Pseudomonas aeruginosa infections in cancer patients. *Br J Clin Pharmacol*. 2023;89(4):1452–1461. doi:10.1111/bcp.15612
29. Bakdach D, Elajez R, Bakdach AR, Awaisu A, De Pascale G, Ait HA. Pharmacokinetics, Pharmacodynamics, and Dosing Considerations of Novel beta-Lactams and beta-Lactam/beta-Lactamase Inhibitors in Critically Ill Adult Patients: focus on Obesity, Augmented Renal Clearance, Renal Replacement Therapies, and Extracorporeal Membrane Oxygenation. *J Clin Med*. 2022;11(23):6898.
30. Goutelle S, Jullien V, Bru JP, et al. Defining standard and high dosages for beta-lactam agents administered by intermittent, prolonged or continuous infusion: a PK/PD simulation study. *J Antimicrob Chemoth*. 2023;78(11):2762–2769. doi:10.1093/jac/dkad300

31. Han R, Sun D, Li S, et al. Pharmacokinetic/pharmacodynamic adequacy of novel β-Lactam/β-Lactamase inhibitors against gram-negative bacterial in critically Ill patients. *Antibiotics*. 2021;10(8):993. doi:10.3390/antibiotics10080993
32. Veiga RP, Paiva JA. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients. *Crit Care*. 2018;22(1):233. doi:10.1186/s13054-018-2155-1
33. Bassetti M, Castaldo N, Cattelan A, et al. Ceftolozane/tazobactam for the treatment of serious Pseudomonas aeruginosa infections: a multicentre nationwide clinical experience. *Int J Antimicrob Agents*. 2019;53(4):408–415. doi:10.1016/j.ijantimicag.2018.11.001
34. Campion M, Scully G. Antibiotic Use in the Intensive Care Unit: optimization and De-Escalation. *J Intensive Care Med*. 2018;33(12):647–655. doi:10.1177/0885066618762747
35. Roberts DM, Roberts JA, Roberts MS, et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. *Crit Care Med*. 2012;40(5):1523–1528. doi:10.1097/CCM.0b013e318241e553
36. Palombo M, Secci B, Bovo F, Gatti M, Ambretti S, Gaibani P. In vitro evaluation of increasing avibactam concentrations on ceftazidime activity against ceftazidime/avibactam-susceptible and resistant KPC-Producing Klebsiella pneumoniae clinical isolates. *Antibiotics*. 2023;12(12):1707. doi:10.3390/antibiotics12121707
37. Dimelow R, Wright JG, MacPherson M, Newell P, Das S. Population pharmacokinetic modelling of ceftazidime and avibactam in the plasma and epithelial lining fluid of healthy volunteers. *Drugs R&D*. 2018;18(3):221–230. doi:10.1007/s40268-018-0241-0
38. Li J, Lovern M, Green ML, et al. Ceftazidime-avibactam population pharmacokinetic modeling and pharmacodynamic target attainment across adult indications and patient subgroups. *Clin Transl Sci*. 2019;12(2):151–163. doi:10.1111/cts.12585
39. Stein GE, Smith CL, Scharmen A, et al. Pharmacokinetic and pharmacodynamic analysis of ceftazidime/avibactam in critically Ill patients. *Surg Infect*. 2019;20(1):55–61. doi:10.1089/sur.2018.141
40. Merdjan H, Tarral A, Das S, Li J. Phase 1 study assessing the pharmacokinetic profile and safety of avibactam in patients with renal impairment. *J Clin Pharmacol*. 2017;57(2):211–218. doi:10.1002/jcph.793
41. Berkhout J, Melchers MJ, van Mil AC, et al. pharmacodynamics of ceftazidime and avibactam in neutropenic mice with thigh or lung infection. *Antimicrob Agent Chemoth*. 2016;60(1):368–375. doi:10.1128/AAC.01269-15
42. MacGowan A, Tomaselli S, Noel A, Bowker K. The pharmacodynamics of avibactam in combination with ceftaroline or ceftazidime against beta-lactamase-producing Enterobacteriaceae studied in an in vitro model of infection. *J Antimicrob Chemoth*. 2017;72(3):762–769. doi:10.1093/jac/dkw480
43. Coleman K, Levasseur P, Girard AM, et al. Activities of ceftazidime and avibactam against beta-lactamase-producing Enterobacteriaceae in a hollow-fiber pharmacodynamic model. *Antimicrob Agent Chemoth*. 2014;58(6):3366–3372. doi:10.1128/AAC.00080-14
44. Yu J, Zuo W, Fan H, et al. Ceftazidime-avibactam for carbapenem-resistant gram-negative bacteria infections: a real-world experience in the ICU. *Infect Drug Resist*. 2023;16:6209–6216. doi:10.2147/IDR.S422545
45. Ong CY, Qin Y. Myoclonus from antibiotic therapy (ceftazidime-induced neurotoxicity): a case report and review. *Cureus*. 2018;10(3):e2250. doi:10.7759/cureus.2250
46. Joseph J, Vimala A. Ceftazidime-induced myoclonus and encephalopathy in hemodialysis patient. *Indian J Nephrol*. 2015;25(1):61–62. doi:10.4103/0971-4065.144426
47. Guo X, Guo M, Li J, Cui X. Central nervous system adverse events of ceftazidime/avibactam: a retrospective study using food and drug administration adverse event reporting system. *J Clin Pharm Ther*. 2022;47(12):2369–2372. doi:10.1111/jcpt.13796
48. Mojica MF, De La Cadena E, Garcia-Betancur JC, et al. Molecular mechanisms of resistance to ceftazidime/avibactam in clinical isolates of Enterobacterales and Pseudomonas aeruginosa in Latin American hospitals. *Msphere*. 2023;8(2):e65122. doi:10.1128/msphere.00651-22
49. Babouee FB, Bosch A, Gisler V, et al. Multifactorial resistance mechanisms associated with resistance to ceftazidime-avibactam in clinical Pseudomonas aeruginosa isolates from Switzerland. *Front Cell Infect Microbiol*. 2023;13:1098944. doi:10.3389/fcimb.2023.1098944