

# Population Pharmacokinetics-Based Evaluation of Ceftazidime-Avibactam Dosing Regimens in Critically and Non-Critically Ill Patients With Carbapenem-Resistant *Klebsiella pneumoniae*

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**Purpose:** This study aimed to describe the population pharmacokinetics (PopPK) of ceftazidime-avibactam (CAZ-AVI) in adult patients, and to develop optimal dosing regimens for both non-critically ill and critically ill patients by combining different pharmacokinetic/pharmacodynamic (PK/PD) targets.

**Patients and Methods:** A prospective, single-center study involving patients who were infected with CRKP and received CAZ-AVI therapy was conducted. Nonlinear mixed-effect modeling was used to develop a PopPK model. The optimal dosing regimen was assessed using Monte Carlo simulation.

**Results:** The PopPK analysis of CAZ-AVI included 91 steady-state concentrations from 45 adult patients. The data were modeled using a one-compartment model. The typical population values of CAZ and AVI clearances were 2.96 L/h and 3.09 L/h, and the volumes of distribution were 17.76 L and 18.25 L, respectively. Our study showed that creatinine clearance (CrCL) calculated using the Cockcroft-Gault equation significantly affected the pharmacokinetics of CAZ-AVI. The Monte Carlo simulation optimized the dosing regimen for both non-critically ill and critically ill patients with varying renal functions, providing detailed supplements to the instructions.

**Conclusion:** Our study established a PopPK model for CAZ-AVI and proposed a reference for dosing regimen adjustment based on the severity of the disease and renal functional status.

**Keywords:** ceftazidime-avibactam, pharmacokinetic modeling, renal function, Monte Carlo simulation, dose optimization

## Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections have become a significant threat to public health, accounting for one of the leading causes of mortality worldwide.<sup>1</sup> New antibiotics are urgently needed to complement clinical antimicrobial therapy. Ceftazidime-avibactam (CAZ-AVI) is a combined product of ceftazidime (CAZ) and the  $\beta$ -lactamase inhibitor avibactam (AVI) in a fixed 4:1 ratio.<sup>2</sup> The Infectious Diseases Society of America and the European Society for Clinical Microbiology and Infectious Diseases have recommended CAZ-AVI as a first-line drug against CRKP infections.<sup>3,4</sup> It is approved for treating complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired pneumonia, and associated bacteremia.<sup>2</sup>

Pharmacokinetic/pharmacodynamic (PK/PD) targets are crucial for optimizing antibiotic dosing. For CAZ, successful bactericidal outcomes hinge on maintaining the free plasma concentration exceeding the minimum inhibitory

concentration (MIC) for a sufficient portion of the dosing interval ( $\% fT > MIC$ ), with 50%  $fT > MIC$  as the widely accepted target. Similarly, in the case of AVI, Nichols et al determined that a  $\% fT >$  a threshold concentration ( $C_T$ ) of 1 mg/L is the most relevant PK/PD index for the efficacy of AVI in restoring CAZ efficacy.<sup>5</sup>

Since the approval of CAZ-AVI by the FDA in 2015, several PK studies have been conducted based on the above PK/PD targets.<sup>6–9</sup> These studies established a standard dosing regimen of 2.5 g q8h (2-h infusion), with adjustments for patients with creatinine clearance (CrCL)  $\leq 50$  mL/min using the Cockcroft-Gault equation.<sup>2</sup> However, with the wide use of CAZ-AVI in clinical practice, concerns have emerged regarding the utility of the instruction-based dosing regimen. For instance, a multicenter study in northern China indicated that a revised regimen of 2.5 g q12h (2-h infusion) also demonstrated sufficient efficacy in patients with a CrCL  $> 51$  mL/min.<sup>10</sup> In contrast, a study in critically ill patients with augmented renal function (ARC) revealed that the standard dosage in the instruction was inadequate for achieving optimal PK/PD targets and microbial eradication in most of these patients.<sup>11</sup> These findings indicate the recommended regimens in the instructions has its limitations. Roberts et al have highlighted that a 100%  $fT > MIC$  target of CAZ is correlated with improved clinical outcomes and inhibiting the development of resistance in critically ill patients compared to the 50%  $fT > MIC$  target.<sup>12</sup> Additionally, the French Society of Pharmacology and Therapeutics (SFPT) has similarly advocated higher PK/PD targets for critically ill patients.<sup>13</sup> Thus, it is essential to distinguish between non-critically and critically ill patients and set different PK/PD targets for patient conditions. Voices have been raised that it is necessary to set different PK/PD targets according to the clinical status of patients. Hereto, there is none of the studies proposed appropriate dosing regimens for the higher PK/PD target of CAZ-AVI.

To address this gap, we conducted a prospective study on patients who received intravenous CAZ-AVI treatment. We developed a population pharmacokinetic (PopPK) model to describe inter-individual and intra-individual variability,<sup>14</sup> and combined the two distinct PK/PD targets to establish the optimal dosing regimen for non-critically and critically ill patients with various renal functions.

## Materials and Methods

### Patients and Ethics

A single-center, prospective PopPK study was conducted at Fujian Medical University Union Hospital from July 2021 to September 2023. The study was approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2019KJCX034). The study was conducted according to the Declaration of Helsinki after informing all patients in our study of the study objectives and providing written consent to participate in this study. The inclusion criteria were as follows: (1) patients  $\geq 18$  years; (2) patients who received intravenous CAZ-AVI therapy for verified infection with CRKP. Exclusion criteria were applied to patients who were missing key information, or whose plasma concentration exceeded the detection limit. The treatment regimen of CAZ-AVI was determined by the healthcare team, with the dose and frequency adjusted according to the renal function of the patients.

The hospital electronic medical record system provided data on CAZ-AVI doses, frequencies, concentrations, demographic information (gender, age, height, weight, indication), acute physiology and chronic health evaluation II (APACHE II, with APACHE II;  $> 15$  defined as critically ill and APACHE II  $\leq 15$  defined as non-critically ill),<sup>15</sup> continuous renal replacement therapy (CRRT), and various laboratory metrics. These metrics included total bilirubin (TBIL), direct bilirubin (DBIL), total protein (TP), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), serum creatinine (SCR), and CrCL, calculated using the Cockcroft-Gault equation.<sup>16</sup>

### Sample Collection and Analysis

Considering patient compliance and ethical issues, a sparse sampling strategy was used to collect 1–3 blood samples at different time points post-infusion of the same dose after reaching a steady state (at least the sixth dose after starting CAZ-AVI therapy).<sup>17</sup> The sampling time points were determined by the clinical healthcare team. Plasma concentrations of CAZ-AVI were quantified using our previously described method of liquid chromatography-tandem mass spectrometry (LC-MS/MS; Shimadzu Jasper<sup>TM</sup> HPLC system coupled to an AB SCIEX Triple Quad<sup>TM</sup> 4500MD-ESI mass

spectrometer, Singapore.<sup>18</sup> The quantification method has been validated according to the bioanalytical validation guidelines of the US Food and Drug Administration.

## PopPK Modeling

PopPK analyses were performed using Phoenix NLME (version 8.1, Pharsight, Mountain View, CA, USA). The model parameters were estimated using the first-order conditional estimation and extended least squares. The base model was determined based on previous reports<sup>6–9</sup> and the fit of the data of our study. Inter-individual variability was described using an exponential residual model, while intra-individual variability was modeled with additive, proportional, and combined error structures. If a continuous covariate was missing, the median value of that covariate was used, and the highest frequent category was employed in cases where a categorical covariate was missing. Model discrimination was based on the  $-2$  log likelihood ( $-2LL$ ), with covariate screening including demographic and laboratory information. The covariates were added to the model after median normalization or as power functions. Covariate screening was performed using a stepwise forward inclusion method (a decrease in OFV  $> 3.84$ ,  $p < 0.05$ ) and a backward elimination method (an increase in OFV  $> 10.83$ ,  $p < 0.001$ ).

## Model Evaluation

Goodness-of-fit (GOF) plots were utilized to evaluate the fit of the final model, including plots of observed concentration (DV) versus individual population prediction (IPRED) and population prediction (PRED), as well as plots of conditional weighted residuals (CWRES) versus time after the last dose (TAD) and PRED. The prediction-corrected visual predictive check (pc-VPC) was employed to assess the predictive accuracy of the final model by comparing the 90% confidence intervals (CIs) of simulated concentrations with 1000 replicates, against the distribution of actual observations. Furthermore, a bootstrap method was used to examine parameter estimation accuracy and model robustness by matching the final model parameter estimates to both the median and the 95% CI of the bootstrap parameter estimates.

## Monte Carlo Simulation

In this study, different PK/PD targets were set for non-critically ill and critically ill patients. The targets were set based on improved clinical efficacy and inhibited the development of resistance. For non-critically ill patients, the PK/PD target was set at  $50\%fT > MIC$  for CAZ and  $50\%fT > 1$  mg/L for AVI,<sup>19</sup> while critically ill patients had a more stringent target of achieving  $100\%fT > 4 \times MIC$  for CAZ and  $100\%fT > 4$  mg/L for AVI.<sup>20</sup> Monte Carlo simulation was performed based on the final model to assess the probability of target attainment (PTA) for optimal PK/PD targets with different regimens in non-critically ill and critically ill patients. The susceptibility breakpoint of CRKP for CAZ-AVI was a MIC of  $\leq 8$  mg/L.<sup>21</sup> The free plasma concentrations of CAZ and AVI were 90% and 92% of the total plasma concentration, respectively.<sup>22,23</sup> PTA evaluation was performed across various dosing regimens and MICs in a cohort of 1000 simulated patients with differing renal function statuses. Considering the time-dependent antimicrobial properties of CAZ-AVI, our study further explored the impact of extended infusion times on PTA in critically ill patients. Achieving the PK/PD target was defined as exceeding 90% of patients meeting both CAZ and AVI targets ( $>90\%$  PTA).<sup>24</sup> From a pharmacoeconomic perspective, the utilization of lower drug doses that ensure the attainment of the target PTA is associated with reductions in healthcare costs and alleviates the financial burden on families.<sup>10</sup> Therefore, the optimal dosing regimen was defined as achieving the PK/PD target at the MIC breakpoint (MIC = 8 mg/L) while minimizing drug costs. We posit that reducing the dosage is feasible when the optimal regimens derived from our simulation result in a lower dosage than the recommended regimens in the instructions.

## Results

### Patients

A cohort of 45 patients, who contributed 91 plasma samples including 33 trough and 31 peak concentrations was enrolled in the PopPK analyses. Of these individuals, 29 patients with renal insufficiency (defined as CrCL  $< 90$  mL/min),<sup>25</sup> and 7 patients with ARC (defined as CrCL  $\geq 130$  mL/min).<sup>26</sup> The median age among the patients was 59 years (range: 18 to 94

years), with 22 patients above 60 years. During the treatment period, 15 patients received CRRT. Except in special circumstances, the blood flow rate, pre-replacement fluid flow rate, and post-replacement fluid flow rate were set to 160 mL/min, 2000 L/h, and 1000 L/h, respectively. The dosing regimen was tailored to the renal function of each patient, with an infusion time of 2 hours. A dosing regimen of 2.5g q8h was employed in 12 non-critically ill patients and 17 critically ill patients. The demographic and clinical characteristics of all patients are presented in Table 1.

**Table 1** Demographics and Clinical Characteristics<sup>a</sup>

Characteristic	All Patients
Gender (male/female), n	36 (80)/9 (20)
Age, years	59.0 (18.0–94.0)
Age group, years	
Age < 60	23 (51.1)
Age ≥ 60	22 (48.9)
Height, cm	170.0 (150.0–180.0)
Weight, kg	62.0 (35.0–80.0)
Continuous renal replacement therapy, n	15 (33.3)
Total bilirubin, μmol/L	13.4 (1.6–125.6)
Direct bilirubin, μmol/L	6.9 (0.4–79.8)
Total protein, g/L	59.6 (46.4–88.1)
Albumin, g/L	35.0 (26.1–53.7)
Alanine aminotransferase, U/L	22.0 (6.0–199.0)
Aspartate aminotransferase, U/L	27.0 (6.0–417.0)
Gamma-glutamyl transferase, U/L	56.0 (11.0–639.0)
Alkaline phosphatase, U/L	113.0 (26.0–523.0)
Serum creatinine, μmol/L	79.0 (17.0–377.0)
Creatinine clearance <sup>b</sup> , mL/min	71.3 (13.9–337.1)
Creatinine clearance group, n	
< 90	29 (64.4)
90–130	9 (20.0)
≥ 130	7 (15.6)
Disease severity status group <sup>c</sup> , n	
Critically ill patients	25 (55.6)
Non-critically ill patients	20 (44.4)
CAZ-AVI regimen (2-hour infusion), n	
Non-critically ill patients	20 (44.4)
1.25 g q8h	2 (4.4)
1.25 g q12h	3 (6.7)
1.25 g q24h	1 (2.2)
2.5 g q8h	12 (26.7)
2.5 g q12h	1 (2.2)
2.5 g q24h	1 (2.2)
Critically ill patients	25 (55.6)
1.25 g q8h	4 (8.9)
2.5 g q8h	17 (37.8)
2.5 g q12h	2 (4.4)
2.5 g q24h	2 (4.4)
Disease group, n	
Complicated intra-abdominal infections	5 (11.1)
Complicated urinary tract infections, including pyelonephritis	4 (8.9)
Hospital-acquired pneumonia, including ventilator-associated pneumonia	31 (68.9)
Bacteremia associated with these infections	5 (11.1)

(Continued)

Table 1 (Continued).

Characteristic	All Patients
Plasma drug concentrations at various sampling times <sup>d</sup>	
Ceftazidime, n (range, mg/L)	
0	33 (8.0–246.5)
1	5 (31.0–211.7)
2	31 (18.2–305.8)
3	4 (56.4–242.1)
4	3 (15.8–79.1)
5	4 (18.3–203.3)
6	2 (54.3–69.9)
7	5 (4.5–143.9)
8	3 (1.6–48.4)
12	1 (25.5)
Avibactam, n (range)	
0	33 (0.8–62.2)
1	5 (7.1–48.1)
2	31 (3.8–104.5)
3	4 (9.6–49.9)
4	3 (3.8–22.6)
5	4 (4.2–39.8)
6	2 (15.3–17.8)
7	5 (1.0–25.8)
8	3 (0.3–10.4)
12	1 (3.7)

**Notes:** <sup>a</sup>Data are expressed as median (range) or n (%). <sup>b</sup>CrCL calculated using the Cockcroft-Gault equation. <sup>c</sup>Disease severity group: APACHE II > 15 was defined as critically ill, and ≤ 15 as non-critically ill. <sup>d</sup>The sampling times represent the time of the blood sample collected relative to the initiation of drug administration. **Abbreviations:** q8h, q12h, and q24h administration every 8 h, 12 h and 24 h, respectively.

## PopPK Modeling

The evaluation of the one-compartment and two-compartment models showed a better fit for the former (CAZ:  $OFV_{\text{one-compartment}}$ : 963.6,  $OFV_{\text{two-compartment}}$ : 984.8; AVI:  $OFV_{\text{one-compartment}}$ : 688.7,  $OFV_{\text{two-compartment}}$ : 735.2). A proportional residual model was applied to both models to assess residual variability. CrCL was identified as a significant covariate in both models after the covariate screening of demographic and laboratory information. Incorporating CrCL into the final model significantly reduced the inter-individual variability in the CLs of CAZ and AVI, from 72.73% and 82.40% to 55.71% and 66.69%, respectively. The estimated parameters of the final models are shown in Tables 2 and 3. All fixed-effects parameters were estimated with high precision, with relative standard errors (RSEs) < 30%. The final PK model equations for CAZ were as follows:

$$CL(L/h) = 2.96 \times \frac{CrCL^{0.44}}{71.3} \times \exp(\eta_{CL}) \quad (1)$$

$$V(L) = 17.76 \times \exp(\eta_V) \quad (2)$$

where 2.96 is the typical value of CL, 17.76 is the typical value of V, 0.44 is the fixed parameter coefficient of CrCL,  $\eta$  is a random variable obeying a normal distribution with a mean of zero, and 71.3 is the median value of CrCL.

The final PK model equations for AVI were as follows:

$$CL(L/h) = 3.09 \times \frac{CrCL^{0.41}}{71.3} \times \exp(\eta_{CL}) \quad (3)$$

$$V(L) = 18.25 \times \exp(\eta_V) \quad (4)$$

**Table 2** Population Pharmacokinetic Model Estimates and Bootstrap Results for Ceftazidime

Parameter	Final Model		Bootstrap	
	Estimate (shrinkage%)	RSE (%)	Median	95% CI
tvCL (L/h)	2.96	11.40	2.92	2.29–3.58
tvV (L)	17.76	12.13	17.80	13.84–23
dCLdCrCL	0.44	27.66	0.44	0.18–0.71
Inter-individual variability				
$\omega^2$ CL	0.56 (5.74)	17.31	0.54	0.35–0.72
$\omega^2$ V	0.41 (19.00)	28.29	0.36	0.16–0.60
Residual variability				
Proportional error	0.30	20.19	0.30	0.17–0.41

**Abbreviations:** CL, clearance; V, volume of distribution; dCLdCrCL, fixed-parameter coefficient of creatinine clearance (CrCL) to CL; RSE, relative standard error; CI, confidence interval;  $\omega$ , interindividual variation.

**Table 3** Population Pharmacokinetic Model Estimates and Bootstrap Results for Avibactam

Parameter	Final Model		Bootstrap	
	Estimate (shrinkage%)	RSE (%)	Median	95% CI
tvCL (L/h)	3.09	12.79	3.09	2.38–4.00
tvV (L)	18.25	13.80	18.51	14.40–24.33
dCLdCrCL	0.41	29.08	0.44	0.17–0.69
Inter-individual variability				
$\omega^2$ CL	0.67(5.31)	17.38	0.65	0.22–0.73
$\omega^2$ V	0.51(16.39)	30.69	0.46	0.14–0.78
Residual variability				
Proportional error	0.32	19.62	0.31	0.20–0.44

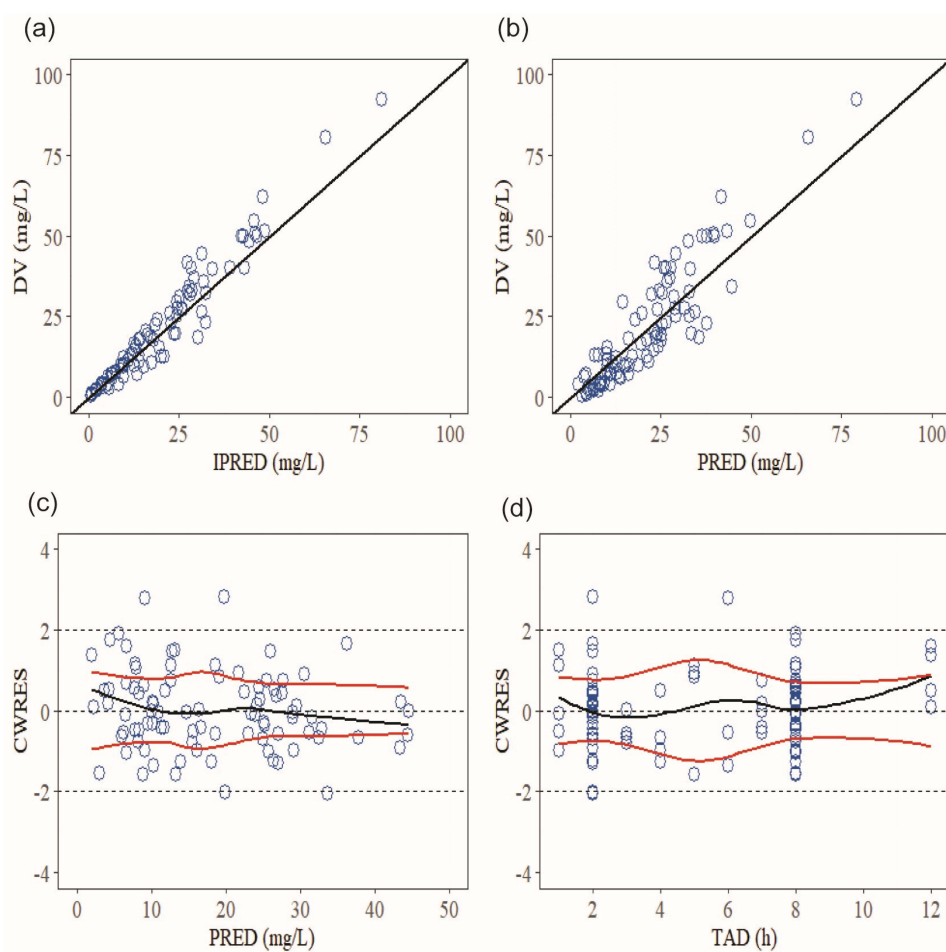
**Abbreviations:** CL, clearance; V, volume of distribution; dCLdCrCL, fixed-parameter coefficient of creatinine clearance (CrCL) to CL; RSE, relative standard error; CI, confidence interval;  $\omega$ , interindividual variation.

where 3.09 is the typical value of CL, 18.25 is the typical value of V, 0.41 is the fixed parameter coefficient of CrCL,  $\eta$  is a random variable obeying a normal distribution with a mean of zero, and 71.3 is the median value of CrCL.

## Model Evaluation

Figures 1 and 2 depict the GOF plots for the CAZ and AVI final models. The DV versus PRED and IPRED plots revealed a high degree of accuracy due to the good fit. Additionally, the CWRES versus PRED and TAD plots showed that the residuals were mainly distributed within  $-2$  to  $2$ , thereby manifesting the reliability of the models. Subsequently, Figure 3 shows the pc-VPC plots of CAZ and AVI concentrations versus TAD, confirming that the most of actual concentrations closely matched the 90% CIs of the simulated distribution, showing the predictive precision of the models.

The robustness of the CAZ and AVI models was further substantiated by Tables 2 and 3, which summarized the results of 1000 bootstrap simulations. The results show that all parameter estimates of the final model were within the 95% CIs obtained through the bootstrap method, and the deviation between the final model estimate and the bootstrap median parameter estimate was  $< 15\%$  for all parameters. These results conspicuously demonstrate the stability and predictive accuracy of models.



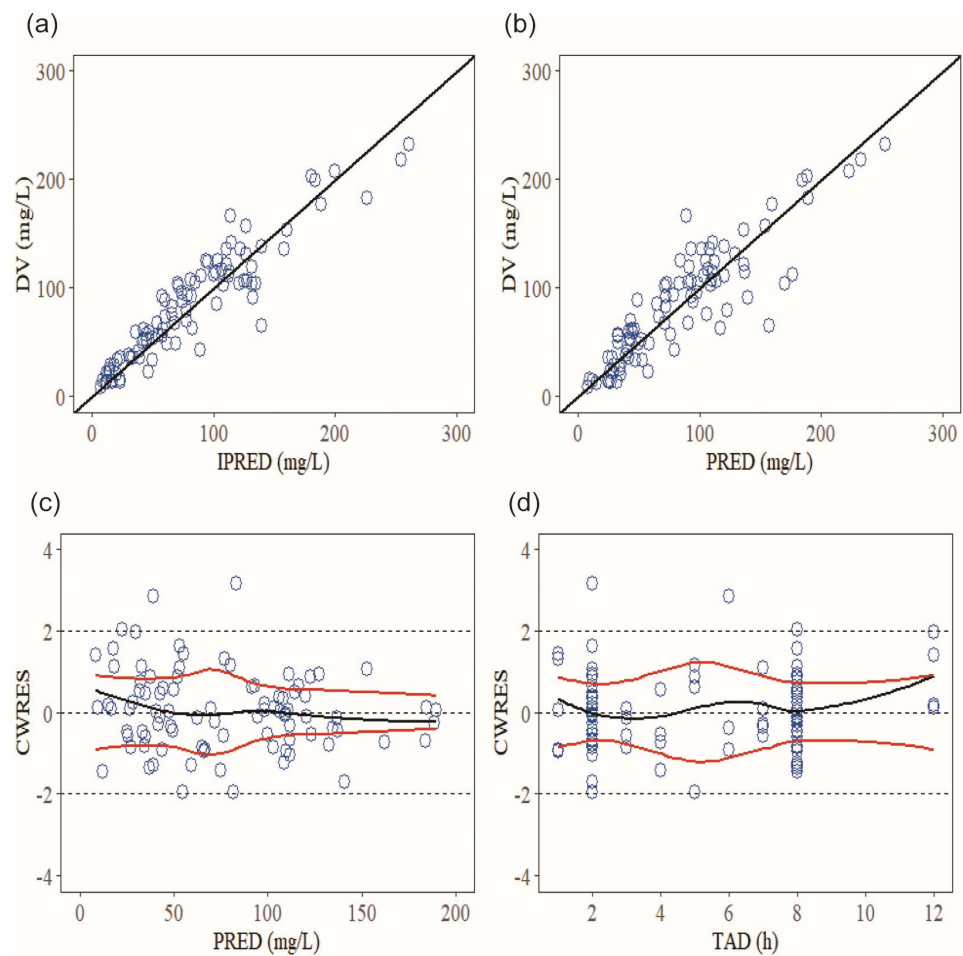
**Figure 1** GOF plots for the final ceftazidime model: (a) observed concentration (DV) versus individual population prediction (IPRED), (b) DV versus population prediction (PRED), (c) conditional weighted residuals (CWRES) versus PRED, (d) CWRES versus time after the last dose (TAD). The black line represents the locally weighted scatterplot smoothing (Loess) curve of the overall residual, and the red line represents the one-sided Loess curve of the residual.

## Monte Carlo Simulation

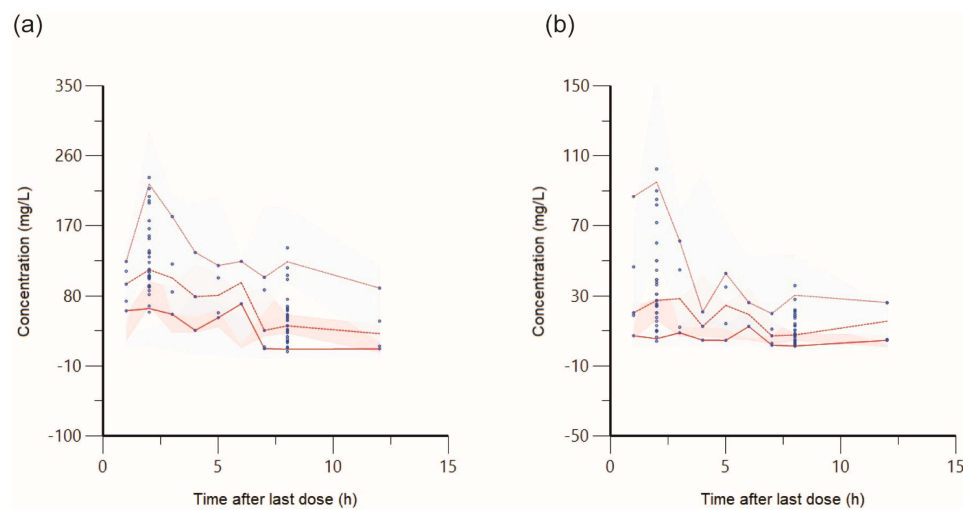
Figures 4 and 5 present the PTA results for PK/PD targets in non-critically ill and critically ill patients, respectively. The results revealed a negative correlation between PTA and renal function in both patient groups within the same regimen, underscoring the necessity for tailored dosage adjustments. The data indicated that extended infusion times were significantly linked to improved PTAs at high MIC levels for critically ill patients. Additionally, Table 4 compares the recommended regimens in the instructions with the optimal regimens derived from our simulation results for both patients under different renal functions. For non-critically ill patients, the optimal dosing regimen identified in our study matches the instructions only in patients with a CrCL of 16–30 mL/min and > 90 mL/min. An increase in the dosage specified in the instructions is required for patients with CrCL ≤ 15 mL/min. Conversely, a reduction in the indicated dose is required for those with a CrCL of 31–90 mL/min. For critically ill patients, the regimen recommended in the instruction fails to achieve the higher exposure required, suggesting an adjustment to increase the dosage. Moreover, in critically ill patients with a CrCL > 30 mL/min, extending the infusion time is essential.

## Discussion

This study developed a PopPK model of CAZ-AVI in Chinese patients, and innovatively proposed optimal dosing regimens for non-critically ill patients aiming for 50% $f_T > MIC$  target, as well as for critically ill patients with 100% $f_T > 4 \times MIC$  target in various renal functional statuses. Our findings revealed that the PopPK of CAZ-AVI is sufficiently characterized by a one-compartment model. CrCL was identified as a significant factor influencing the exposure of CAZ and AVI. Therefore, adjusting the CAZ-AVI dose based on renal function is imperative to ensure effective drug exposure.

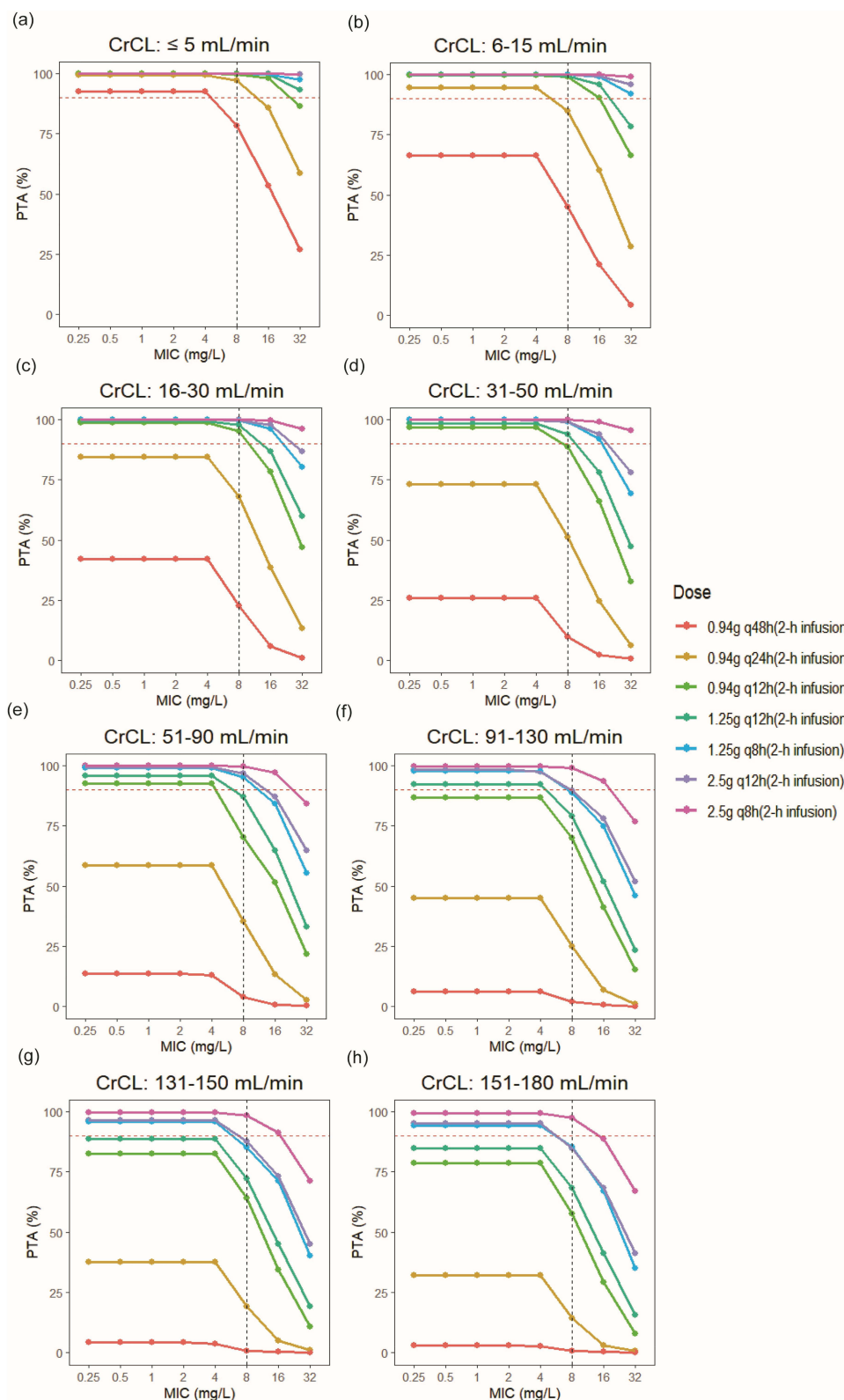


**Figure 2** GOF plots for the final avibactam model: (a) observed concentration (DV) versus individual population prediction (IPRED), (b) DV versus population prediction (PRED), (c) conditional weighted residuals (CWRES) versus PRED, (d) CWRES versus time after the last dose (TAD). The black line represents the locally weighted scatterplot smoothing (Loess) curve of the overall residual, and the red line represents the one-sided Loess curve of the residual.

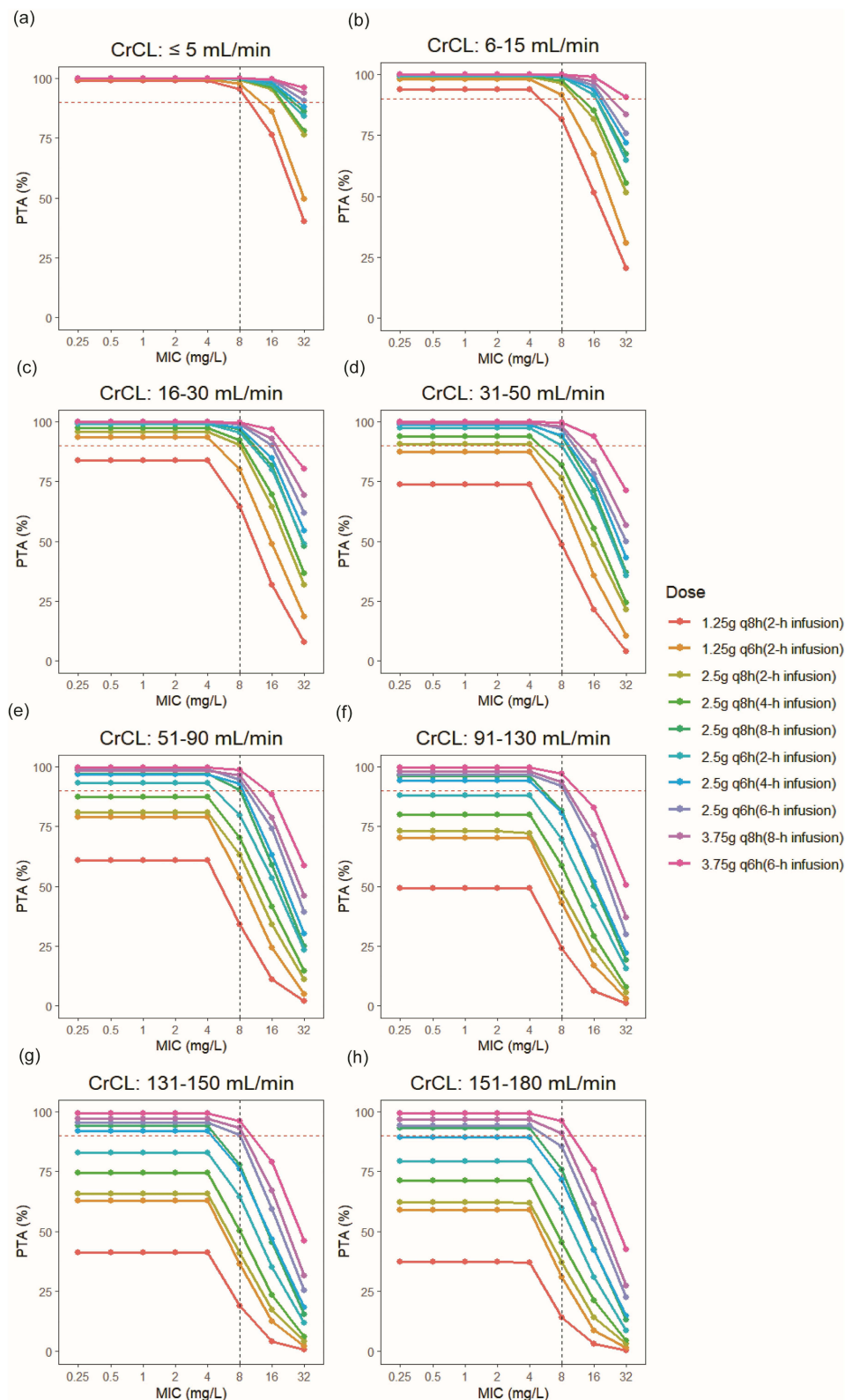


**Figure 3** Prediction-corrected visual predictive check of the simulation of the final ceftazidime (a) and avibactam (b) models. The blue circles indicate the prediction-corrected observed concentrations. The red lines indicate the 5th, 50th, and 95th percentiles of the prediction-corrected observed data. The shaded areas represent 90% prediction intervals of the prediction-corrected simulated data.





**Figure 4** Probability of target attainment (PTA) for the PK/PD target of the non-critically ill patient stratified by creatinine clearance (CrCL). The PTA target is  $50\%T > \text{MIC}$  for ceftazidime and  $50\%T > 1$  mg/L for avibactam. The horizontal dotted line represents the PTA of 90%. The vertical dotted line represents the minimum inhibitory concentration (MIC) of 8 mg/L. The Figure represents the PTA attainment rate of different dosing regimens in patients with CrCL  $\leq 5$  mL/min (a), CrCL 6–15 mL/min (b), CrCL 16–30 mL/min (c), CrCL 31–50 mL/min (d), CrCL 51–90 mL/min (e), CrCL 91–130 mL/min (f), CrCL 130–150 mL/min (g), and CrCL 150–180 mL/min (h), respectively.



**Figure 5** Probability of target attainment (PTA) for the PK/PD target of the critically ill patient stratified by creatinine clearance (CrCL). The PTA target is  $100\%fT > 4 \times \text{MIC}$  for ceftazidime and  $100\%fT > 4 \text{ mg/L}$  for avibactam. The horizontal dotted line represents the PTA of 90%. The vertical dotted line represents the minimum inhibitory concentration (MIC) of 8 mg/L. The Figure represents the PTA attainment rate of different dosing regimens in patients with CrCL  $\leq 5$  mL/min (a), CrCL 6–15 mL/min (b), CrCL 16–30 mL/min (c), CrCL 31–50 mL/min (d), CrCL 51–90 mL/min (e), CrCL 91–130 mL/min (f), CrCL 130–150 mL/min (g), and CrCL 150–180 mL/min (h), respectively.

**Table 4** Comparison Between the Recommended Regimens in the Instructions and the Recommended Regimen From the Simulation Results in Our Study <sup>a,b</sup>

CrCL (mL/min)	Non-Critically Ill Patients				Critically Ill Patients				
	Recommended Regimens in the Instructions		Recommended Regimens from the Simulation Results in our Study		Recommended Regimens in the Instructions		Recommended Regimens in the Instructions		
	Dosing regimens <sup>c</sup>	PTA (%)	Dosing regimens <sup>c</sup>	PTA (%)	Dosing regimens <sup>c</sup>	PTA (%)	Dosing regimens	Infusion time (h)	PTA (%)
≤5	0.94g q48h	78.3	0.94 g q24h	97.2	0.94g q48h	5.0	1.25 g q8h	2	95.4
6–15	0.94g q24h	84.8	0.94 g q12h	99.0	0.94g q24h	9.7	1.25 g q6h	2	91.8
16–30	0.94g q12h	95.1	0.94 g q12h	95.1	0.94g q12h	25.2	2.5 g q8h	2	90.5
31–50	1.25g q8h	99.1	1.25 g q12h	94.0	1.25g q8h	48.7	2.5 g q8h	8	94.0
51–90	2.5g q8h	99.6	1.25 g q8h	95.1	2.5g q8h	63.3	2.5 g q8h	8	90.4
91–130	2.5g q8h	99.0	2.5 g q8h	99.0	2.5g q8h	47.6	2.5 g q6h	6	91.9
131–150	2.5g q8h	98.4	2.5 g q8h	98.4	2.5g q8h	40.8	2.5 g q6h	6	90.5
151–180	2.5g q8h	97.6	2.5 g q8h	97.6	2.5g q8h	36.8	3.75 g q8h	8	96.1

**Notes:** <sup>a</sup>The green portion represents consistency between the recommended regimen and the instructions. The yellow portion represents a necessary reduction in dosage, while the blue portion represents requirements for either an increase in dosage or an extension of the infusion time. <sup>b</sup>CrCL calculated using the Cockcroft-Gault equation. <sup>c</sup>Infusion time for the dosing regimen is 2 hours.

**Abbreviations:** q6h, q8h, q12h, and q24h administration every 6, 8, 12, and 24 h, respectively.

For critically ill patients, an increase in dosage and an extension of infusion times were deemed necessary to achieve a higher PK/PD target.

In our study, the one-compartment model demonstrated better fitting compared to the two-compartment model. Consequently, the one-compartment model was selected to describe the PK parameters of CAZ and AVI. However, a two-compartment model for CAZ and AVI was successfully developed in a PopPK study of adult indications.<sup>8</sup> The discrepancy may be attributed to the smaller patient sample size in our study and the limited amount of plasma concentration data obtained, which were insufficient to build a more complex two-compartment model. Based on the final PopPK model in this study, the typical population values of CL for CAZ and AVI were 2.96 L/h and 3.09 L/h, respectively, and V for CAZ and AVI were 17.76 L and 18.25 L, respectively. These findings were consistent with the values of V from a PK study in healthy volunteers ( $V_{CAZ}$ : 19.98 L,  $V_{AVI}$ : 24.22 L). However, a notable difference was observed in the CL between our study and that study ( $CL_{CAZ}$ : 8.14 L/h,  $CL_{AVI}$ : 13.93 L/h),<sup>27</sup> with our findings being significantly lower. This lower CL could be largely explained by the inclusion of 64.4% of patients with renal insufficiency in our study population, highlighting the potential impact of renal function on drug clearance. Furthermore, our results aligned closely with a study focused on a population with an average eGFR of 50 mL/min ( $CL_{CAZ}$ : 3.2 L/h,  $CL_{AVI}$ : 4.9 L/h).<sup>28</sup> Although incorporating CrCL into the final models significantly reduced the inter-individual variability of CL, unexplained inter-individual variability remained in both models. Therefore, a larger-scale PopPK study incorporating more comprehensive covariates is warranted.

CAZ and AVI are excreted primarily by the kidneys.<sup>29</sup> Therefore, renal functional status is the critical determinant of the CL of both drugs. The covariate analysis results showed that CrCL as a replacement indicator of renal function was the sole significant covariate influencing the CL of CAZ and AVI, which is consistent with previously reported studies.<sup>6–9</sup> Despite including 33.3% of patients undergoing CRRT in our study, this factor exhibited no substantial effect on the PK of either drug. Some studies suggest that CRRT affects CL only in patients with severely impaired renal function (CrCL <10 mL/min).<sup>30–32</sup> Since the patients with CRRT in our study had residual renal function (median CrCL for patients receiving CRRT: 69.3 mL/min), CRRT was found to be nonrelevant to CL. Li et al<sup>33</sup> also supported the standard dosing

regimen in patients receiving CRRT. However, given the small sample size of CRRT patients in our study, further research is needed to ascertain the extent to which CRRT affects the PK of both drugs.

Despite covariate analysis indicating that APACHE II scores do not significantly impact the PK of CAZ-AVI, research by Póvoa et al points out that alterations in blood flow distribution, plasma protein levels, and extracellular fluid volume among critically ill patients may influence the PK of  $\beta$ -lactam antibiotics.<sup>34</sup> These alterations may result in standard dosages insufficient for achieving therapeutic drug concentrations.<sup>35</sup> Moreover, the prevalence of deep-seated or multidrug-resistant infections in critically ill patients requires increased drug exposure to effectively manage such infections or minimize the development of resistance. Therefore, for critically ill patients, there is a compelling need to adjust the PK/PD targets from those for non-critically ill patients ( $50\%fT > MIC$  for CAZ and  $50\%fT > 1 \text{ mg/L}$  for AVI) to more stringent targets of  $100\%fT > 4 \times MIC$  for CAZ and  $100\%fT > 4 \text{ mg/L}$  for AVI.

In recent years, personalized medication has received increasing attention, emphasizing the adjustment of dosing regimens based on individual clinical conditions. The instruction supports using 2.5 g q8h (2-h infusion) as the standard dosing regimen for CAZ-AVI, with dose adjustment required only for patients with  $CrCL \leq 50 \text{ mL/min}$ ,<sup>2</sup> as shown in Table 4. However, studies have questioned these regimens. For instance, Teng et al suggested that patients with ARC may require a higher daily dose of CAZ-AVI than the standard dose.<sup>36</sup> A multicenter observational study demonstrated a significant correlation between the adjustments of CAZ-AVI dosages and bacterial clearance rates.<sup>37</sup> Also, inappropriate dosing may lead to drug accumulation in patients with renal insufficiency and sub-therapeutic exposures in patients with ARC.<sup>36</sup> In addition, the different PK/PD targets of CAZ and AVI in non-critically ill and critically ill patients also dictate differences in optimal dosage regimens. Therefore, it is essential to tailor dosage regimens to individual clinical scenarios.

For non-critically ill patients, we found that the dosing regimens of instruction may be inadequate for patients with a  $CrCL \leq 15 \text{ mL/min}$ . In addition, our simulation results suggested a more cost-effective dosing regimen for patients with a  $CrCL$  of 31–90 mL/min compared to the instruction. In patients with  $CrCL \leq 15 \text{ mL/min}$ , the regimen based on instruction failed to achieve a PTA of  $> 90\%$ , indicating a potential risk of treatment failure. Our simulations suggest a regimen of 0.94 g q24h (2-h infusion) for patients with a  $CrCL \leq 5 \text{ mL/min}$ , and a regimen of 0.94 g q12h (2-h infusion) for patients with a  $CrCL$  of 6–15 mL/min. In patients with a  $CrCL$  of 31–50 mL/min, our simulation results showed that a regimen of 1.25 g q12h (2-h infusion) effectively achieved  $> 90\%$  PTA, contrasting with the instruction advocating the regimen of 1.25 g q8h (2-h infusion). Additionally, it was determined that the regimen of 1.25 g q8h (2-h infusion) was sufficient for patients with a  $CrCL$  of 51–90 mL/min, deviating from the recommended regimen of 2.5 g q8h (2-h infusion) from the instruction. These findings align with two dosing evaluation studies in China,<sup>10,38</sup> and bolster the argument for a cost-effective dosing regimen for patients with a  $CrCL$  of 31–90 mL/min. It should be noted that the number of patients included in our study was relatively limited, necessitating a larger sample size to validate our simulation findings. Nonetheless, our study offers a detailed and innovative perspective on tailoring CAZ-AVI treatment for non-critical patients with renal insufficiency.

For critically ill patients, we found that the PTA of the recommended regimens in the instructions was far below 90%, significantly increasing the risk of treatment failure and the development of resistance. A study conducted on the continuous infusion of CAZ-AVI in critically ill patients indicated that extending the infusion time offers more benefits than adjusting the dosing regimen based on renal function in these patients.<sup>39</sup> Similarly, our simulation results suggested that extended infusion should be considered in critically ill patients with  $CrCL > 30 \text{ mL/min}$ . A key requirement for extended infusion is adequate drug stability after dilution. For CAZ-AVI, the reported stability extends up to 24 h at 2 to 8°C and up to 12 h below 25°C.<sup>2</sup> Gatti et al<sup>40</sup> and Tumbarello et al<sup>41</sup> noted that extended infusion of CAZ-AVI was linked to higher clinical cure rates and lower mortalities. Furthermore, a study involving 10 patients with critical kidney disease who received a continuous infusion of CAZ-AVI demonstrated that none experienced CAZ-AVI-related adverse events during treatment, which indicated that extended infusion may not worsen renal dysfunction.<sup>40</sup> Therefore, extended infusion of CAZ-AVI could be a feasible and desirable dosing strategy for critically ill patients. Han et al<sup>42</sup> advocate for the routine use of a 4–6h infusion regime in critically ill patients. It must be emphasized that extended infusion time poses certain operational difficulties in real-world settings, particularly for critically ill patients with complex conditions and multiple medications. In such patients, extended infusion times remain a challenge. To address this, multi-channel infusion may be a viable solution.

Our study acknowledges several limitations that merit attention. Firstly, the scope of this research is limited to a single-center with a relatively small sample size which restricted our ability to develop a more complex two-compartment model, and 64.4% of the patients suffered from renal insufficiency which limited the generalizability of our results. Consequently, larger-sample studies are needed. Secondly, the lack of MIC data for the pathogens isolated from the patients limited our capacity to link the PTA results of our study with the tangible clinical outcomes observed in patients. Thirdly, there may have been some unexamined covariates, which prevented us from fully capturing inter-individual variability among patients. Therefore, more comprehensive covariate studies are needed. Fourthly, it is crucial to emphasize that the CrCL-based dose adjustments were tailored for patients with stable renal function. It has been shown that a significant portion of patients with acute kidney injury on admission experienced a reversal of their condition within 48 hours.<sup>43</sup> In such cases, recalibrating doses based on initial CrCL may pose a risk for adverse outcomes. Consequently, implementing therapeutic drug monitoring coupled with strict renal function surveillance is advocated for these patients. To improve the clinical implementation of TDM, it is crucial to strengthen the collaboration within the medical team, including clinical pharmacists. Additionally, establishing more monitoring centers or offering remote monitoring services in regions with limited resources can improve the accessibility of TDM.<sup>44</sup>

## Conclusion

In conclusion, this study successfully developed a PopPK model of CAZ-AVI in Chinese patients. It was determined that CrCL significantly influences the CL of CAZ-AVI. Monte Carlo simulation indicated that the recommended regimens in the instructions have limitations, necessitating adjustments to the dosing regimen based on the severity of the disease and renal functional status. Our study provides an innovative perspective on the individualized dosing of CAZ-AVI in non-critically ill patients with renal insufficiency. Additionally, extending the infusion times is necessary for critically ill patients. Our simulation results provide a reference for the clinical application of CAZ-AVI.

## Abbreviations

ALB, Albumin; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; APACHE II, Acute physiology and chronic health evaluation II; ARC, Augmented renal function; AST, Aspartate aminotransferase; AVI, Avibactam; CAZ, Ceftazidime; CAZ-AVI, Ceftazidime-avibactam; CI, Confidence interval; CRRT, Continuous renal replacement therapy; CL, Clearance; CrCL, Creatinine clearance;  $C_T$ , The threshold concentration; CWRES, Conditional weighted residuals; DBIL, Direct bilirubin; DV, Observed concentration; GGT, Gamma-glutamyl transferase; GOF, Goodness-of-fit; IPRED, Individual population prediction; MDR, Multidrug-resistant; MIC, The minimum inhibitory concentration; OFV, Objective function value; pc-VPC, Prediction-corrected visual predictive check; PD, Pharmacodynamic; PK, Pharmacokinetic; PopPK, Population pharmacokinetics; PRED, Population prediction; PTA, Probability of target attainment; SCR, Serum creatinine; TAD, Time after the last dose; TBIL, Total bilirubin; TP, Total protein; V, Volume of distribution.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval

This work was supported by the Fujian Medical University Union Hospital Research and Ethics Committee (No. 2019KJCX034). The study was conducted according to the Declaration of Helsinki after informing all patients in our study of the study objectives and providing written consent to participate in this study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or 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 report no conflicts of interest in this work.

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