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Research Article

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Implications of Ceftazidime-Avibactam Clearance Correlation for Target Selection and Single-Analyte Therapeutic Drug Monitoring During Continuous Infusion: A Pharmacometric Simulation and Individual Patient Data Analysis

Running title: Joint ceftazidime-avibactam clearance modelling

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Highlights

- The correlation between ceftazidime and avibactam clearance was 0.70, notably lower than the 0.94 assumed in current models.
- Assuming a lower correlation means measuring ceftazidime alone misclassifies avibactam target attainment in nearly 1 in 10 critically ill patients.
- The choice of avibactam target (1 vs. 4 vs. 8 mg/L) drastically alters the perceived adequacy of continuous-infusion regimens.
- Direct measurement of avibactam warrants evaluation in critically ill patients when precise target attainment is required.

Abstract

Objectives: Continuous-infusion ceftazidime-avibactam is increasingly used in critically ill patients. Target attainment depends on the correlation between the clearances of the two components and on the avibactam target selected. We estimated this correlation and evaluated its consequences for therapeutic drug monitoring (TDM) and target selection.

Methods: We developed a joint two-analyte model from individual patient data (21 adults, 238 observations) to estimate the clearance correlation. The primary attainment analyses retained the published correlation of 0.94 and the estimated value was applied in the monitoring analysis. We simulated 100,000 critically ill adults across five renal-function classes to evaluate joint probability of target attainment and cumulative fraction of response (CFR) at avibactam targets of 1, 4 and 8 mg/L. We also tested the accuracy of predicting avibactam attainment from ceftazidime alone.

Results: In the first confrontation of this assumption with individual patient data, the clearance correlation was 0.70 (95% CI 0.38–0.87); the assumed value of 0.94 lies outside that interval ($p = 0.0006$). Joint CFR varied markedly with the avibactam target: 93.4–98.6% (1 mg/L), 73.5–88.6% (4 mg/L) and 44.0–60.7% (8 mg/L). At the estimated correlation, predicting avibactam attainment from ceftazidime alone gave a 9.2% rate of false reassurance, against 3.6% at the assumed correlation.

Conclusions: The clearance correlation is lower than previously assumed, and single-analyte TDM is correspondingly less reliable. The avibactam target selected also alters dosing conclusions substantially. Measurement of both components, or a more conservative avibactam target, warrants evaluation in critically ill patients.

Keywords: ceftazidime-avibactam; population pharmacokinetics; continuous infusion; target attainment; therapeutic drug monitoring; renal function

1. Introduction

Continuous infusion of ceftazidime-avibactam is increasingly recommended to maximize pharmacokinetic/pharmacodynamic (PK/PD) target attainment in critically ill adults with carbapenem-resistant Gram-negative infections [1-3]. However, the practical implementation of therapeutic drug monitoring (TDM) for this combination raises a critical clinical question: must both components be measured, or is the concentration of ceftazidime sufficient to infer whether avibactam has reached its target? The answer depends on the physiological correlation between the clearances of the two drugs, a parameter that has been assumed rather than estimated from individual patient data, and also on assay error, the pharmacodynamic target chosen and the decision rule applied.

A further complication is the lack of consensus regarding the optimal pharmacodynamic target for avibactam. While ceftazidime dosing is rationally adjusted against the minimum inhibitory concentration (MIC), avibactam is evaluated against a fixed plasma threshold. Published studies and clinical guidelines alternate between 1 mg/L (from registrational analyses) and 4 mg/L (derived from susceptibility testing breakpoints), with some advanced analyses pushing for higher thresholds [4-6]. This ambiguity fundamentally alters whether a standard continuous-infusion regimen appears "successful" or "suboptimal."

Target-attainment analyses of the combination depend on how strongly the clearances of the two components co-vary. That correlation determines the joint attainment rate, and it sets a ceiling on how much a measurement of one component can say about the other. The registrational population analysis recognised this dependence and accounted for it non-parametrically, by bootstrapping paired random effects, without reporting a coefficient [7]. Continuous-infusion analyses have since adopted a value of 0.94 [8]. We therefore developed a joint two-analyte non-linear mixed-effects model, fitted to individual patient data, to estimate this correlation directly and with an uncertainty interval, and then examined what its value implies both for target selection and for single-analyte therapeutic drug monitoring.

2. Materials and methods

2.1. Study design and evidence sources

This pharmacometric simulation used published continuous-infusion clearance relationships, variability estimates, and MIC distributions. The simulation itself was not fitted to individual patient data. Separately, a joint two-analyte model was fitted to individual patient data to estimate the cross-drug clearance correlation on which single-analyte monitoring depends (Section 2.5). The primary scenario focused on critically ill adults who were not receiving renal replacement therapy. The main pharmacokinetic and pharmacodynamic inputs for continuous infusion were obtained from Cojutti et al. [8]. Data from Gatti et al. and O'Jeanson et al. were used as donor inputs in the sensitivity analyses [9,10]. Additional published pharmacokinetic and pharmacodynamic studies were used for contextual analyses and to examine structural uncertainty [11-13]. MIC distributions for KPC-producing and OXA-48-like *Klebsiella pneumoniae* were obtained from ATLAS surveillance reports [14,15].

We classified each input as directly reported, inherited, donor-derived, user-specified, model-inferred, or scenario-generated. If an input needed for the primary scenario was not available, it was kept as an explicit gap rather than imputed. Input values, their sources, and any transformations applied are provided in Supplementary Tables S1-S3.

2.2. Virtual population and pharmacokinetic implementation

We simulated 100,000 adults across five European Kidney Function Consortium (EKFC) renal-function classes: 0-30, 31-60, 61-90, 91-120, and 121-150 mL/min/1.73 m². Within each class, 20,000 individuals were uniformly sampled. Ceftazidime and avibactam clearances were calculated separately using the renal-function relationships reported in the source model. Correlated lognormal interindividual variability was then applied to the clearance of both components. The reported coefficients of variation were 67.92% for ceftazidime and 76.91% for avibactam, with a correlation of 0.94. The random seed was set to 20260707.

Under constant continuous infusion, the steady-state concentration of each component was calculated from the infusion rate and individual clearance. We did not simulate the loading phase or time-varying concentration profiles.

2.3. Targets, regimens, and outcomes

The primary pharmacodynamic targets were a free steady-state ceftazidime concentration/MIC ratio of at least 4 and a free steady-state avibactam concentration of at least 4 mg/L [8,16]. We treated the 4-mg/L avibactam target as a free plasma concentration assumption rather than a value converted from the susceptibility-testing concentration [17,18]. Sensitivity to the avibactam target was examined across concentrations from 1 to 8 mg/L.

We evaluated 11 continuous-infusion regimens ranging from 0.625 to 2.5 g every 6, 8, or 12 h. For each EKFC class, we selected the regimen with the highest joint probability of target attainment (PTA) at an MIC of 4 mg/L among those with no more than a 15% probability of exceeding a total ceftazidime steady-state concentration of 104 mg/L. We used this cutoff as an operational exposure screen based on the source cohort, not as a validated neurotoxicity threshold [8,19].

The outcomes included component-specific PTA, joint PTA, MIC-weighted cumulative fraction of response (CFR), exposure-screen exceedance, model-derived daily product dose, and the operating characteristics of

ceftazidime-based prediction of avibactam attainment. The limiting component was assessed using marginal attainment, single-component failures among joint failures, and the component requiring the higher daily dose. For population-level CFR, we used prespecified renal-function weights derived from the source-cohort quartiles. Class-specific results were not population weighted. Complete regimen grids, MIC distributions, and derivations are provided in the Supplementary Material.

Prediction of avibactam target attainment from ceftazidime was evaluated as an explicit classifier. For each simulated patient the true state was a free steady-state avibactam concentration at or above the 4 mg/L target. The ceftazidime steady-state concentration was then treated as the only available measurement, with lognormal assay error of coefficient of variation 0%, 10% or 20% applied to it; avibactam was not measured. The observed ceftazidime concentration was converted to an implied ceftazidime clearance and hence to a realised random effect, from which the conditional distribution of the avibactam clearance random effect follows, with mean equal to the correlation times the ratio of the two between-subject standard deviations times the observed ceftazidime deviate, and standard deviation equal to the avibactam term multiplied by the square root of one minus the squared correlation. A patient was predicted to attain when that conditional probability was at least 0.5. Because the avibactam target is a fixed concentration rather than a multiple of the MIC, the classification does not depend on MIC. Patients were pooled across the five selected regimens, one per renal-function class, without population weighting. False reassurance is reported as the number of patients predicted to attain who did not, divided by all simulated patients.

2.4. Calibration and sensitivity analyses

We compared the implementation with 72 regimen-MIC benchmarks from the source study. An absolute difference of 5 percentage points or less was considered concordant. Monte Carlo convergence was assessed against the 100,000-subject reference simulation, and reproducibility was evaluated across five random seeds according to established principles for target-attainment simulations [20]. Deterministic and probabilistic sensitivity analyses varied pharmacokinetic inputs, unbound fractions, clearance correlation, and the exposure-screen definition. We also used a 300-sample Latin hypercube analysis to examine the influence of individual parameters on joint CFR. Structural uncertainty was evaluated using three additional published adult population pharmacokinetic models [9-13]. For the epithelial lining fluid scenarios, we used published component-specific penetration ratios from an ICU pneumonia trial and a healthy-volunteer study [21,22].

2.5. Joint two-analyte model of ceftazidime and avibactam clearance

Individual ceftazidime and avibactam concentrations were obtained from an openly licensed cohort of 21 critically ill adults receiving intermittent 8-hourly infusion during continuous renal replacement therapy, comprising 238 paired observations [23] (Dryad 10.5061/dryad.fxpnvx16s, CC0). One compartment per analyte was solved in closed form at steady state and verified against explicit superposition of 400 doses. Clearance and volume were lognormally distributed, with the two clearance random effects correlated and a single shared random effect for volume. A first fit with independent volume deviates estimated the ceftazidime-avibactam volume correlation at the boundary value of 1.000; the reduced structure imposes that constraint, is consistent with distribution of both agents into extracellular water, and gives an identical objective function with one parameter fewer.

Estimation was first-order conditional with the Laplace approximation, with the individual objective solved by Levenberg-Marquardt and curvature taken from the Gauss-Newton form. Convergence alternated Nelder-Mead and L-BFGS-B passes until successive rounds improved the objective by less than 10^{-4} , and both fits stopped on that tolerance. The confidence interval for the correlation was obtained by profile likelihood rather than from the Hessian. The model was evaluated using conditional weighted residuals, a visual predictive check of 1,000 replicates of the observed design, leave-one-subject-out refitting, and sensitivity to the infusion-duration coding of the source dataset. The estimator was validated by simulation-based calibration: 75 replicate datasets across three known correlation values were simulated on the observed design and refitted with the same estimator, including one scenario simulated from a two-compartment model that the estimator does not assume.

Large language models (OpenAI ChatGPT and Codex; Anthropic Claude) were used to assist with drafting and with the implementation and checking of analysis code. All modelling decisions, results and conclusions are the author's. All figures were generated from the analysis outputs by the scripts named in the code availability statement; no generative artificial intelligence was used to create any figure or image.

The likelihood-ratio statistic is the difference in objective function value, defined as minus twice the log-likelihood, between the constrained and unconstrained fits, referred to a chi-squared distribution with one degree of freedom. The unconstrained model estimates eleven parameters and each constrained model ten, with the correlation held fixed. The correlation was free to take negative values, bounded only by the requirement that the covariance matrix remain positive definite. Uncertainty in the correlation was carried into

160 the classification analysis by repeating that analysis at the estimate and at both profile-likelihood bounds rather
161 than by propagating a distribution.

162 **3. Results**

163 **3.1. Primary attainment and the limiting component**

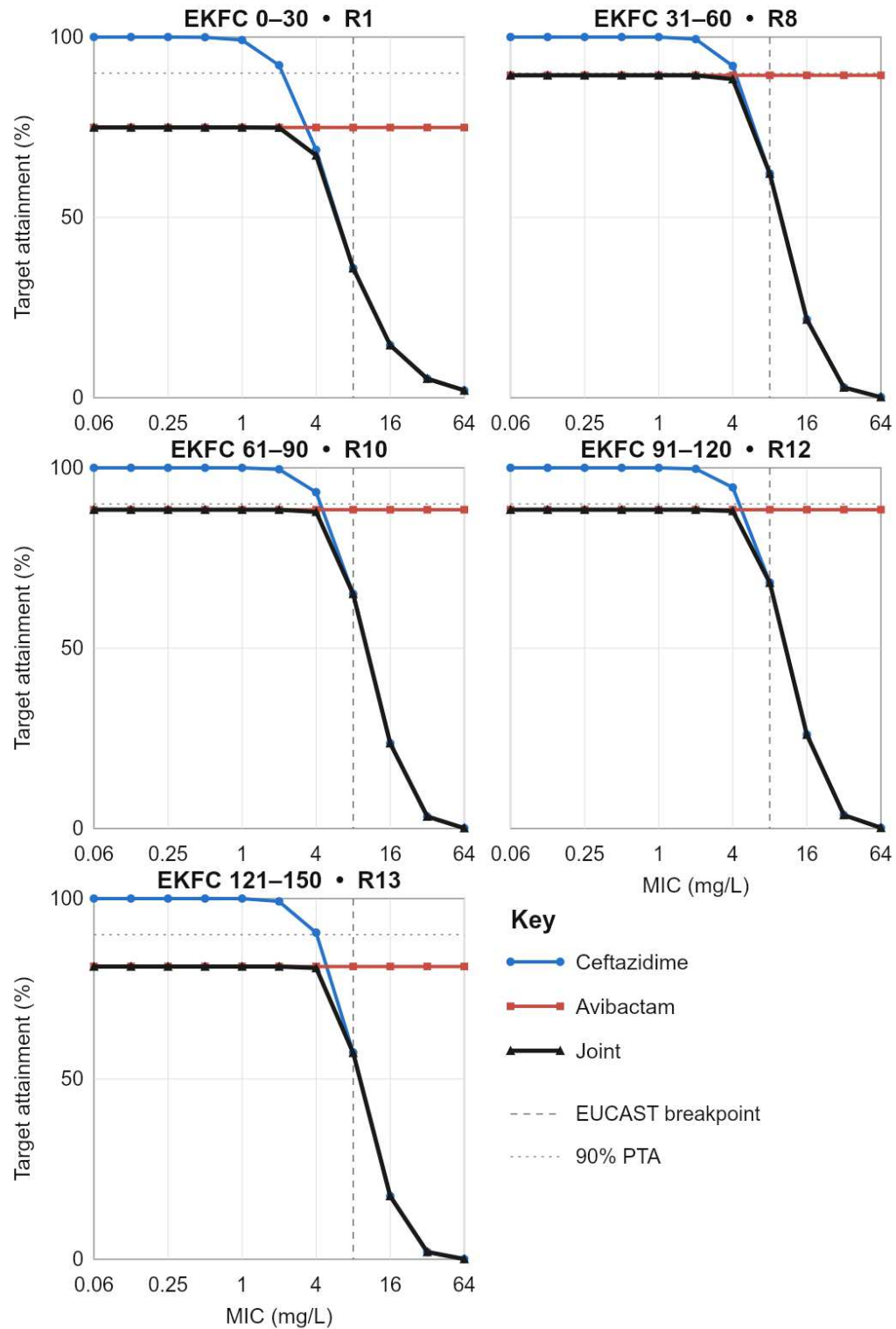
164 Table 1 shows the selected regimens and the main results. At the primary avibactam target of 4 mg/L, joint
165 PTA at an MIC of 4 mg/L ranged from 67.1% to 88.3% across the renal-function classes. At an MIC of 2 mg/L,
166 avibactam was the limiting component in all 11 regimens. At the EUCAST clinical breakpoint of 8 mg/L,
167 however, ceftazidime became the limiting component in all regimens. At this MIC, joint PTA ranged from
168 10.1% to 68.1% (Figure 1). The three methods used to identify the limiting component produced consistent
169 results (Supplementary Table S21).

170

171 **Table 1. Selected regimen definitions and outputs from the primary 100,000-subject simulation (continuous**
172 **infusion).**

EKFC class	Selected regimen	Total daily product dose	CAZ/AVI infusion rate	Joint PTA at MIC 4	Exposure-screen exceedance
0–30	R1: 0.625 g every 12 h	1.25 g/day	41.7 / 10.4 mg/h	67.1%	8.9%
31–60	R8: 2.5 g every 12 h	5.0 g/day	166.7 / 41.7 mg/h	88.3%	9.3%
61–90	R10: 2.5 g every 8 h	7.5 g/day	250.0 / 62.5 mg/h	87.8%	10.9%
91–120	R12: 2.5 g every 6 h (EKFC 91-120)	10.0 g/day	333.3 / 83.3 mg/h	88.1%	12.3%
121–150	R13: 2.5 g every 6 h (EKFC 121-150)	10.0 g/day	333.3 / 83.3 mg/h	80.8%	7.3%

173 CAZ, ceftazidime; AVI, avibactam; EKFC, European Kidney Function Consortium; MIC, minimum inhibitory concentration; PTA, probability
174 of target attainment. The exposure screen is the probability of exceeding a total ceftazidime steady-state concentration of 104 mg/L.



3.2. Avibactam-target sensitivity

Changing the avibactam target had a substantial effect on joint target attainment (Table 2; Figure 2). Joint CFR ranged from 93.4% to 98.6% with an avibactam target of 1 mg/L, from 73.5% to 88.6% at the primary target of 4 mg/L, and from 44.0% to 60.7% at 8 mg/L. Across the selected regimens, avibactam attainment decreased from 99.2%-100.0% at 1 mg/L to 44.2%-61.0% at 8 mg/L. The 4-mg/L concentration comes from susceptibility testing and has not been directly established as a plasma exposure-response threshold. Hollow-fibre studies have instead reported a range of concentration conditions associated with maintained antibacterial activity or prevention of regrowth (Figure 3; Supplementary Table S14) [24,25].

Table 2. Effect of the avibactam threshold on attainment and the limiting component across selected regimens.

Avibactam target (mg/L)	Avibactam attainment (%)	Joint CFR (%)	Limiting component at MIC 2	Limiting component at MIC 4	Limiting component at MIC 8
1	99.2–100.0	93.4–98.6	Ceftazidime	Ceftazidime	Ceftazidime
2	93.3–98.7	89.5–97.6	Mixed	Ceftazidime	Ceftazidime
4 (primary)	74.9–89.4	73.5–88.6	Avibactam	Avibactam	Ceftazidime
6	58.7–75.2	58.1–74.7	Avibactam	Avibactam	Ceftazidime
8	44.2–61.0	44.0–60.7	Avibactam	Avibactam	Mixed

CFR, cumulative fraction of response; MIC, minimum inhibitory concentration. The limiting component is the one with the lower marginal attainment at that MIC.

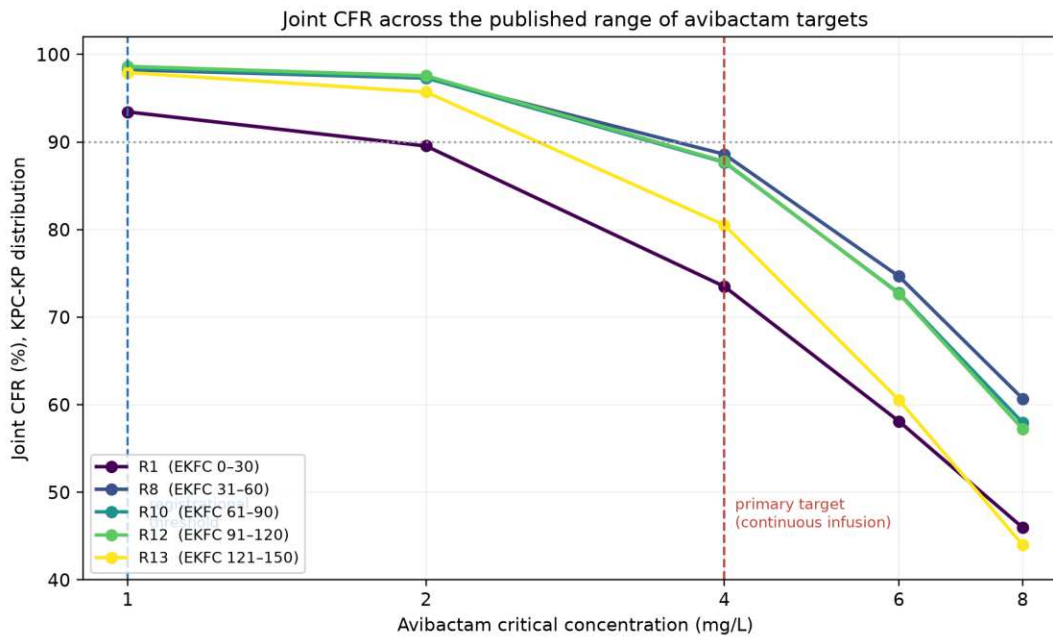


Figure 2. Joint CFR across the prespecified range of avibactam targets for the selected continuous-infusion regimens. The apparent avibactam ceiling observed at the primary 4-mg/L target is not present at the 1-mg/L target used in registrational analyses.

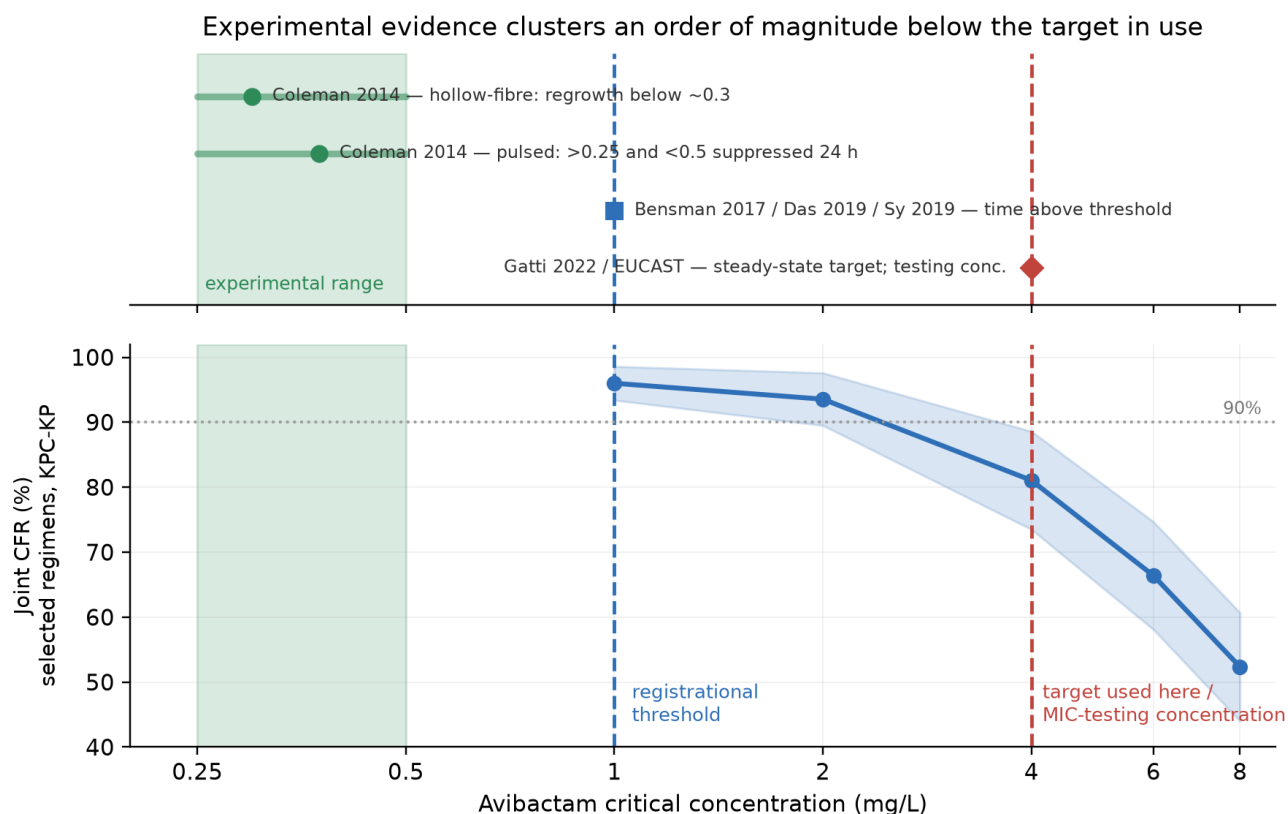


Figure 3. Evidence supporting the evaluated avibactam targets and the corresponding joint CFR across selected regimens. The shaded band shows the concentration range in which hollow-fibre experiments reported maintained antibacterial activity (Supplementary Table S14).

3.3. Site-of-infection and dose-requirement scenarios

In the plasma scenario, population-weighted joint CFR was 84.3%. Applying the median epithelial lining fluid penetration ratios from the ICU pneumonia trial reduced joint CFR to 45.9%. Joint CFR was 44.0% in the healthy-volunteer scenario and 26.7% in the conservative scenario (Table 3; Figure 4). These scenarios applied fixed penetration ratios to plasma-modelled concentrations and therefore should not be interpreted as empirical distributions of target-site concentrations. The healthy-volunteer ratios are further limited in that they are concentration-specific values taken from non-linear plasma-epithelial lining fluid relationships, evaluated at plasma concentrations (15.3 mg/L ceftazidime, 2.4 mg/L avibactam) well below those produced by the continuous-infusion regimens simulated here. Applied at steady-state concentrations, the same source model implies substantially lower penetration, so the healthy-volunteer scenario should be read as an optimistic bound rather than a central estimate. All ELF scenarios were applied to the same simulated population, so differences between them reflect the penetration ratios alone. The healthy-volunteer scenario gives a slightly

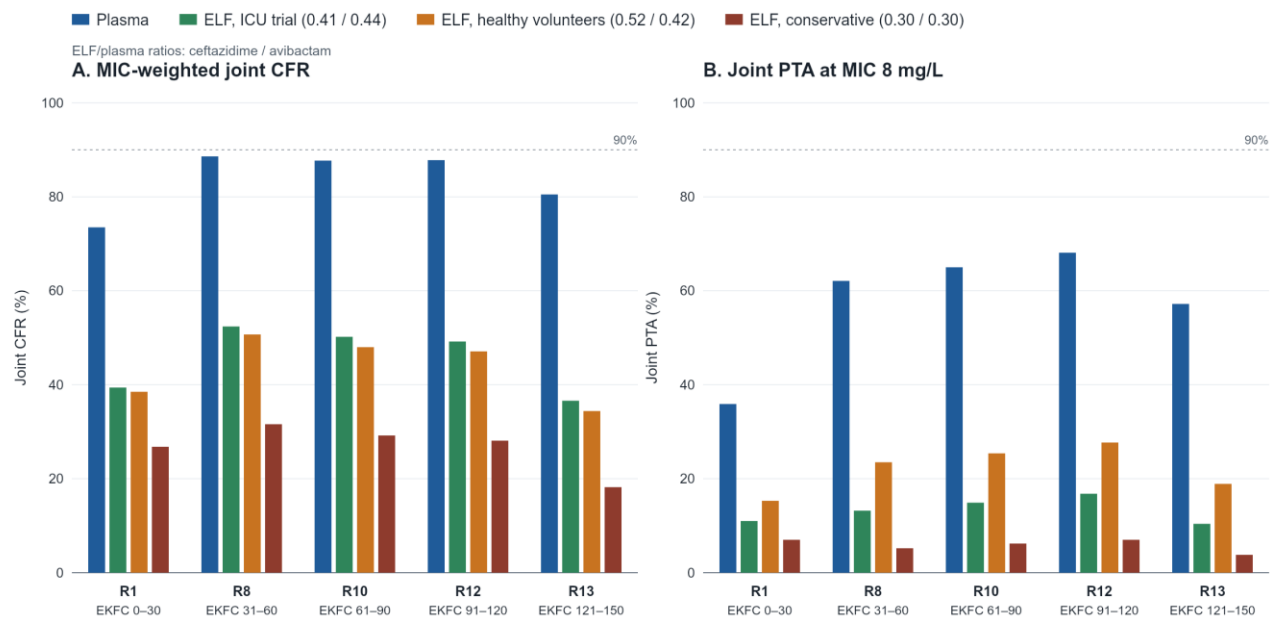
211 lower joint CFR than the ICU-trial scenario (44.0% versus 45.9%) despite a higher ceftazidime ratio (0.52
212 versus 0.41), because its avibactam ratio is lower (0.42 versus 0.44) and avibactam is the limiting component
213 at these MICs.

214 **Table 3. Joint target attainment and cumulative fraction of response in plasma and epithelial lining fluid under**
215 **patient-derived and historical penetration scenarios.**

Compartment/scenario	Penetration applied (CAZ / AVI)	Joint PTA at MIC 8 mg/L (%)	Joint CFR, selected regimens (%)	Population-weighted joint CFR (%)
Plasma	—	35.9–68.1	73.5–88.6	84.3
ELF, ICU pneumonia trial	0.41 / 0.44	10.4–16.8	36.6–52.4	45.9
ELF, healthy-volunteer estimate	0.52 / 0.42	15.3–27.7	34.4–50.7	44.0
ELF, conservative scenario	0.30 / 0.30	3.8–7.0	18.2–31.6	26.7

216 AVI, avibactam; CAZ, ceftazidime; CFR, cumulative fraction of response; ELF, epithelial lining fluid; MIC, minimum inhibitory
217 concentration; PTA, probability of target attainment. Penetration ratios were applied as fixed multipliers to plasma-modelled concentrations
218 and are scenario assumptions, not measured distributions.

219



220 **Figure 4. Modelled joint cumulative fraction of response and joint target attainment at an MIC of 8 mg/L in plasma and epithelial lining fluid**
221 **(ELF). The ICU-trial scenario uses median component-specific ELF-to-plasma ratios measured in critically ill adults with nosocomial**
222 **pneumonia receiving continuous-infusion ceftazidime-avibactam. All ELF results represent scenarios applied to the primary plasma model.**
223

224

At an MIC of 8 mg/L, the median model-derived daily product dose increased from 1.71 g/day in the lowest renal-function class to 8.94 g/day in the augmented-clearance class (Table 4; Figure 5). Across these classes, the proportion of subjects remaining below the prespecified modelled limit of 10 g/day decreased from 99.2% to 57.2%.

Table 4. Model-derived daily product dose required to attain both pharmacodynamic targets, and the proportion of each renal-function class not exceeding the prespecified 10-g/day modelled dose cap.

EKFC class (mL/min/1.73 m²)	MIC 4: median dose (g/day)	MIC 4: ≤10 g/day (%)	MIC 8: median dose (g/day)	MIC 8: ≤10 g/day (%)	MIC 16: median dose (g/day)	MIC 16: ≤10 g/day (%)
0–30	0.87	99.9	1.71	99.2	3.41	92.2
31–60	2.25	98.6	4.10	92.0	8.20	62.2
61–90	3.38	94.5	5.88	80.0	11.77	40.0
91–120	4.53	88.0	7.42	68.1	14.85	26.0
121–150	5.62	80.8	8.94	57.2	17.85	17.5

EKFC, European Kidney Function Consortium; MIC, minimum inhibitory concentration. The dose shown is the model-derived requirement to attain both pharmacodynamic targets. The 10 g/day threshold is a cap prespecified for this analysis, not a regulatory licence boundary.

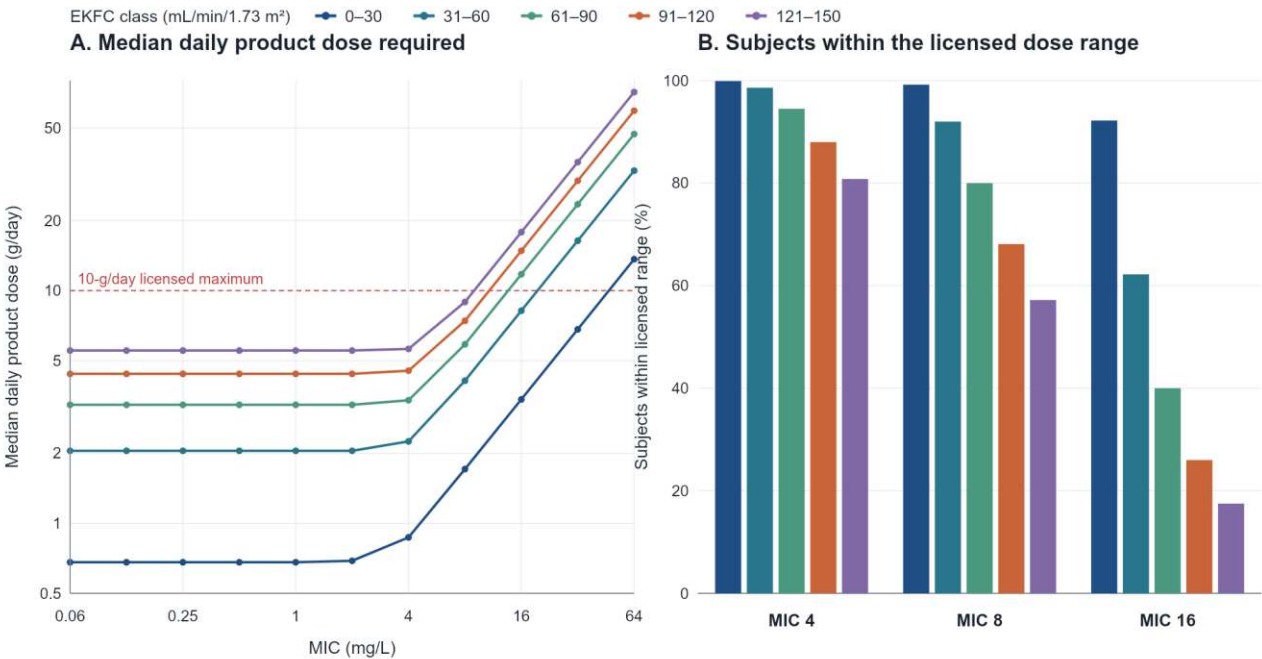


Figure 5. (a) Median daily product dose required to attain both pharmacodynamic targets across renal-function classes and MICs, shown relative to the prespecified modelled dose cap of 10 g/day. **(b)** Proportion of each renal-function class in which the required dose does not exceed this cap.

3.4. Incremental value of an avibactam assay and robustness

Using the clearance correlation from the source model, ceftazidime-based prediction of avibactam target attainment had positive and negative predictive values of 95.8% and 83.6%, respectively. Overall, 5.9% of simulated subjects were misclassified, including 3.6% who were incorrectly predicted to attain the avibactam target (Table 5; Figure 6). When lower correlations between ceftazidime and avibactam clearance were assumed, both overall accuracy and negative predictive value decreased. At the correlation of 0.703 estimated from individual patient data (Section 3.5), the negative predictive value fell to 69.3%, specificity fell from 77.0% to 40.7%, and the proportion of subjects incorrectly predicted to attain the avibactam target rose from 3.6% to 9.2%; at the upper bound of the interval it was 5.5%.

Table 5. Operating characteristics of ceftazidime-based prediction of avibactam target attainment, by assumed clearance correlation and assay error.

Clearance correlation (ρ)	Assay CV (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Wrongly reported as attaining (%)
0.94	0	94.1	97.2	77.0	95.8	83.6	3.6
0.94	20	92.1	95.5	74.0	95.2	75.0	4.0
0.874 (upper bound)	0	91.7	96.6	64.7	93.7	77.9	5.5
0.874 (upper bound)	20	90.3	95.2	63.6	93.4	71.0	5.7
0.75	0	88.7	96.5	46.6	90.8	70.7	8.3
0.75	20	88.1	95.6	47.2	90.8	66.2	8.2
0.703 (estimate)	0	88.0	96.7	40.7	89.8	69.3	9.2
0.703 (estimate)	20	87.5	95.9	41.8	89.9	65.3	9.1
0.50	0	85.8	97.7	21.4	87.1	63.2	12.3
0.50	20	85.7	97.4	22.4	87.2	61.1	12.1
0.380 (lower bound)	0	85.2	98.1	15.0	86.2	59.8	13.3
0.380 (lower bound)	20	85.1	98.0	15.2	86.2	58.9	13.2
0.00	0	84.5	98.3	10.5	85.5	53.0	14.0
0.00	20	84.5	98.3	10.5	85.5	53.0	14.0

CV, coefficient of variation; NPV, negative predictive value; PPV, positive predictive value; ρ, correlation between the ceftazidime and avibactam clearance random effects. Wrongly reported as attaining is the number of patients predicted to attain who did not, as a percentage of all simulated patients. Rows labelled estimate, upper bound and lower bound are the value fitted in this study and its 95% profile-likelihood interval; the remaining rows are prespecified scenario values.

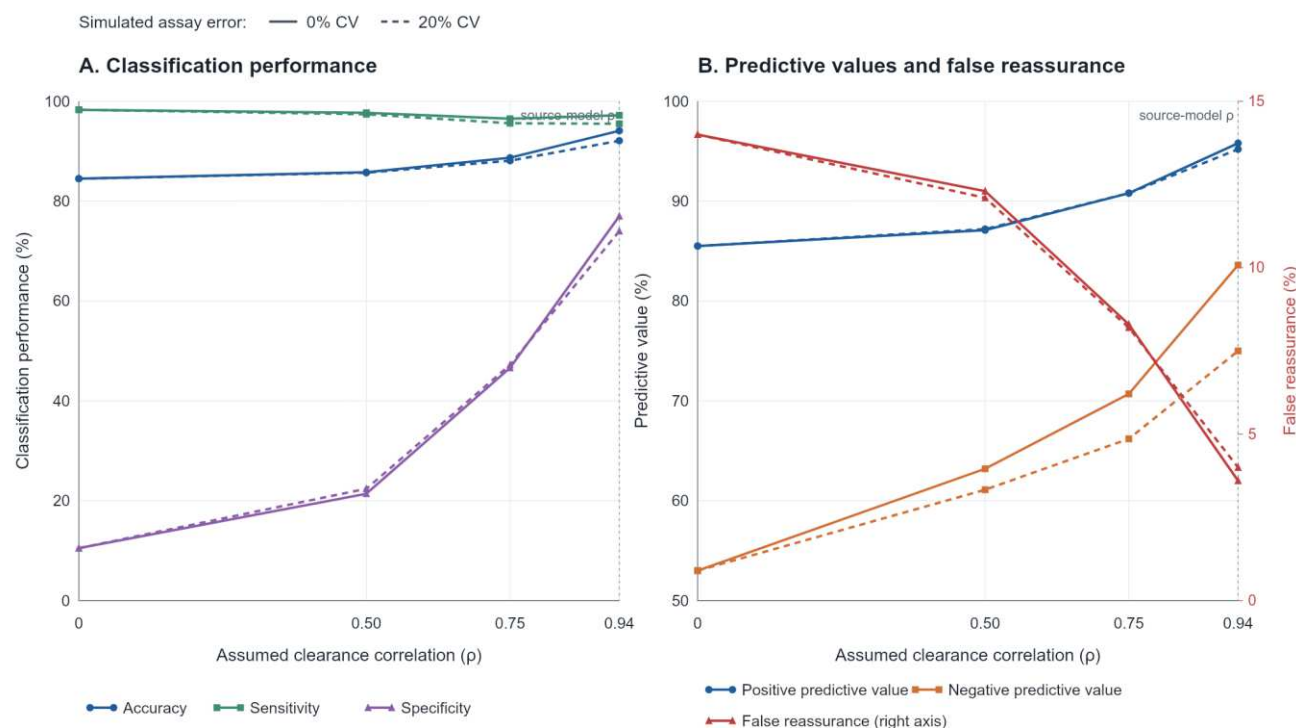


Figure 6. Performance of ceftazidime-based prediction of avibactam target attainment across different assumed correlations between component clearances. Panel A shows accuracy, sensitivity, and specificity. Panel B shows positive and negative predictive values and the proportion of subjects incorrectly classified as attaining the avibactam target (false reassurance; right axis). Solid and dashed lines represent simulated assay coefficients of variation of 0% and 20%, respectively.

The main findings were generally maintained across the alternative pharmacokinetic models and most prespecified scenario changes (Table 6). The change in the limiting component was observed in all four population pharmacokinetic models, although population joint CFR ranged from 70.2% to 94.5%. Treating the 4-mg/L threshold as a total rather than a free concentration increased avibactam attainment by 2.0-3.0 percentage points. Joint PTA at an MIC of 8 mg/L changed by no more than 0.1 percentage point.

Table 6. Robustness of selected findings to modelling and scenario assumptions.

Assumption varied	Range examined	Effect on the result
Clearance variability	10%–67.9% CV	Classes in which the exposure screen was reached before 90% joint attainment: 1/5 at 10%, 20%, or 30%; 3/5 at 45%; and 5/5 at 67.9%
Exposure-screen definition	80–500 mg/L; allowable exceedance 5%–30%	Ordering retained at thresholds of 80–150 mg/L and exceedance cut-offs ≤15%; not retained at 200 mg/L
Cohort restriction	All EKFC values versus EKFC ≥15 mL/min/1.73 m ²	Lowest-class exceedance: 9.37% to 0.28%; escalation ordering unchanged in all five classes
Avibactam threshold interpretation	4 mg/L free versus total concentration	Avibactam attainment increased by 2.0–3.0 points; joint PTA at MIC 8 changed by ≤0.1 point
Population pharmacokinetic model	Primary model plus three published adult models	Population joint CFR: 70.2%–94.5%; limiting-component transition reproduced in all models

CFR, cumulative fraction of response; EKFC, European Kidney Function Consortium; MIC, minimum inhibitory concentration; PTA, probability of target attainment.

3.5. Joint clearance model and the estimated correlation

The correlation between the ceftazidime and avibactam clearance random effects was 0.703, with a 95% profile-likelihood interval of 0.380 to 0.874 that excludes the value of 0.94 used in the primary simulation. The profile was smooth and unimodal (Supplementary Table S23). At 0.94 the objective function was 11.78 units worse than at the estimate ($p = 0.0006$). The assumed value therefore lies outside the range these data support. Both components are eliminated through a shared extracorporeal circuit in this cohort, which is the condition most favourable to a high correlation, so an estimate of 0.70 in this setting is difficult to reconcile with a population value of 0.94. The cohort nevertheless differs from the simulated population in renal replacement, infusion mode and size, and the magnitude should be read with that in mind. Against a model with no cross-drug correlation the objective improved by 12.41 units on one degree of freedom ($p = 0.0004$): the existence of the correlation is strongly supported, and it is its magnitude that differs from the assumed value. Fixed-effect estimates were 2.572 and 3.223 L/h for ceftazidime and avibactam clearance and 19.98 and 27.03 L for their volumes; the full parameter set is given in Supplementary Table S22 and goodness of fit in Figure 7.

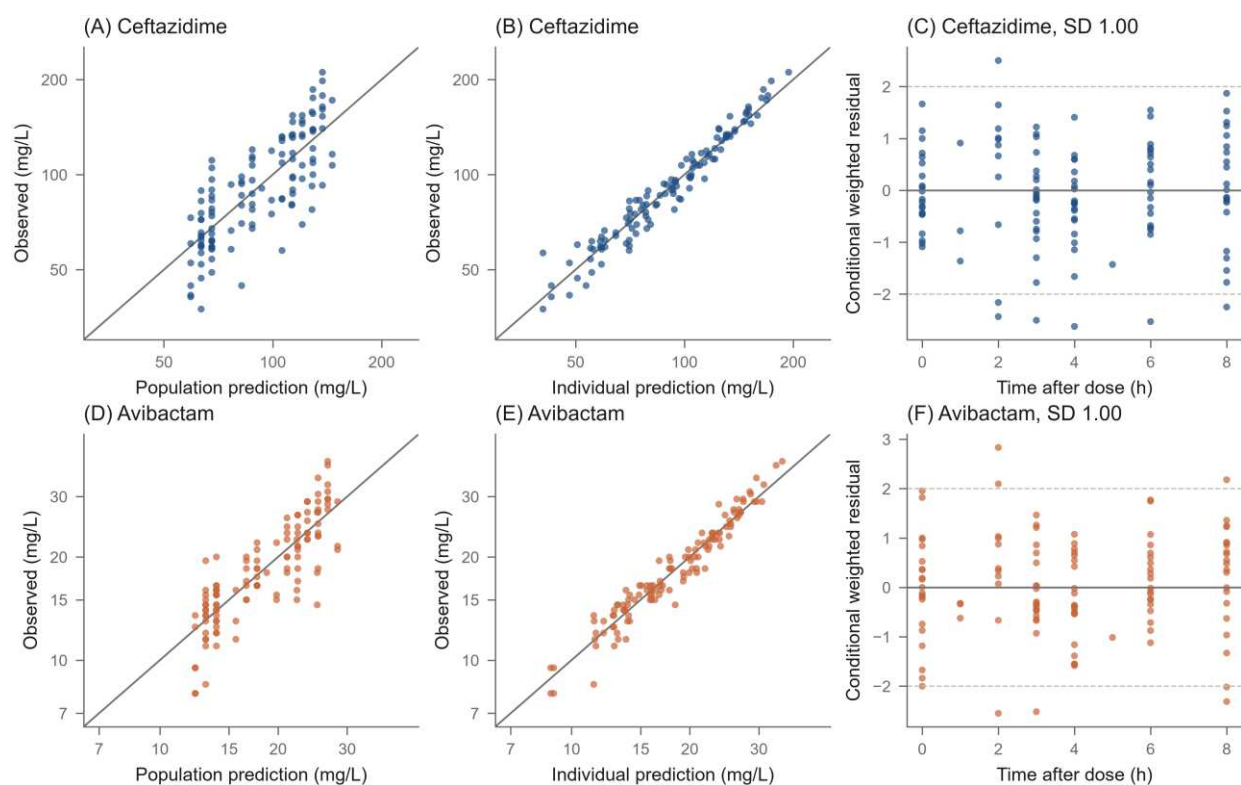
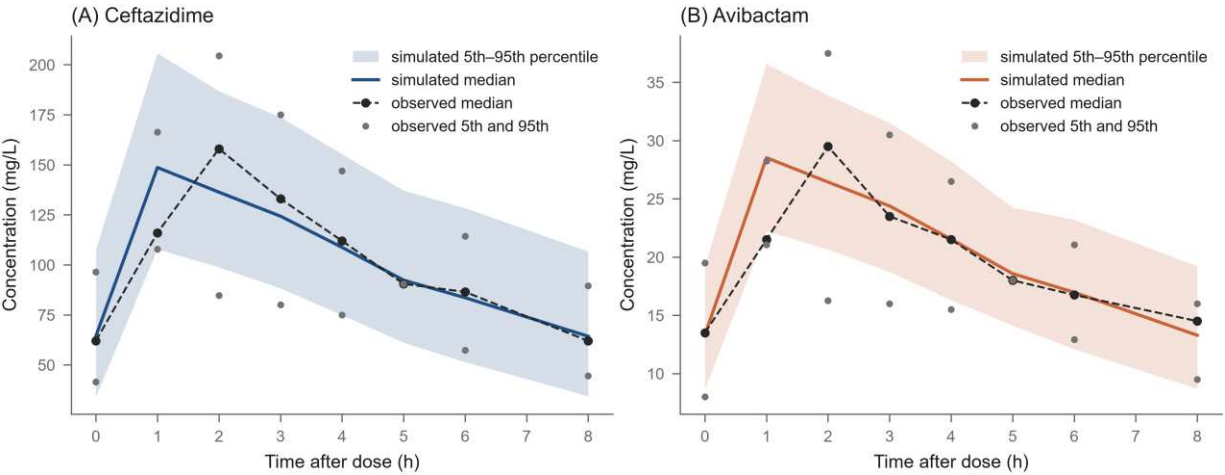


Figure 7. Goodness of fit of the joint two-analyte model in the individual-patient cohort (21 adults receiving continuous renal replacement therapy, 238 observations). (A, D) Observed concentrations against population predictions and (B, E) against individual predictions, for ceftazidime (upper row) and avibactam (lower row); the diagonal is the line of identity and both axes are logarithmic. (C, F) Conditional weighted residuals against time after dose, with the solid line at zero and dashed lines at ± 2 . Residuals were centred on zero with a standard deviation of 1.00 for both analytes and showed no trend against time. Individual predictions track the observations along the line of identity; population predictions scatter around it, as expected in the presence of between-subject variability.

Shrinkage of the clearance random effects was below 1% for both analytes, so individual clearances were determined by the data rather than by the population distribution; proportional residual error was 10.0% for ceftazidime and 9.3% for avibactam. Conditional weighted residuals were centred on zero with unit standard deviation for both analytes and showed no trend against time. Leave-one-subject-out refits ranged from 0.651 to 0.756 with a median of 0.700, and every variant of the infusion-duration coding gave a correlation between 0.70 and 0.78 (Supplementary Table S25). The visual predictive check (Figure 8) covered 82.7% of observations within the nominal 90% interval, a mild under-prediction of variability consistent with the absence of a covariate model for renal replacement settings. In simulation-based calibration the estimator was essentially unbiased (+2.6% at a true correlation of 0.703 and +1.1% at 0.94), simulating from a two-compartment truth shifted the bias by 0.003, indicating that the one-compartment assumption does not

305 materially affect the correlation estimate, and all 25 correctly specified replicates returned a value below 0.94
306 (Supplementary Table S24).

307



308

309 **Figure 8.** Visual predictive check of the joint two-analyte model, from 1,000 replicates of the observed sampling design. (A) Ceftazidime
310 and (B) avibactam. The shaded band is the simulated 5th–95th percentile and the solid line the simulated median; the dashed line with
311 filled circles is the observed median, and grey points are the observed 5th and 95th percentiles. Observed medians lie within the
312 simulated interval at every sampling time for both analytes. Coverage of the nominal 90% interval was 82.7% (ceftazidime 85.4%,
313 avibactam 79.9%). The simulated median peaks at the end of infusion whereas the observed median peaks at 2 h, reflecting the infusion-
314 duration coding of the source dataset and the absence of samples before 2 h in most patients; the 1 h bin contains three observations.

315 **4. Discussion**

316 **4.1. Principal findings**

317 In this steady-state simulation, the avibactam target had a greater effect on joint target attainment than the
318 pharmacokinetic assumptions examined in the sensitivity analyses. PTA and CFR changed considerably when
319 the avibactam target was varied from 1 to 8 mg/L. Therefore, these estimates need to be interpreted based on
320 the avibactam target used and whether it represents a free or total concentration. The 4-mg/L value provides a
321 clearly defined assumption for the scenario analysis, but it should not be considered an established in vivo
322 exposure-response threshold.

323 The clearance correlation reported here is, to our knowledge, the first for this combination to be obtained by
324 fitting both analytes jointly and reported with an uncertainty interval. The wider point is not that 0.703 should
325 replace 0.94, but that 0.94 has been carried through the target-attainment literature without ever being

estimated from paired individual concentrations. An analysis that relies on it now has a value to justify rather than an assumption to inherit. Its value matters in two ways. It is one of the inputs that determines joint attainment, and it sets the ceiling on how much a ceftazidime measurement can say about avibactam. At the estimated value, ceftazidime-based inference wrongly reassures nearly three times as many patients as it does at the assumed value.

4.2. Clinical interpretation

The limiting component changed with MIC. This is expected because the ceftazidime target depends on MIC, whereas the avibactam target is based on a fixed concentration. At lower MICs, avibactam was the main limiting component. At the clinical breakpoint, ceftazidime became the limiting component.

At the same MIC, model-derived dose requirements differed by more than five-fold across renal-function classes. This finding shows the importance of renal function when evaluating dosing requirements and supports further investigation of individualized, concentration-guided dosing. Current therapeutic drug monitoring guidance supports individualized assessment of beta-lactam exposure in critically ill adults. However, whether measuring avibactam separately provides additional clinical value will depend on assay performance, clinical benefit, and cost [6,26-28]. The case for direct measurement is strengthened rather than weakened if the true clearance correlation is nearer the value estimated here from individual patient data than the value assumed in the source model.

4.3. Strengths and limitations

This analysis used component-specific pharmacodynamic targets and explicitly classified the source of each input. It also incorporated correlated clearances of ceftazidime and avibactam and included target-sensitivity, calibration, and structural-uncertainty analyses. However, the model was reconstructed from published equations and parameters rather than fitted to individual patient data. The calibration should therefore be considered an implementation check and not an external validation. The clearance correlation was estimated in patients receiving continuous renal replacement therapy [23], in whom both components are eliminated through a shared extracorporeal circuit; a common clearance pathway would be expected to raise rather than lower the correlation between them. That expectation is mechanistic rather than demonstrated here, but it makes it unlikely that the present estimate understates the correlation in patients with intact renal clearance. The cohort also differs in infusion mode and in size, so the estimate establishes that the assumed

value is unverified rather than providing a substitute for it. Only the correlation is carried into the present analysis, and only as a sensitivity bound: the clearance and volume estimates from that cohort are not transferred, and the primary simulation retains the source-model value of 0.94. A two-compartment structure was not tested, although simulation-based calibration indicates that this assumption does not materially affect the correlation estimate. The renal-function weights were assumptions based on reported quartiles and did not represent observed frequencies within each renal-function class. The exposure screen was also based on an operational ceiling reported in a small cohort and should not be considered a validated neurotoxicity threshold [19,29]. The regimen selected for each renal-function class follows a prespecified rule (Section 2.3) and is common to every avibactam target compared, so the target-sensitivity result does not depend on that selection; absolute attainment under a fixed labelled regimen would differ.

Several limitations should be considered. We did not simulate the loading phase, time-varying concentrations, interoccasion variability, residual error, or empirical distributions of epithelial lining fluid penetration. The site-of-infection analyses used fixed penetration ratios from published studies and therefore cannot determine target-site exposure in individual patients. Our results apply only to critically ill adults who were not receiving renal replacement therapy and who received ceftazidime-avibactam by continuous infusion. The pharmacodynamic targets evaluated in this study were related to bacterial killing and not to mutant suppression. Further details and sensitivity-analysis results are provided in the Supplementary Material.

5. Conclusion

The choice of avibactam target had a substantial effect on estimated target attainment for continuous-infusion ceftazidime-avibactam. This effect was greater than that of the pharmacokinetic assumptions examined in the sensitivity analyses. Joint CFR ranged from 93.4%-98.6% with an avibactam target of 1 mg/L to 44.0%-60.7% with a target of 8 mg/L. Thus, the same pharmacokinetic data may lead to different conclusions about regimen adequacy depending on the avibactam target used.

The 4-mg/L continuous-infusion scenario can be used as a conservative and clearly defined assumption, but this concentration should not be interpreted as an established in vivo avibactam exposure-response threshold. Future target-attainment studies should report the avibactam target, indicate whether it refers to free or total concentration, and examine sensitivity across plausible thresholds. Differences in these assumptions should also be considered when comparing results between studies. Renal function and MIC affected the

model-derived dose requirement and whether it remained below the prespecified modelled limit of 10 g/day. Prospective studies evaluating avibactam exposure-response relationships and epithelial lining fluid exposure in critically ill patients are needed to better define clinically relevant targets.

Data availability statement

Processed simulation inputs, output workbooks, provenance registers, runtime metadata, checksums, and figure-generation scripts are publicly available at <https://github.com/piranfar/caz-avi-evidence-composite-pkpd>. Source article PDFs are not redistributed because of copyright restrictions. The repository is intended for reproducibility and methodological transparency and is not a clinical dosing tool. The individual patient data analysed in Section 2.5 are openly available from Dryad (10.5061/dryad.fxpnvx16s) under a CC0 waiver.

Code availability statement

Analysis code and figure-generation scripts are available at <https://github.com/piranfar/caz-avi-evidence-composite-pkpd>. The repository includes frozen output tables used for the reproduction check. It will be archived with a persistent DOI upon publication, subject to journal policy.

Ethics statement

This study did not involve new experiments on human participants. The simulation used published aggregate data. The individual patient concentrations analysed in Section 2.5 are from a de-identified dataset released into the public domain by the original investigators under a CC0 waiver [23] (Dryad 10.5061/dryad.fxpnvx16s). That study was approved by the ethics committees of Jinling Hospital (2024DZKY-066-02) and conducted in accordance with the Declaration of Helsinki, and all patients gave written informed consent for the use of their clinical data for research; its bioanalytical method is reported in the same publication. No additional ethics approval was required for the present secondary analysis of that de-identified public dataset.

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Declarations of interest

The author declares no competing interests.

Author contributions

Vahhab Piranfar: Conceptualization, methodology, software, formal analysis, data curation, writing - original draft, writing - review and editing, visualization, project administration. The author approved the final version for submission and accepts responsibility for the work.

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References

- [1] Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 399(10325):629–55. [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
- [2] World Health Organization (2024) WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance, to guide research, development and strategies to prevent and control antimicrobial resistance. World Health Organization, Geneva
- [3] Shields RK, Chen L, Cheng S, Chavda KD, Press EG, Snyder A, et al (2017) Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne blaKPC-3 Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections. *Antimicrob Agents Chemother* 61(3):e02097-16. <https://doi.org/10.1128/AAC.02097-16>
- [4] Kang MS, Baek JY, Ko JH, Cho SY, Lee KY, Lee YH, et al (2024) Antimicrobial activity of ceftazidime-avibactam against KPC-2-producing Enterobacterales: a cross-combination and dose-escalation titration study with relebactam and vaborbactam. Warren BG, editor. *Microbiol Spectr* 12(6):e00344-24. <https://doi.org/10.1128/spectrum.00344-24>

- 432 [5] Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al (2014) Individualised
433 antibiotic dosing for patients who are critically ill: challenges and potential solutions. *The Lancet Infectious*
434 *Diseases* 14(6):498–509. [https://doi.org/10.1016/S1473-3099\(14\)70036-2](https://doi.org/10.1016/S1473-3099(14)70036-2)
- 435 [6] Abdul-Aziz MH, Alffenaar JWC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al (2020) Antimicrobial
436 therapeutic drug monitoring in critically ill adult patients: a Position Paper#. *Intensive Care Med*
437 46(6):1127–53. <https://doi.org/10.1007/s00134-020-06050-1>
- 438 [7] Li J, Lovern M, Green ML, Chiu J, Zhou D, Comisar C, et al (2019) Ceftazidime-Avibactam Population
439 Pharmacokinetic Modeling and Pharmacodynamic Target Attainment Across Adult Indications and Patient
440 Subgroups. *Clin Transl Sci* 12(2):151-63. <https://doi.org/10.1111/cts.12585>
- 441 [8] Cojutti PG, Pai MP, Gatti M, Rinaldi M, Ambretti S, Viale P, et al (2024) An innovative population
442 pharmacokinetic/pharmacodynamic strategy for attaining aggressive joint PK/PD target of continuous
443 infusion ceftazidime/avibactam against KPC- and OXA-48- producing Enterobacterales and preventing
444 resistance development in critically ill patients. *Journal of Antimicrobial Chemotherapy* 79(11):2801–8.
445 <https://doi.org/10.1093/jac/dkae290>
- 446 [9] Gatti M, Rinaldi M, Gaibani P, Siniscalchi A, Tonetti T, Giannella M, et al (2023) A descriptive
447 pharmacokinetic/pharmacodynamic analysis of continuous infusion ceftazidime-avibactam for treating DTR
448 gram-negative infections in a case series of critically ill patients undergoing continuous veno-venous
449 haemodiafiltration (CVVHDF). *Journal of Critical Care* 76:154301.
450 <https://doi.org/10.1016/j.jcrc.2023.154301>
- 451 [10] O'Jeanson A, Nielsen EI, Friberg LE (2025) Therapeutic drug monitoring (TDM) of β -lactam/ β -lactamase
452 inhibitor (BL/BLI) drug combinations: insights from a pharmacometric simulation study. *Journal of*
453 *Antimicrobial Chemotherapy* 80(1):79–86. <https://doi.org/10.1093/jac/dkae375>
- 454 [11] Curtiaud A, Petit M, Chommeloux J, Pineton De Chambrun M, Hekimian G, Schmidt M, et al (2024)
455 Ceftazidime/avibactam serum concentration in patients on ECMO. *Journal of Antimicrobial Chemotherapy*
456 79(5):1182–6. <https://doi.org/10.1093/jac/dkae091>

- 457 [12] Wölfl-Duchek M, Van Os W, Al Jalali V, Rabl U, Wohlrab P, Bauer M, et al (2025) Cerebrospinal fluid
458 concentrations of ceftaroline and ceftazidime/avibactam in healthy volunteers: Pharmacokinetics and
459 probability of target attainment. *International Journal of Antimicrobial Agents* 66(2):107512.
460 <https://doi.org/10.1016/j.ijantimicag.2025.107512>
- 461 [13] Aubry R, Buyck JM, Chauzy A, Prouvensier L, Decousser JW, Nordmann P, et al (2025) PKPD modeling
462 of the inoculum effect of combined ceftazidime/avibactam and colistin against KPC-3 *Klebsiella*
463 *pneumoniae* isolate. Leggett JE, editor. *Antimicrob Agents Chemother* 69(5):e01797-24.
464 <https://doi.org/10.1128/aac.01797-24>
- 465 [14] Lee YL, Ko WC, Hsueh PR (2022) Geographic patterns of global isolates of carbapenem-resistant
466 *Klebsiella pneumoniae* and the activity of ceftazidime/avibactam, meropenem/vaborbactam, and
467 comparators against these isolates: Results from the Antimicrobial Testing Leadership and Surveillance
468 (ATLAS) program, 2020. *International Journal of Antimicrobial Agents* 60(5–6):106679.
469 <https://doi.org/10.1016/j.ijantimicag.2022.106679>
- 470 [15] Bakthavatchalam YD, Routray A, Mane A, Kamat S, Gupta A, Bari AK, et al (2022) In vitro activity of
471 Ceftazidime–Avibactam and its comparators against Carbapenem resistant Enterobacterales collected
472 across India: results from ATLAS surveillance 2018 to 2019. *Diagnostic Microbiology and Infectious*
473 *Disease* 103(1):115652. <https://doi.org/10.1016/j.diagmicrobio.2022.115652>
- 474 [16] Gatti M, Giannella M, Rinaldi M, Gaibani P, Viale P, Pea F (2022) Pharmacokinetic/Pharmacodynamic
475 Analysis of Continuous-Infusion Fosfomycin in Combination with Extended-Infusion Cefiderocol or
476 Continuous-Infusion Ceftazidime-Avibactam in a Case Series of Difficult-to-Treat Resistant *Pseudomonas*
477 *aeruginosa* Bloodstream Infections and/or Hospital-Acquired Pneumonia. *Antibiotics (Basel)* 11(12):1739.
478 <https://doi.org/10.3390/antibiotics11121739>
- 479 [17] Sy SKB, Zhuang L, Sy S, Derendorf H (2019) Clinical Pharmacokinetics and Pharmacodynamics of
480 Ceftazidime-Avibactam Combination: A Model-Informed Strategy for its Clinical Development. *Clin*
481 *Pharmacokinet* 58(5):545–64. <https://doi.org/10.1007/s40262-018-0705-y>

- 482 [18] European Committee on Antimicrobial Susceptibility Testing (2026) Breakpoint tables for interpretation of
483 MICs and zone diameters, version 16.1, valid from 24 June 2026. <https://www.eucast.org>
- 484 [19] Das S, Li J, Riccobene T, Carrothers TJ, Newell P, Melnick D, et al (2019) Dose Selection and Validation
485 for Ceftazidime-Avibactam in Adults with Complicated Intra-abdominal Infections, Complicated Urinary
486 Tract Infections, and Nosocomial Pneumonia. *Antimicrob Agents Chemother* 63(4):e02187-18.
487 <https://doi.org/10.1128/AAC.02187-18>
- 488 [20] Kidd JM, Stein GE, Nicolau DP, Kuti JL (2020) Monte Carlo Simulation Methodologies for β -Lactam/ β -
489 Lactamase Inhibitor Combinations: Effect on Probability of Target Attainment Assessments. *J Clin*
490 *Pharmacol* 60(2):172–80. <https://doi.org/10.1002/jcph.1510>
- 491 [21] Benítez-Cano A, Sancho-Araiz A, Carazo J, Ramos I, Sánchez-Font A, Chalela R, et al (2026)
492 Intrapulmonary penetration of ceftolozane/tazobactam and ceftazidime/avibactam administered by
493 continuous infusion in critically ill patients with nosocomial pneumonia: a randomized pharmacokinetic trial.
494 *Crit Care* 30(1):305. <https://doi.org/10.1186/s13054-026-06075-w>
- 495 [22] Dimelow R, Wright JG, MacPherson M, Newell P, Das S (2018) Population Pharmacokinetic Modelling of
496 Ceftazidime and Avibactam in the Plasma and Epithelial Lining Fluid of Healthy Volunteers. *Drugs R D*
497 18(3):221–30. <https://doi.org/10.1007/s40268-018-0241-0>
- 498 [23] Li C, Wang Y, Chen F, Huang L, Dong J, Fan W, et al (2026) Pharmacokinetics/pharmacodynamics of
499 ceftazidime-avibactam in critically ill adult patients receiving continuous renal replacement therapy.
500 *Antimicrob Agents Chemother* 70(2):e0143825. <https://doi.org/10.1128/aac.01438-25>
- 501 [24] Coleman K, Levasseur P, Girard AM, Borgonovi M, Miossec C, Merdjan H, et al (2014) Activities of
502 ceftazidime and avibactam against β -lactamase-producing Enterobacteriaceae in a hollow-fiber
503 pharmacodynamic model. *Antimicrob Agents Chemother* 58(6):3366–72.
504 <https://doi.org/10.1128/AAC.00080-14>
- 505 [25] Kroemer N, Amann LF, Farooq A, Pfaffendorf C, Martens M, Decousser JW, et al (2023)
506 Pharmacokinetic/pharmacodynamic analysis of ceftazidime/avibactam and fosfomycin combinations in an

507 in vitro hollow fiber infection model against multidrug-resistant *Escherichia coli*. *Microbiol Spectr*
508 12(1):e0331823. <https://doi.org/10.1128/spectrum.03318-23>

509 [26] Wicha SG, Mårtson A, Nielsen EI, Koch BCP, Friberg LE, Alffenaar J, et al (2021) From Therapeutic Drug
510 Monitoring to Model-Informed Precision Dosing for Antibiotics. *Clin Pharma and Therapeutics* 109(4):928–
511 41. <https://doi.org/10.1002/cpt.2202>

512 [27] Tumbarello M, Raffaelli F, Giannella M, Mantengoli E, Mularoni A, Venditti M, et al (2021) Ceftazidime-
513 Avibactam Use for *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* Infections: A
514 Retrospective Observational Multicenter Study. *Clinical Infectious Diseases* 73(9):1664–76.
515 <https://doi.org/10.1093/cid/ciab176>

516 [28] Falcone M, Viale P, Tiseo G, Pai M (2018) Pharmacokinetic drug evaluation of avibactam + ceftazidime
517 for the treatment of hospital-acquired pneumonia. *Expert Opin Drug Metab Toxicol* 14(3):331–40.
518 <https://doi.org/10.1080/17425255.2018.1434142>

519 [29] Barreto EF, Webb AJ, Pais GM, Rule AD, Jannetto PJ, Scheetz MH (2021) Setting the Beta-Lactam
520 Therapeutic Range for Critically Ill Patients: Is There a Floor or Even a Ceiling? *Crit Care Explor*
521 3(6):e0446. <https://doi.org/10.1097/CCE.0000000000000446>

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