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# Ceftazidime-avibactam (CAZ-AVI) pharmacokinetics in critically ill patients undergoing continuous venovenous hemodiafiltration (CVVHDF)

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ABSTRACT

*Purpose:* To investigate the pharmacokinetics (PK) of ceftazidime-avibactam (CAZ-AVI) in critically ill patients undergoing continuous venovenous hemodiafiltration (CVVHDF), and compare with a general phase III trial population.

*Methods:* A prospective PK study was conducted in critically ill patients who received CVVHDF for acute kidney injury, treated with CAZ-AVI (1000/250 mg or 2000/500 mg q8h). Plasma and CVVHDF-circuit samples were collected to determine CAZ-AVI concentrations. Individual PK parameters at steady-state were estimated using non-compartmental analysis. For visual comparison, plasma concentrations from CVVHDF patients were overlaid with simulated data from patients not receiving CVVHDF based on previously developed population PK models.

*Results:* A total of 35 plasma samples and 16 CVVHDF-circuit samples were obtained from four patients, with two patients sampled on two separate occasions. Median total clearance and volume of distribution were 4.54 L/h and 73.2 L for CAZ and 10.5 L/h and 102 L for AVI, respectively. Median contribution of CVVHDF to total clearance was 19.8% for CAZ and 5.3% for AVI. Observed CAZ-AVI PK profiles were generally within the 90% confidence interval of model predictions, but the observed concentrations were notably lower early (0–2 h) and higher later (4–8 h) in the dosing interval, suggesting a higher volume of distribution.

*Conclusions:* These results suggest that the CAZ-AVI dose regimens used in this study can be applicable in critically ill patients undergoing CVVHDF, despite the different shape of the PK profiles observed in this population. Further research with a larger patient cohort is warranted to validate and refine these findings.



Take home message

PK of CAZ-AVI in critically ill patients undergoing CVVHDF demonstrates divergent profiles compared to a general phase III trial population not on CVVHDF. Despite the differences, the studied dose regimens (1000/250 mg q8h or 2000/500 mg q8h) appear suitable for CAZ-AVI therapy in this setting.

## 1. Introduction

Ceftazidime-avibactam (CAZ-AVI) is a $\beta$-lactam/$\beta$-lactamase inhibitor combination, which has been commercially available since 2015 in the European Union and the United States for the treatment of severe Gram-negative bacterial infections, particularly

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those with limited therapeutic options. Given the predominantly renal clearance of CAZ and AVI, dose recommendations are tailored according to the patient's renal function, as outlined in the drug label. However, the management of dosing in patients undergoing renal replacement therapy (RRT) presents unique challenges. Drug removal is influenced by multiple factors, including the extent of protein binding, residual renal function, and the characteristics of the RRT technique used. These factors vary depending on whether the procedure is continuous or intermittent, the membranes or filters used, the blood, ultrafiltrate, and dialysate flow rates, and whether the mechanisms of drug removal is through convection, diffusion or a combination of both. Maintaining optimal therapeutic drug concentrations is essential, as subtherapeutic levels risk reducing efficacy and potentially lead to treatment failure and/or development of antimicrobial resistance, while excessive dosing can increase the risk of drug toxicities.

Despite the increasing use of RRT, notably continuous venovenous hemodiafiltration (CVVHDF) in critically ill patients, data on the pharmacokinetics (PK) of CAZ-AVI during these interventions remains limited. Current summary of products characteristics (SmPC) focus on hemodialysis, but do not address hemodiafiltration [1,2]. Case studies by Wenzler et al. (continuous venovenous hemofiltration, CVVH), and Soukup and colleagues (CVVHDF) provide valuable insights, although their findings are limited by small sample sizes and varying RRT techniques [3,4]. Zhang et al. explored both intermittent and continuous hemodialysis [5], but gaps persist in understanding CAZ-AVI PK during CVVHDF due to the limited scope and generalizability of these studies.

Two clinical studies on a limited number of patients studied PK of CAZ-AVI during CVVHDF: those conducted by Shields et al. [6,7] and by Gatti et al. [8]. Shields and colleagues focused on intermittent infusion of CAZ-AVI in a cohort of critically ill patients undergoing CVVHDF (n=6), while Gatti and team explored continuous infusion in a slightly larger cohort of similar patients (n=8). Although both studies provided important information about the plasma PK of CAZ-AVI during CVVHDF, neither investigated drug removal by CVVHDF. Consequently, further investigations specifically tailored to this RRT technique are needed to fully understand CAZ-AVI PK during CVVHDF.

The aim of this study was to characterize the PK of both CAZ and AVI administered as intermittent infusions in critically ill patients undergoing CVVHDF. Our findings were compared with simulated PK data from a general patient population included in previously published phase III trials (ClinicalTrials.gov identifier: NCT01808092).

## 2. Materials and methods

### 2.1. Subjects

Patients admitted to the intensive care unit of Hygeia General Hospital in Athens, Greece, between February and November 2020 were eligible for inclusion in the study if they met the following criteria: (i) patient is ≥18 y of age; (ii) receiving treatment with CAZ-AVI as part of standard care due to a probable or microbiologically documented infection by extensively drug-resistant Gram-negative bacteria; and (iii) CVVHDF as RRT for acute kidney injury. Patients with a known hypersensitivity to CAZ-AVI, or who required the use of conventional hemodialysis rather than CVVHDF, were excluded from the study. Data collected for each patient included demographics, primary diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score, source of infection, serum albumin, serum hemoglobin, serum sodium, fluid balance, serum creatinine, and creatinine clearance (CrCL). CrCL was measured using a 4-h urine collection and calculated as follows [9]:

$$CrCL_{4h}\left(mL/min\right) = \frac{creatinine_{urine}\left(mg/dL\right)}{creatinine_{serum}\left(mg/dL\right)} \times \frac{urine\ volume\ (mL)}{time\ \left(min\right)} \quad (1)$$

The study protocol received ethics approval from the local ethics committee (registration number: 627/26-09-2018), and all patients (or their legal representatives) provided written informed consent. The handling of samples and data was conducted under the number 2023-05104-01. The study was conducted in accordance with good clinical practice guidelines.

### 2.2. Renal replacement therapy specifications

Patients underwent CVVHDF therapy for a minimum of 72 h before PK sampling. CVVHDF was conducted using a high-flux hemofilter (AN69ST) with a membrane surface area of 1.5 $m^2$ (ST150 SET predilution filter set; BAXTER, Guyancourt, France). Hemosol B0 solution (Gambro Lundia AB, Lund, Sweden) served as the substitution and dialysate fluid. Blood flow rate was set at 100–150 mL/min, dialysate flow rate at 1000 mL/h, ultrafiltrate rate at 1000–1500 mL/h and a CVVHDF dose intensity of 25–30 mL/kg/h. Net removal rate ranged from 0 to 250 mL/h over the dosing interval, with maximum transmembrane pressures of 450 mmHg.

### 2.3. Drug administration

CAZ-AVI (2000/500 mg, Zavicefta, Pfizer) diluted in 100 mL of NS 0.9% was administered as a 2h-infusion every 8 h (q8h). The dosage could be adjusted to 1000/250 mg at the discretion of the physician.

### 2.4. Sampling

The study employed two distinct sampling schemes: one for venous blood and another for the CVVHDF circuit. Venous blood were collected at different time points over the 8-h dosing interval, including at infusion start and hourly intervals thereafter, with a final trough sample obtained 15-20 min before the next infusion.

For the CVVHDF-circuit, three samples were collected simultaneously once per dosing interval: (1) a prefiltration blood sample, taken from the intravenous tubing connecting the patient to the CVVHDF machine; (2) a postfiltration blood sample, taken from a port on the blood return line; and (3) an ultrafiltrate sample, collected from the ultrafiltrate and spent dialysate container.

All blood samples (venous, pre- and postfiltration) were collected in sterile tubes containing EDTA as an anticoagulant, centrifuged at 2,000 x g for 10 min, and the resulting plasma was frozen at -80°C within 30 min of collection for stability purposes. Ultrafiltrate samples were also frozen at -80°C until assayed.

### 2.5. Analytical method for simultaneous determination of CAZ and AVI in human plasma and CVVHDF-circuit samples

Total CAZ and AVI concentrations in plasma and CVVHDF-circuit samples were simultaneously quantified using Acquity ultra-performance liquid chromatography (UPLC) coupled with Xevo TQ-S Micro triple quadrupole mass spectrometer (MS/MS) (Waters Corporation, Milford, MA, USA). The method for the assessment of plasma concentrations was developed based on previously published protocols with modifications [10–12], while the method for measurement of CAZ and AVI in CVVHDF-circuit samples was developed *de novo*. The bioanalytical method was validated according to the FDA guidance [13] and is described in detail

in Supplementary Appendix A. Additionally, protein binding characterization of CAZ and AVI in plasma samples was performed using the equilibrium dialysis technique, as detailed in Supplementary Appendix B.

### 2.6. Pharmacokinetic analysis

Prior to data analysis, total plasma concentrations of CAZ and AVI were dose-normalized to allow the identification of outlying data points. Individual PK parameters at assumed steady-state (>4 half-lives) for both drugs were estimated from total plasma concentrations using non-compartmental analysis (NCA). The AUC was integrated with the linear-up log-down method. NCA was performed using PKanalix 2023R1 (Lixoft SAS, Antony, France).

Unbound concentrations of CAZ and AVI were derived by correcting total plasma concentrations using the median fraction unbound (fu) values computed for the current study population, as determined from equilibrium dialysis (described in Supplementary Appendix B). These median fu values were applied across all patients and for all datasets (observed and simulated) in the analysis. The correction was applied using the following equation:

$$C_{unbound} = C_{total} \times fu \quad (2)$$

Plots were generated to compare unbound concentrations across three datasets: (i) unbound CAZ and AVI plasma PK observations from the patients in the current study, (ii) digitized CAZ-AVI plasma PK observations from similar patients (i.e., critically ill patients undergoing CVVHDF who received intermittent CAZ-AVI dosing) from the study by Shields et al. [6,7], and (iii) unbound CAZ-AVI concentration-time profiles simulated using CAZ and AVI population PK (PopPK) models from Li et al. [14], reflecting a typical phase III patient population, i.e., for pneumonia patients not receiving RRT. For the simulated population, a virtual cohort of 10,000 individuals was generated, assuming a normal distribution of CrCL values. For the cohort receiving CAZ-AVI 2000/500 mg q8h, CrCL values were set to a mean of 100 mL/min with a standard deviation of 12.5 mL/min. Conversely, for the cohort receiving 1000/250 mg q8h, a mean of 40 mL/min and a standard deviation of 2.8 mL/min were selected, with CrCL estimated using the Cockcroft-Gault equation [15]. Other covariates in the PopPK models were set to median values (Caucasian male patients with a weight of 75 kg, and age of 45 y). Unbound concentrations were derived using plasma protein binding values determined by the equilibrium dialysis technique. Simulations and visualization were done in R, using ggplot2 and mrgsolve packages [16].

Finally, parameters related to drug removal by the CVVHDF machine were calculated, using drug concentrations in CVVHDF-circuit samples. The saturation coefficients (SA, fraction of a solute removed by the filtration process) for CAZ and AVI were computed as:

$$SA = \frac{2 \times C_{ULTRA}}{C_{PRE} + C_{POST}} \quad (3)$$

where $C_{ULTRA}$, $C_{PRE}$ and $C_{POST}$ are the drug total concentrations (mg/L) in the ultrafiltrate and spent dialysate container, the prefiltration blood, and the postfiltration blood, respectively [17]. CAZ and AVI clearance across the CVVHDF membrane ($CL_{CVVHDF}$; L/h) was calculated as:

$$CL_{CVVHDF} = (Q_{UF} + Q_D) \times SA \quad (4)$$

where $Q_{UF}$ is the ultrafiltrate flow rate (L/h) and $Q_D$ the dialysate flow rate. The percentage of total drug clearance at steady-state ($CL_{SS}$) contributed by $CL_{CVVHDF}$ was calculated by the formula ($CL_{CVVHDF}/CL_{SS}$) × 100.

**Table 1**
Demographics and biological characteristics of patients included in the study.

| Variable | n (%) | Mean (SD) | Median | Range |
|---|---|---|---|---|
| Male | 4 (100) | | | |
| Age (year) | | 53.2 (14.3) | 45.5 | 44–78 |
| Ideal body weight (kg) | | 77.5 (8.29) | 75.0 | 70–90 |
| Serum creatinine (mg/dL) | | 1.02 (0.32) | 1.10 | 0.40–1.30 |
| $CrCL_{4h}$ (mL/min) | | 9.17 (7.31) | 10.0 | 5–20 |
| Serum albumin (g/dL) | | 2.78 (0.46) | 2.70 | 2.2–5.9 |
| Serum Hb (g/dL) | | 7.60 (1.35) | 7.90 | 5.0–8.1 |
| Daily fluid balance (L) | | 0.49 (1.31) | 0.45 | −1.7 to 2.4 |
| APACHE II score | | 15.6 (4.50) | 17 | 16–20 |

### 2.7. Pharmacokinetic-Pharmacodynamic (PK/PD) target attainment

To evaluate target attainment in patients receiving CAZ-AVI, a joint PK/PD target was defined based on the EUCAST guidelines [18]. CAZ efficacy was assessed using the percentage of time that the unbound concentration remained above a minimum inhibitory concentration ($fT>MIC$), with a target of 100% $fT>MIC$ at 8 mg/L, i.e., the breakpoint for CAZ-AVI. AVI efficacy was determined by the percentage of time with unbound concentration remaining above a threshold concentration ($fT>C_T$), with a target of 100% $fT>C_T$ at 1 mg/L [18].

## 3. Results

### 3.1. Demographic and clinical data

A total of 35 plasma samples and 16 circuit samples were obtained from four critically ill patients undergoing CVVHDF. Two patients were sampled after more than one dose administration, i.e., at multiple occasions. All patients required mechanical ventilation and were administered vasopressors. A summary of the patients' demographic and biological characteristics can be found in Table 1.

One patient received CAZ-AVI for the empirical treatment of ventilator-associated pneumonia, one patient for a bacteraemia due to carbapenemase-producing *Klebsiella pneumoniae*, another for a bacteraemia due to *Pseudomonas aeruginosa*, which later evolved into septic shock, and the fourth patient for sepsis of suspected bacterial origin. All clinical isolates were fully susceptible to CAZ-AVI, with minimum inhibitory concentration (MIC) values well below 8 mg/L. CAZ-AVI was co-administered with intravenous colistin methanesulfonate in all four patients.

### 3.2. Pharmacokinetic analysis

Three plasma samples exhibiting notably lower concentrations than expected (based on the observed trends) were identified as outliers and excluded from the analysis (see Supplementary Appendix C for details). Median PK parameters for the two drugs calculated using NCA are given in Table 2.

The observed plasma concentrations of CAZ-AVI in patients from the current study were within the anticipated range based on model-predictions for a phase III population not receiving RRT. In patients undergoing CVVHDF, flatter PK profiles were observed with smaller differences between peak and trough concentrations (Fig. 1 and Fig. C.1). The median (range) unbound fractions measured in plasma were 1.07 (0.80-1.14) for CAZ, and 0.73 (0.55-0.92) for AVI.

Median (range) SA during CVHHDF for CAZ and AVI were estimated to be approximately 0.41 (0.26-0.49) and 0.23 (0.14-0.28), respectively. Median (range) $CL_{CVVHDF}$ was 0.87 (0.57-1.06) L/h for CAZ and 0.50 (0.29-0.61) L/h for AVI. Approximately 19.8% and

**Table 2**
PK parameters at steady-state for CAZ and AVI estimated by NCA and stratified by dose group.

| Drug | Parameter | 2000/500 mg q8h as 2h-inf.[1] | | 1000/250 mg q8h as 2h-inf.[2] | |
|---|---|---|---|---|---|
| | | Observed (n=4) | Simulated (n=10,000) | Observed (n=2) | Simulated (n=10,000) |
| CAZ | $C_{max}$ (mg/L) | 70.2 [40.1–77.2] | 69.5 [35.8–137] | 33.9 [31.6–36.2] | 58.7 [30.9–118] |
| | $C_{min}$ (mg/L) | 41.0 [30.3–59.0] | 12.0 [4.33–54.3] | 18.5 [15.9–21.1] | 26.7 [13.1–71.3] |
| | $t_{1/2}$ (h) | 12.0 [8.05–28.1] | 2.55 [2.02–8.77] | 9.04 [6.38–11.7] | 5.97 [5.09–13.8] |
| | $CL_{SS}$ (L/h) | 4.61 [4.00–7.32] | 7.18 [3.04–15.3] | 4.54 [4.34–4.74] | 3.05 [1.41–5.93] |
| | $V_{SS}$ (L) | 107 [53.1–173] | 24.6 [33.2–43.3] | 58.2 [37.4–79.1] | 25.6 [26.6–42.8] |
| | $AUC_{tau}$ (mg·h/L) | 440 [278–500] | 279 [130–657] | 220 [211–230] | 328 [168–709] |
| AVI | $C_{max}$ (mg/L) | 7.76 [4.13–8.55] | 13.3 [4.77–36.8] | 3.71 [3.50–3.92] | 10.3 [3.66–29.3] |
| | $C_{min}$ (mg/L) | 3.99 [2.80–6.07] | 1.19 [0.38–7.07] | 1.72 [1.65–1.80] | 3.05 [1.17–10.6] |
| | $t_{1/2}$ (h) | 7.05 [4.21–30.0] | 2.02 [1.54–4.75] | 5.81 [4.82–6.81] | 3.76 [3.57–6.89] |
| | $CL_{SS}$ (L/h) | 10.3 [9.29–18.6] | 11.4 [3.71–29.8] | 11.0 [10.2–11.9] | 5.13 [1.80–13.7] |
| | $V_{SS}$ (L) | 177 [65.0–432] | 27.8 [18.5–68.5] | 97.0 [73.6–120] | 26.5 [15.5–70.2] |
| | $AUC_{tau}$ (mg·h/L) | 48.9 [28.2–53.8] | 43.9 [16.8–134] | 22.7 [21.0–24.5] | 48.7 [18.3–138] |

Reported values are presented as median [90% confidence interval].
1: Standard of care dose regimen; 2: Recommended dose regimen for adults with estimated CrCL ≤ 50 mL/min. "Observed" data correspond to CAZ and AVI total plasma concentrations from patients in this study; "Simulated" data correspond to median [90% CI] CAZ and AVI PopPK profiles for a population of pneumonia patients (n=10,000, Caucasian male with a weight of 75 kg, age of 45 y, and normal distribution of CrCL values). Cmax: Maximum plasma concentration; Cmin: Minimum plasma concentration; t1/2: Half-life; CLSS: Clearance at steady-state; VSS: Volume of distribution at steady-state; AUCtau: Area under the concentration-time curve for a dosing interval.

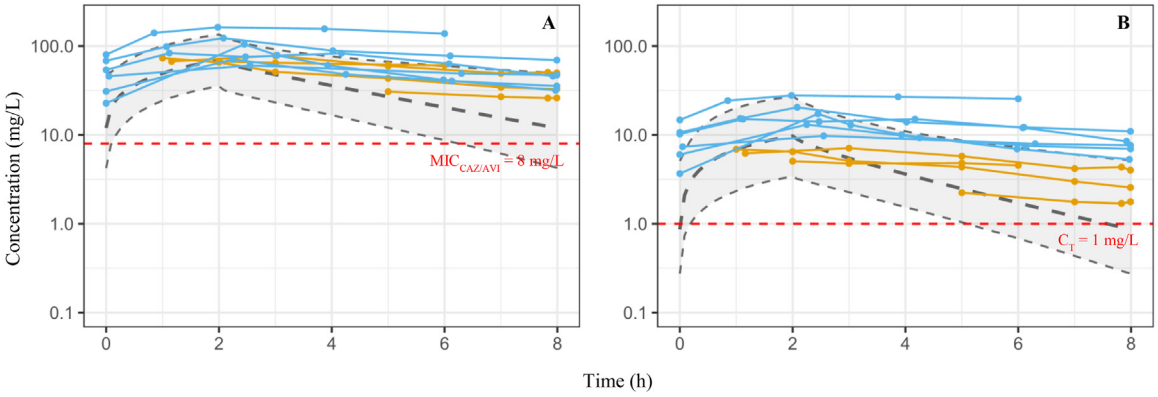


**Fig. 1.** Visual comparison plots for CAZ (A) and AVI (B) at doses of 2000 mg and 500 mg, respectively, administered every 8 h as a 2 h-infusion. In orange: unbound plasma drug concentrations from patients in the current study; in blue: unbound plasma drug concentrations for the six patients from the study by Shields et al. In grey: unbound concentration-time profiles simulated for typical pneumonia patients receiving CAZ-AVI 2000/500 mg q8h as 2 h-infusion, using PopPK models from Li et al. [14]. Grey dashed lines correspond to the 5th, median and 95th percentiles of simulated concentration-time profiles.

5.32% of the median $CL_{SS}$ were contributed by membrane clearance during CVVHDF for CAZ and AVI, respectively.

### 3.3. Pharmacodynamic analysis

The lowest unbound trough concentrations observed for CAZ and AVI were 15.6 and 1.02 mg/L, respectively. Consequently, all patients achieved the joint PK/PD target for CAZ-AVI (100% $fT>$MIC of 8 mg/L and 100% $fT>C_T$ of 1 mg/L).

## 4. Discussion

This study presents an in-depth analysis of the PK of CAZ-AVI in critically ill patients undergoing CVVHDF. We evaluated two intermittent dose regimens (2000/500 mg or 1000/250 mg given every 8 h as 2h-infusion) while also assessing the plasma protein binding of both drugs and the extent of drug removal attributable to CVVHDF. Furthermore, PK profiles in CVVHDF patients were compared with simulated data from a general patient population included in previously published phase III trials [14].

A notable strength of this study lies in its characterization of drug removal facilitated by the CVVHDF apparatus. Analysing CAZ-AVI removal provided valuable insights into the PK of critically ill patients undergoing this specific modality of RRT, thereby enhancing our comprehension of the role played by the CVVHDF machine in the overall clearance of medications, which has direct implications for clinical decision-making.

Previous studies have explored the PK of CAZ-AVI in patients receiving either continuous [8] or intermittent infusion [6,7], some of which were partially used herein for graphical comparison. A similar shape of the concentration-time profiles was observed for patients in the study by Shields et al., although concentrations were typically higher in those patients. The median $CL_{SS}$ for CAZ in our study (4.54 L/h) was similar to what was reported by Shields and colleagues, where patients received CAZ-AVI intermittently (4.0 L/h). However, the median $CL_{SS}$ for AVI in our study was more than twice as high (10.5 L/h vs. 4.2 L/h). When comparing volumes of distribution, both CAZ and AVI showed higher median $V_{SS}$ values in our CVVHDF patients compared to the CVVHDF cohort from Shields et al. (73.2 L vs 43.2 L and 102 L vs 56.1 L, respectively). Higher $V_{SS}$ values are often observed in intensive care patients [19,20], and can be linked to various factors, including augmented total body water (aggravated by renal failure) and alterations in fluid compartments due to sepsis-related changes, such as increased capillary permeability [21], blood loss, extensive fluid resuscitation, oedema, and ascites. Differences in $V_{SS}$ could also be explained by differences in patient management and other unreported factors between the two populations.

A decrease in plasma protein binding leads to an increased $V_{SS}$. This was the case for CAZ, where a higher unbound fraction was observed, with a median value of 1.07. Since a value >1 is theoret-

ically implausible, we used an fu value of 1.0, indicating no protein binding. This is higher than the unbound fraction of 0.90 reported in the SmPC for CAZ [1,22], but aligns with a previous study in critically ill patients, which reported an increased unbound fraction of 1.02 for CAZ [23]. However, for AVI, an increased plasma protein binding was characterized, with a median unbound fraction value of 0.73, compared to the 0.92 typically referenced in the literature [24]. This suggests additional factors at play, such as increased tissue binding or altered tissue permeability. Further investigations are warranted to dissect the specific mechanisms influencing the volume of distribution, ensuring a comprehensive understanding of how these factors collectively contribute to the unique drug disposition observed during CVVHDF.

The median saturation coefficient and the contribution of CVVHDF to CAZ total clearance in our study were lower (0.41 and 20%, respectively) compared to previous findings. In a study involving CVVHDF patients receiving CAZ alone, Mariat and colleagues reported a mean sieving/saturation coefficient of 0.81 for CAZ [25]. This coefficient was derived from the ratio of drug concentration in the dialysate/ultrafiltrate to that in the serum. Additionally, the mean contribution of CVVHDF clearance to total CAZ clearance was reported to be 55%. These differences could be attributed to variations in CVVHDF settings employed (membrane types and configurations, as well as variations in flow rates for blood, dialysate, ultrafiltration, and substitution fluids).

In light of earlier studies on RRT, a dosage of 2000/500 mg of CAZ-AVI was here implemented in patients undergoing CVVHDF. The patients had residual renal function and deep-seated infections, supported by clinical evidence. The generated data further support the selected dose in this patient population. Established dosing guidelines only partially address considerations for patients with renal impairment [1,2], and lack specific dosing recommendations for patients on CVVHDF. It is clear that CAZ-AVI undergoes extensive removal during continuous RRT, particularly in scenarios with elevated effluent flow rates or for patients with significant residual renal function, but appear to still meet the PK/PD target. For example, in the case report by Wenzler et al. [3], CAZ-AVI was administered a dose regimen of 1000/250 mg q8h to effectively manage a difficult-to-treat resistant *P. aeruginosa* bacteraemia in a critically ill patient undergoing CVVH. PK analysis revealed that plasma concentrations of CAZ-AVI remained consistently above the MIC of 8 mg/L throughout the dosing interval. Notably, clearance via CVVH significantly contributed to the overall drug elimination, representing 57.1% of total CAZ clearance and 54.3% of total AVI clearance [3].

Antibiotic removal via continuous RRT can vary significantly depending on both RRT-related and patient-specific factors [26]. Consequently, dosing adjustment based on renal function as outlined in SmPCs may not be directly applicable to continuous RRT, posing a risk of antibiotic underexposure and potentially compromising therapeutic efficacy [8]. Furthermore, a previous study has highlighted the association between continuous RRT, pneumonia, and the risk of treatment failure to CAZ-AVI among patients with carbapenem-resistant *Enterobacterales* infections [27]. Additionally, dosing reduction in impaired renal function has been linked to negative treatment outcomes [28]. Notably, in a case study involving a critically ill patient with multi-drug resistant *P. aeruginosa* pneumonia undergoing CVVHDF, administration of CAZ-AVI 2000/500 mg q8h as a 2h-infusion yielded serum concentrations exceeding MIC and $C_T$ values for both CAZ and AVI throughout the dosing interval, indicating favourable PK profiles and potential therapeutic efficacy [4]. This observation aligns with our study results (Fig. 1), where CAZ and AVI concentrations were high in relation to MIC (100% $fT$>MIC) and $C_T$ (100% $fT$>$C_T$), further supporting the adequacy of the chosen dose regimen in maintaining therapeutic drug levels.

While acknowledging the potential limitation of our study's modest sample size (n=6 occasions), it is noteworthy that the observed data closely align with findings from a comparable investigation [6,7]. This consistency is particularly robust given the known PK variability inherent in critically ill patients. Although there we observed lower AVI concentrations than those of Shields et al., the CAZ:AVI ratio in our study was similar to that in the phase III population.

## 5. Conclusion

In conclusion, our study characterized the PK of CAZ-AVI in critically ill patients undergoing CVVHDF, revealing flat PK profiles due to an increased volume of distribution. Despite the relatively flat concentration-time profiles, the selected dose regimens (2000/500 mg q8h or 1000/250 mg q8h) appeared well-tolerated and effective in maintaining therapeutic concentrations during CVVHDF. Further assessments of clinical outcomes and efficacy would be valuable for confirming the appropriateness of these dosing strategies in the complex context of CVVHDF.

## Declaration of competing interest

H.G. has received speaker honoraria from Pfizer and MSD. I.K. has received speaker honoraria from Pfizer. Menarini and bioMérieux. All other authors declare no conflict of interest.

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## Ethics approval

The study protocol was approved by the local ethics committee at Hygeia General Hospital (registration number: 627/26-09-2018). The handling of samples and data was approved by Uppsala University and conducted under the number 2023-05104-01. The study was conducted in accordance with good clinical practice guidelines.

## Consent to participate

All patients (or their legal representatives) provided written informed consent.

## Consent for publication

Not applicable as patient information was anonymized.

## Data availability

The data and materials used in this study are available upon request.

## Authors' contribution

**AOJ:** Conceptualization, Methodology, Formal analysis, Writing – original draft preparation. **KI:** Conceptualization, Methodology, Investigation. **EIN:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **LG:** Investigation, supervision. **AG:** Formal analysis, Methodology, Validation, Writing – review & editing. **HP:** Investigation. **IL:** Formal analysis, Methodology, Validation, Writing – review & editing. **HG:** Investigation, supervision. **LEF:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **IK:** Conceptualization, Investigation, Supervision, Writing – review & editing. The final submitted version of manuscript was reviewed and approved by all authors.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2024.107394.

## References


[1] Pfizer. Zavicefta 2 g/0.5 g (ceftazidime/avibactam) powder for concentrate for solution for infusion. European Medecine Agency (EMA) Summary of Product Characteristics (SmPC), 2021. https://www.ema.europa.eu/en/documents/product-information/zavicefta-epar-product-information_en.pdf. Accessed December 9, 2024.

[2] Allergan. Avycaz 2 g/0.5 g (ceftazidime/avibactam) for injection, for intravenous use. Food and Drug Administration (FDA) Summary of Product Characteristics (SmPC). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206494s005,s006lbl.pdf. Accessed December 9, 2024.

[3] Wenzler E, Bunnell KL, Bleasdale SC, et al. Pharmacokinetics and dialytic clearance of ceftazidime-avibactam in a critically ill patient on continuous venovenous hemofiltration. Antimicrob Agents Chemother 2017;61:e00464 -17. doi:10.1128/AAC.00464-17.

[4] Soukup P, Faust AC, Edpuganti V, et al. Steady-state ceftazidime-avibactam serum concentrations and dosing recommendations in a critically ill patient being treated for pseudomonas aeruginosa pneumonia and undergoing continuous venovenous hemodiafiltration. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2019;39:1216–22. doi:10.1002/phar.2338.

[5] Zhang X-S, Wang Y-Z, Shi D-W, et al. Efficacy and pharmacodynamic target attainment for ceftazidime-avibactam off-label dose regimens in patients with continuous or intermittent venovenous hemodialysis: two case reports. Infect Dis Ther 2022;11:2311–19. doi:10.1007/s40121-022-00621-z.

[6] Shields RK. Pharmacokinetics of ceftazidime-avibactam among critically-ill patients receiving CVVHDF. ClinicalTrials.gov identifier: NCT04358991. Study Report, 2020. https://cdn.clinicaltrials.gov/large-docs/91/NCT04358991/Prot_SAP_000.pdf. Accessed December 9, 2024.

[7] Kline EG, Nguyen MHT, McCreary EK, et al. Population pharmacokinetics of ceftazidime-avibactam among critically-ill patients with and without receipt of continuous renal replacement therapy. Open Forum Infect Dis 2020;7:S663–4. doi:10.1093/ofid/ofaa439.1481.

[8] Gatti M, Rinaldi M, Gaibani P, et al. A descriptive pharmacokinetic/pharmacodynamic analysis of continuous infusion ceftazidime-avibactam for treating DTR gram-negative infections in a case series of critically ill patients undergoing continuous veno-venous haemodiafiltration (CVVHDF). Journal of Critical Care 2023;76:154301. doi:10.1016/j.jcrc.2023.154301.

[9] Pickering JW, Frampton CM, Walker RJ, et al. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. Crit Care 2012;16:R107. doi:10.1186/cc11391.

[10] Cheng Y, Chen M, Zhang B, et al. Rapid, simple, and economical LC–MS/MS method for simultaneous determination of ceftazidime and avibactam in human plasma and its application in therapeutic drug monitoring. Journal of Clinical Pharmacy and Therapeutics 2022;47:1426–37. doi:10.1111/jcpt.13693.

[11] Martens-Lobenhoffer J, Angermair S, Bode-Böger SM. Quantification of ceftazidime/avibactam in human plasma and dried blood spots: implications on stability and sample transport. Journal of Chromatography B 2022;1193:123164. doi:10.1016/j.jchromb.2022.123164.

[12] Sillén H, Mitchell R, Sleigh R, et al. Determination of avibactam and ceftazidime in human plasma samples by LC-MS. Bioanalysis 2015;7:1423–34. doi:10.4155/bio.15.76.

[13] Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). Guidance for industry: Bioanalytical method validation. 2018. https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf. Accessed December 9, 2024.

[14] 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;12:151–63. doi:10.1111/cts.12585.

[15] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41. doi:10.1159/000180580.

[16] Baron KT, Gastonguay MR. Simulation from ODE-based population PK/PD and systems pharmacology models in R with mrgsolve. J Pharmacokinet Pharmacodyn 2015;42:S84–5. doi:10.1007/s10928-015-9432-2.

[17] Colton CK, Henderson LW, Ford CA, Lysaght MJ. Kinetics of hemodiafiltration. I. In vitro transport characteristics of a hollow-fiber blood ultrafilter. The Journal of Laboratory and Clinical Medicine 1975;85:355–71.

[18] European Committee on Antimicrobial Susceptibility Testing (EUCAST). Ceftazidime-avibactam: rationale for the clinical breakpoints, version 1.0. 2020. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Ceftazidime-avibactam_Rationale_Document_20200730.pdf. Accessed December 9, 2024.

[19] Traunmüller F, Schenk P, Mittermeyer C, et al. Clearance of ceftazidime during continuous venovenous haemofiltration in critically ill patients. Journal of Antimicrobial Chemotherapy 2002;49:129–34. doi:10.1093/jac/49.1.129.

[20] Benko AS, Cappelletty DM, Kruse JA, Rybak MJ. Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected gram-negative infections. Antimicrob Agents Chemother 1996;40:691–5.

[21] van Dalen R, Vree TB. Pharmacokinetics of antibiotics in critically ill patients. Intensive Care Med 1990;16:S235–8. doi:10.1007/BF01709707.

[22] O'Callaghan CH, Acred P, Harper PB, et al. GR 20263, a new broad-spectrum cephalosporin with anti-pseudomonal activity. Antimicrob Agents Chemother 1980;17:876–83.

[23] Schießer S, Hitzenbichler F, Kees MG, et al. Measurement of free plasma concentrations of beta-lactam antibiotics: an applicability study in intensive care unit patients. Therapeutic Drug Monitoring 2021;43:264. doi:10.1097/FTD.0000000000000827.

[24] Mawal Y, Critchley IA, Riccobene TA, Talley AK. Ceftazidime–avibactam for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. Expert Review of Clinical Pharmacology 2015;8:691–707. doi:10.1586/17512433.2015.1090874.

[25] Mariat C, Venet C, Jehl F, et al. Continuous infusion of ceftazidime in critically ill patients undergoing continuous venovenous haemodiafiltration: pharmacokinetic evaluation and dose recommendation. Critical Care 2006;10:R26. doi:10.1186/cc3993.

[26] Gatti M, Pea F. Antimicrobial dose reduction in continuous renal replacement therapy: myth or real need? A practical approach for guiding dose optimization of novel antibiotics. Clin Pharmacokinet 2021;60:1271–89. doi:10.1007/s40262-021-01040-y.

[27] Shields RK, Nguyen MH, Chen L, et al. Pneumonia and renal replacement therapy are risk factors for ceftazidime-avibactam treatment failures and resistance among patients with carbapenem-resistant enterobacteriaceae infections. Antimicrob Agents Chemother 2018;62:e02497 -17. doi:10.1128/AAC.02497-17.

[28] Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-avibactam use for klebsiella pneumoniae carbapenemase–producing K. Pneumoniae infections: a retrospective observational multicenter study. Clinical Infectious Diseases 2021;73:1664–76. doi:10.1093/cid/ciab176.