RESEARCH | Article in Press

Optimising tazobactam dosing in critically ill adult patients without renal replacement therapy: a population pharmacokinetic analysis of individual patient data pooled from multiple clinical studies

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Received: 6 July 2026 / Accepted: 3 September 2026

Abstract

Background Critically ill patients exhibit altered β-lactam pharmacokinetics (PK), yet β-lactamase inhibitor exposure is often overlooked during dose optimisation. This study characterised the PK of tazobactam in critically ill patients and defined optimal dosing regimens that achieve different pharmacokinetic/pharmacodynamic (PK/PD) targets.

Methods Tazobactam concentration-time data from nine clinical studies were analysed using nonlinear mixed-effects modelling with Monolix. One- and two-compartment models with linear elimination were evaluated, and covariates were identified. The probability of target attainment at steady state was evaluated across multiple dosing regimens for various PK/PD targets at estimated glomerular filtration rates (eGFR) of 40, 80, and 140 mL/min.

Results A total of 1771 plasma concentration-time data points for tazobactam from 421 patients were included in the analysis. A two-compartment model with linear elimination adequately described tazobactam PK. eGFR, weight and co-administered antimicrobial (piperacillin or ceftolozane) were identified as factors influencing tazobactam clearance. Standard dosing regimens achieved the conservative target of 20% $fT_{>1\ mg/L}$ at 80 mL/min and 140 mL/min. However, aggressive targets (50%, 85%, and 100% $fT_{>2\ mg/L}$; 100% $fT_{>4\ mg/L}$), which may be relevant for high-level β-lactamase expression, were rarely met in patients with an eGFR of 140 mL/min. Achieving these targets required higher tazobactam doses administered through continuous infusion.

Conclusion Standard tazobactam dosing often failed to meet the aggressive PK/PD targets at higher eGFR, indicating a substantial risk of underexposure in critically ill patients with augmented renal clearance, supporting the need for dose optimisation, particularly in scenarios of high-level β-lactamase expression.

Keywords Tazobactam · PK/PD targets · Piperacillin · Ceftolozane · Dose optimisation

https://doi.org/10.1186/s13054-026-06321-1

Published online: 09 September 2026

Introduction

Tazobactam is a β-lactamase inhibitor co-formulated with β-lactam antimicrobials, mainly piperacillin and ceftolozane, to treat serious infections caused by Gram-negative bacteria, including Enterobacterales. This inhibitor extends the spectrum of antimicrobial coverage by protecting the β-lactam against β-lactamase inactivation. To maximise the clinical efficacy of β-lactam/β-lactamase inhibitor combinations, it is crucial to optimise the exposure of not only the β-lactam antimicrobial, but also the β-lactamase inhibitor (e.g., tazobactam). This has led to the concept of joint pharmacokinetic/pharmacodynamic (PK/PD) target attainment in the assessment and optimisation of dosing regimens for β-lactam/β-lactamase inhibitor combinations [1–3].

The PK/PD metrics of β-lactam antimicrobials (e.g. piperacillin and ceftolozane) that best relates exposure to efficacy is the percentage of time that the free (unbound) drug concentration exceeds the minimum inhibitory concentration ($\%fT_{>MIC}$) [4]. For tazobactam, the PK/PD exposure metric is considered to be the percentage of time the free drug concentration exceeds a threshold concentration required to inhibit β-lactamases ($\%fT_{>CT}$) [5, 6]. In pre-clinical studies, the reported optimal magnitudes of exposure for this PK/PD metric are inconsistent and vary mainly with the level of β-lactamase expression, bacterial species, and inoculum, which has been reviewed in detail previously [7, 8].

Regardless, most studies suggest that, with conventional doses in standard β-lactam/tazobactam combinations, tazobactam concentrations often fall below the level required for effective β-lactamase inhibition [1, 2, 9–11]. This underexposure might be one of the reasons for the clinical and microbiological failure of conventional dosing regimens of piperacillin/tazobactam and ceftolozane/tazobactam against β-lactamase-producing organisms [12]. Consistent with this, the MERINO trial reported higher mortality with piperacillin/tazobactam than with meropenem in bloodstream infections caused by ceftriaxone-resistant *Escherichia coli* and *Klebsiella pneumoniae* [13]. However, the findings remain the subject of ongoing debate, as interim analyses from the PETER-PEN trial (NCT03671967) indicate that piperacillin/tazobactam achieved non-inferiority for early clinical failure endpoints compared with meropenem in patients with ESβL-producing *E. coli* or Klebsiella spp. bacteraemia [14, 15]. Nevertheless, the uncertainty remains, and some guidelines preferentially recommend carbapenems for serious infections caused by extended-spectrum β-lactamase-producing organisms, reflecting persistent concerns about reduced clinical effectiveness of piperacillin/tazobactam in severe, high-inoculum infections [16, 17]. PK/PD and infection model studies have further demonstrated that standard tazobactam exposures are often insufficient to suppress high levels of β-lactamase expression that may be more likely in high-inoculum infections [18, 19].

Therefore, the aim of this study was to characterise the population PK of tazobactam in critically ill adult patients without renal replacement therapy and define optimal dosing regimens that attain different PK/PD targets for efficacy at steady state (48–72 h).

Methods

Study design

This study was a population PK analysis of tazobactam using individual patient-level data from previously published clinical studies. The final population PK model was used for drug dosing simulations to identify dosing regimens that attain different PK/PD targets for optimal efficacy.

Data set preparation

PK studies of tazobactam, administered in combination with piperacillin or ceftolozane, published up to March 2025, were identified through systematic searches of PubMed, Scopus, Embase, Web of Science, and the Cochrane Library.

Studies reporting total and/or free plasma concentration-time data for tazobactam in critically ill patients were eligible for inclusion in this population PK analysis. Studies were excluded if they involved paediatric patients (< 18 years), patients receiving renal replacement therapy, healthy volunteers, or if samples were obtained from matrices other than plasma (e.g., urine or cerebrospinal fluid).

The first or senior (or corresponding) authors of eligible studies were invited to collaborate and provide anonymised individual patient-level data. Studies were also excluded if the authors did not respond to data requests. In addition to published data, we have included tazobactam data from DECISIVE [20] and PNEUDOS [21] trials. All included studies had received ethics approval permitting secondary use of de-identified data under the original study approvals.

Plasma tazobactam concentration-time data, patient demographic and clinical characteristics (sex, age, weight, height, serum creatinine) as well as dosing regimen details (dose, infusion duration, dosing interval, and total duration of therapy) were sourced from the included studies. Creatinine clearance (CrCl) and estimated glomerular filtration rate (eGFR) were subsequently calculated using the Cockcroft-Gault [22] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [23]. Components of each study dataset were thoroughly reviewed. Inconsistencies in dosing records or patient characteristics were identified and resolved in consultation with the authors to ensure data accuracy.

Population pharmacokinetics model development

Tazobactam plasma concentrations-time data were analysed using non-linear mixed-effects (NLME) modelling with the stochastic approximation expectation maximisation (SAEM) algorithm in Monolix (version 2024R1; Lixoft, Antony, France) using default settings. The included studies reported either free concentrations (C_{free}), total concentrations (C_{total}), or both. The PK model was developed using both C_{free} and C_{total}. A linear model was used to relate C_{free} and C_{total} ($C_{free} = C_{total} \times fu$), where f_u is the estimated free fraction.

Base model development

One- and two-compartment structural models with linear elimination were tested. Both the free and total tazobactam concentrations were assumed to be normally distributed, and all individual parameters were assumed to follow a log-normal distribution, except for fu, which was assumed to follow a logit distribution. Between-subject variability (BSV) was described using an exponential model. Different error models inbuilt within Monolix were tested to explain the residual variability (Supplementary Table S1).

Covariate analysis

Demographic and clinical patient characteristics, including age, gender, weight, CrCl, eGFR, and the antimicrobial co-administered with tazobactam (piperacillin or ceftolozane), were considered for inclusion as covariates in the model development, using a stepwise forward addition and backward deletion process. A covariate was considered significant during forward inclusion if it reduced the objective function value (OFV) by at least 3.84 ($P < 0.05$), and during backward elimination if it increased the OFV by more than 10.83 ($P < 0.001$) (Supplementary Table S2).

Model evaluation

Model performance was evaluated based on biological plausibility and precision of parameter estimates (assessed using relative standard error, RSE), changes in OFV, and the corrected Bayesian Information Criterion (BICc). The predictive performance of the model was assessed using goodness-of-fit (GOF) diagnostics, including observed versus predicted concentrations at both the population and individual levels; plots of weighted residuals versus predictions and time; normalised prediction distribution error (NPDE) plots versus population predictions and time; and a visual predictive check (VPC). The VPC was performed using 500 simulations based on the final model. Model robustness and parameter precision were further evaluated using a nonparametric bootstrap with 1,000 resamples in Monolix. For each parameter, the median and 95% confidence intervals (2.5th −97.5th percentiles) derived from the bootstrap were compared with the original parameter estimates.

Dosing simulation

Using the final population PK model, the probability of target attainment (PTA) for tazobactam regimens at steady state (48–72 h) was evaluated based on renal function with Simulx2024R1 (Lixoft SAS, a Simulations Plus company). Simulations were performed at three levels of renal function: a GFR of 40 mL/min (first quartile in the patient population), 80 mL/min (median in the patient population) and 140 mL/min (third quartile in the patient population and also representing a suspected state of augmented renal clearance (ARC)).

Twenty-four tazobactam dosing regimens were simulated by considering its combination with piperacillin and ceftolozane, including 0.5, 1, 1.5, and 2 g of tazobactam infused over 0.5, 1, 3, or 4 h, every 6–8 h, and a 24 h infusion of 1.5–8 g, as shown in Supplementary Table S3. Additional simulations were performed using the same total daily dose to enable comparison across dosing regimens when coadministered with piperacillin and ceftolozane (Supplementary Table S5). Five PK/PD targets from pre-clinical and clinical studies were assessed: 20% $fT_{> 1\ mg/L}$ [24, 25], 50%, 85% and 100% $fT_{> 2\ mg/L}$ [6], and 100% $fT_{> 4\ mg/L}$ [2, 26]. An acceptable PTA was defined as ≥ 90% at 48–72 h across all analyses.

Results

Data and patient characteristics

A total of 1771 tazobactam plasma concentration-time data from 421 patients across nine studies conducted in nine countries were included in the analysis [2, 20, 21, 27–32], of which 72% were total concentrations (Table 1). Among the included patients, 71 (16.9%) received intermittent infusion (0.5–1 h), 13 (3.1%) received extended infusion (4 h), and 337 (80.0%) received continuous infusion. Piperacillin/tazobactam was administered to 399 patients (94.8%), while 22 patients (5.2%) received ceftolozane/tazobactam. Tazobactam doses ranging from 0.5 to 1 g were administered as an intermittent (0.5–1 h) or extended infusion (4 h) every 6–8 h, whereas doses of 0.5–2.5 g were administered as a continuous 24 h infusion. The peak, trough, and steady-state concentrations varied across dosing regimens and levels of renal function, as shown in Table 2. Based on the observed tazobactam concentrations, PK/PD target was not attained in most of the study patients following intermittent infusion administration when considering 100% $fT_{> 2\ mg/L\ or\ 4\ mg/L}$. The proportion of patients attaining these targets was relatively high following continuous infusion administration (Fig. 1).

Pharmacokinetic model

A two-compartment model with first-order elimination best described both free and total tazobactam concentrations in plasma (Supplementary Material II). The unexplained variability in free tazobactam concentrations was

Table 1 Patient demographics and clinical characteristics

Author	Study conducted	No. of participants	No of samples	Patient population	Age (years)	WT (kg)	SCr (mg/dL)	CG-CrCl (mL/min)	CKD-EPI eGFR (mL/min)	Co-administered drug
Carrie et al. [27]	France	33	49*	Critically ill patients with OA/VAC	67 (53.0-72.5)	80 (69.0–90.0)	1.31 (0.78–1.86)	52.0 (34.5-113.5)	63.5 (37.5-104.4)	piperacillin
Cheng et al. [28]	Australia	7	54	Critically ill patients on ECMO	45 (40.5–63.8)	80 (63.0-98.8)	0.78 (0.56–1.03)	111 (100.2-181.5)	98.4 (67.4-122.8)	piperacillin
Cojutti et al. [2]	Italy	257	506	Critically ill patients with IAI, BSI, and HAP	66 (57.0–78.0)	75 (65.0–80.0)	1.04 (0.69–1.83)	64.1 (36.8-113.9)	72.2 (37.4-101.7)	piperacillin
Kumta et al. [29]	Australia, S. Korea, Switzerland	7	41	Critically ill neurosurgical patients	60 (49.0-64.2)	70 (58.2–78.5)	0.74 (0.67–0.79)	92.5 (69.4-141.8)	98.6 (94.8-109.8)	piperacillin
Sime et al. [30]	Australia	12	121*	Critically ill patients	56 (51.0–61.0)	79.5 (63.5-100.5)	0.51 (0.41–0.87)	176.9 (111.6–201)	112.2 (91.5-121.9)	ceftolozane
Sime et al. [31]	Australia	10	100*	Critically ill patients with an indwelling external ventricular drain	60.5 (52.0–65.0)	75 (65.0–90.0)	0.55 (0.47–0.67)	128.7 (106-179.8)	108.8 (97.4-113.5)	ceftolozane
Wulkersdorfer et al. [32]	Austria	7	79	Critically ill patients with severe burns	55 (31.0-59.5)	82 (72.8–110)	0.88 (0.68–1.68)	114.2 (73.1-150.5)	92.3 (47.5-113.5)	piperacillin
Sulaiman et al.[20]	Malaysia	45	381	Critically ill patients with preserved renal function	63 (36.0-72.8)	62 (56.0–70.0)	0.93 (0.70–1.62)	71 (39.2–100)	82 (41.9-105.3)	piperacillin
PNEUDOS study [21]	Australia, Belgium, France, Malaysia, Hong Kong	43	220/220*	Critically ill patients with pneumonia	62 (56.0–70.0)	72 (65.8–85.0)	0.94 (0.60–1.30)	78.6 (55.9-112.5)	82.9 (60.9-106.2)	piperacillin
Overall		421	1771		66 (55.0–76.0)	74 (65.0–82.0)	0.99 (0.67–1.67)	69.44 (39.0-118.5)	78.7 (41.2-104.2)	

An asterisk (*) indicates free (unbound) concentration; other concentrations represent total drug concentrations. Continuous variables are presented as median (Q1–Q3), where Q1 = first quartile and Q3 = third quartile. BSI, bloodstream infection; CG-CrCl, creatinine clearance calculated using the Cockcroft–Gault equation; CKD-EPI eGFR, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation; ECMO, extracorporeal membrane oxygenation; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; OA/VAC, open abdomen/vacuum-assisted closure; SCr, serum creatinine; WT, body weight

modelled using a proportional error model, whereas a combined error model was applied to total tazobactam concentrations. BSV was estimated for clearance (CL). Due to high η-shrinkage values, BSV was not estimated for the central volume (V1), the peripheral volume (V2), and intercompartmental clearance (Q).

The inclusion of CKD-EPI eGFR, weight, and the antimicrobial co-administered with tazobactam improved the model fit (Supplementary Table S2). In the final population PK model, CL was described as a function of eGFR, body weight, and the co-administered antimicrobial (ceftolozane or piperacillin) using power and log-linear models as follows:

https://doi.org/10.1186/s13054-026-06321-1

Table 2 Summary of dosing regimens and corresponding peak (Cmax) and trough (Cmin) or steady-state (Css) plasma concentrations, along with renal function, across the included studies

Author	Dosing regimen	Cmax (mg/L)	Css (mg/L)	Cmin (mg/L)	eGFR (mL/min)
Carrie et al. [27]	1.5 g 24 h CI	—	22.5 (15.0–36.0)	—	38.1 (15.6–96.0)
	2.0 g 24 h CI	—	15.7 (1.0–44.0)	—	75.1 (16.1–130.8)
	2.5 g 24 h CI	—	12.3 (6.0–29.0)	—	109.8 (102.5–121.3)
Cheng et al. [28]	0.5 g 0.5 h inf q6h	23.3 (15.8–30.1)	—	2.1(0.9–3.7)	98.1 (58.6–134.9)
Cojutti et al.[2]	0.5 g 24 h CI	—	15.2 (2.5–30.5)	—	23.1 (5.7–79.4)
	0.75 g 24 h CI	—	11.8 (4.1–38.7)	—	43.5 (9.3–100.8)
	1.0 g 24 h CI	—	14.4 (3.9–44.5)	—	49.0 (8.9–126.7)
	1.5 g 24 h CI	—	15.6 (3.1–53.2)	—	66.2 (9.4–146.3)
	2.0 g 24 h CI	—	13.5 (2.5–66.6)	—	83.5 (16.3–138.6)
	2.5 g 24 h CI	—	4.5 (2.2–8.5)	—	117.6 (84.8–136.6)
Kumta et al. [29]	0.5 g 0.5 h inf q6h	24.1 (16.1–32.7)	—	1.5 (0.6–5.1)	101.9 (86.8–121.2)
Sime et al. [30]	0.5 g 1 h inf q8h	9.7 (4.5–17.2)	—	1.3 (0.1–4.4)	89.7 (18.1–126.6)
	1.0 g 1 h inf q8h	20.3 (13.8–26.0)	—	0.5 (0.1–1.6)	119.2 (106.5–142.5)
Sime et al. [31]	1 g 1 h inf q8h	21.8 (13.8–32.2)	—	0.8 (0.1–3.2)	104.2 (48.5–142.5)
Wulkersdorfer et al. [32]	0.5 g 0.5 h inf q8h	25.2 (18.9–32.6)	—	2.2 (0.1–7.5)	86.3 (33.5–31.1)
Sulaiman et al. [20]	0.50 g 1 h inf q6h	18.6 (8.5–44.7)	—	3.3 (0.6–8.6)	88.4 (22.6–140.6)
	0.50 g 1 h inf q8h	21.5 (12.5–28.5)	—	3.8 (1.1–6.7)	56.5 (33.8–99.2)
	0.50 g 4 h inf q6h	9.2 (3.0–25.2)	—	3.9 (0.6–18.4)	101.3 (51.7–136.3)
	0.50 g 4 h inf q8h	15.6 (6.2–29.5)	—	4.5 (0.8–8.3)	74.1 (23.2–96.8)
	0.50 g 6 h CI	—	20.5 (6.0–44.7)	—	61.9 (18.8–113.2)
PNEUDOS study [21]	0.5 g 0.5 h inf q6h	28.2 (13.4–50.8)	—	3.0 (0.9–8.1)	87.2 (43.4–148.8)
	0.5 g 6 h CI	—	15.1 (4.0–43.7)	—	87.7 (9.5–142.5)
	0.5 g 8 h CI	—	16.4 (6.3–29.5)	—	47.0 (24.2–81.6)

CI, continuous infusion; inf, infusion; q6h, every 6 h; q8h, every 8 h; g, gram; h, hour; Cmax, maximum plasma concentration; Css, steady-state plasma concentration; Cmin, minimum (trough) plasma concentration; eGFR, estimated glomerular filtration rate (mL/min), calculated using the CKD-EPI equation. Continuous variables are expressed as mean (min–max)

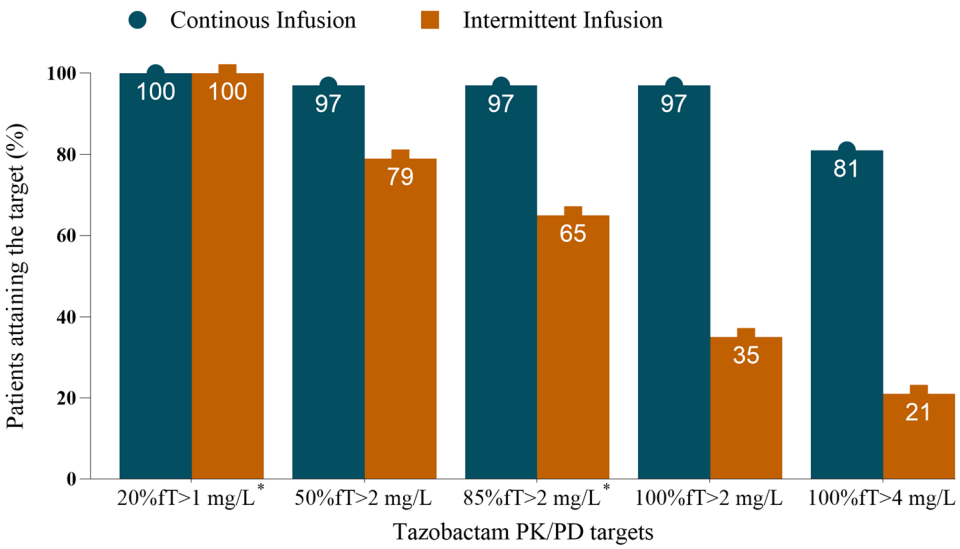

Fig. 1 A bar graph showing proportion of the study population attaining different tazobactam pharmacokinetic/pharmacodynamic targets (*for intermittent infusion, target attainment for 20% $fT_{>1\ mg/L}$ and 85% $fT_{>2\ mg/L}$ was estimated based on individual posterior model predictions)

$$CL_i = CL_{pop} \times \left(\frac{eGFR}{80}\right)^{0.92} \times \left(\frac{WT}{74}\right)^{0.67} \times e^{0.57CEFTi} \times e^{\eta CL,i}$$

Where CL_i is the estimated tazobactam clearance (L/h) in a specific individual; CL_{pop} is the typical population value of tazobactam clearance when co-administered with piperacillin (reference drug), eGFR is the individual's estimated glomerular filtration rate based on the CKD-EPI equation (in mL/min) [23], WT is the individual patient's weight (kg), $CEFT_i$ is a categorical covariate indicating the co-administered antimicrobial (0 = piperacillin, 1 = ceftolozane). Patients receiving ceftolozane exhibited a 77% higher tazobactam CL than those receiving piperacillin. $\eta_{CL,i}$ is a random effect for the i^{th} individual, describing interindividual variability in CL, assumed to follow a log-normal distribution.

Goodness-of-fit diagnostics (Figs. 2 and 3) and VPC plots (Fig. 4) indicated that the final model fit the data reasonably well. Additionally, results from 1000 bootstrap runs revealed close agreement between the bootstrap median and the final median parameter estimate, with all final estimates falling within the corresponding 95% bootstrap confidence intervals (Table 3). The confidence intervals were generally narrow, indicating good parameter precision and model stability. The η-shrinkage for CL was low (13.2%), indicating that individual clearance estimates were well informed by the data. Likewise, ε-shrinkage was low, with values of 5.1% for free tazobactam concentrations and 15.2% for total tazobactam concentrations, suggesting that residual-based diagnostics were unlikely to be substantially affected by shrinkage.

Probability of target attainment

Table 4 summarises the PTA for tazobactam dosing regimens at eGFR of 80 and 140 mL/min. The PTAs for a reduced renal function at eGFR of 40 mL/min are summarised in Supplementary Table S4. All tazobactam regimens met the 20% $fT_{>1\ mg}$ target at all renal function levels and the 50% $fT_{>2\ mg}$ target at eGFR of 40 mL/min when tazobactam is combined with either piperacillin or ceftolozane, and the 50% $fT_{>2\ mg}$ target at eGFR of 80 mL/min, but only when combined with piperacillin. When coadministered with ceftolozane, a 0.5 g dose given as a 4 h infusion every 8 h was required to achieve 50% $fT_{>2\ mg}$ at eGFR of 80 mL/min. However, 85% $fT_{>2\ mg/L}$, 100% $fT_{>2\ mg/L}$, and 100% $fT_{>4\ mg/L}$ targets were not met with standard tazobactam dosing regimens (0.5 g as a 0.5-h infusion every 6 h with piperacillin or as a 1-h infusion every 8 h with ceftolozane). Continuous infusion of 4.0–8.0 g of tazobactam met 100% $fT_{>4\ mg/L}$ target at 140 mL/min, when coadministered with piperacillin; however, at least 4.5 g was required to achieve this target when combined with ceftolozane. Overall, considering equal total daily doses of tazobactam (Supplementary Table S5), a higher PTA was observed when combined with piperacillin compared to ceftolozane.

Discussion

This is the largest population PK analysis of tazobactam in critically ill patients, combining data from nine clinical studies conducted across nine countries. The clinical implications of the dosing evaluations are important. First, standard intermittent tazobactam dosing regimens often result in underexposure, particularly when aggressive PK/PD targets such as 50%, 85%, 100% $fT_{>2\ mg/L}$ and 100% $fT_{>4\ mg/L}$ are applied in critically ill patients with higher eGFR, underscoring the potential inadequacy of current dosing strategies in critically ill patients, including those with ARC. Second, underexposure was more pronounced when tazobactam was co-administered with ceftolozane than with piperacillin under standard dosing regimens, suggesting that the co-administered antimicrobial may influence tazobactam PK. Finally, our results indicate that tazobactam exposure can be optimised by increasing the dose and administering it as a continuous infusion, providing a rationale for the potential need to individualise tazobactam dosing in critically ill patient populations.

https://doi.org/10.1186/s13054-026-06321-1

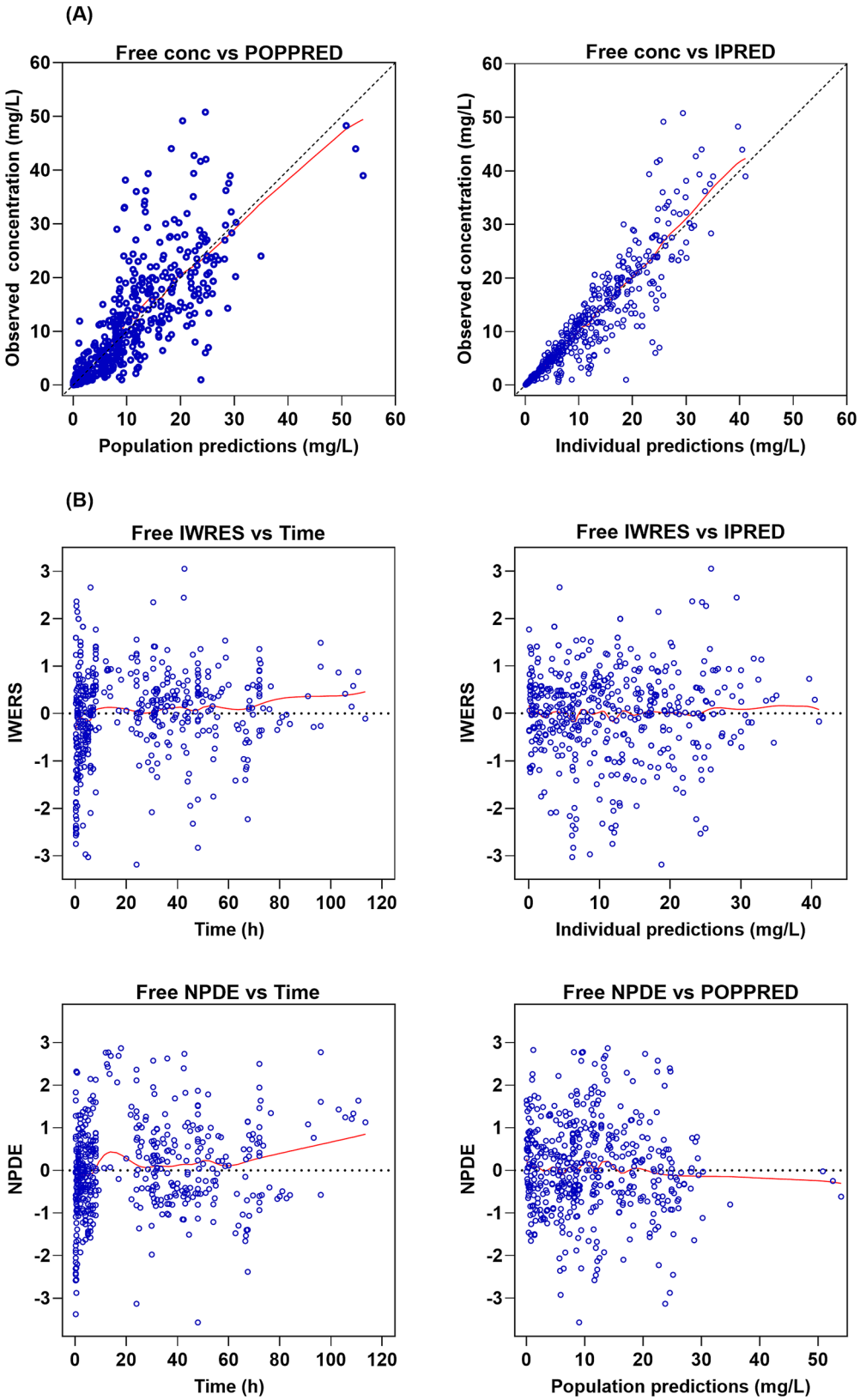

Fig. 2 Goodness of fit (GOF) plots for free tazobactam concentrations. (**A**) Observed versus population or individual predicted concentrations; (**B**) Scatter plots of residuals; IWRES versus time or individual predicted concentrations and NPDE versus time or individual predicted concentrations, IWERS; Individual Weighted Residuals, NPDE, Normalized Prediction Distribution Errors

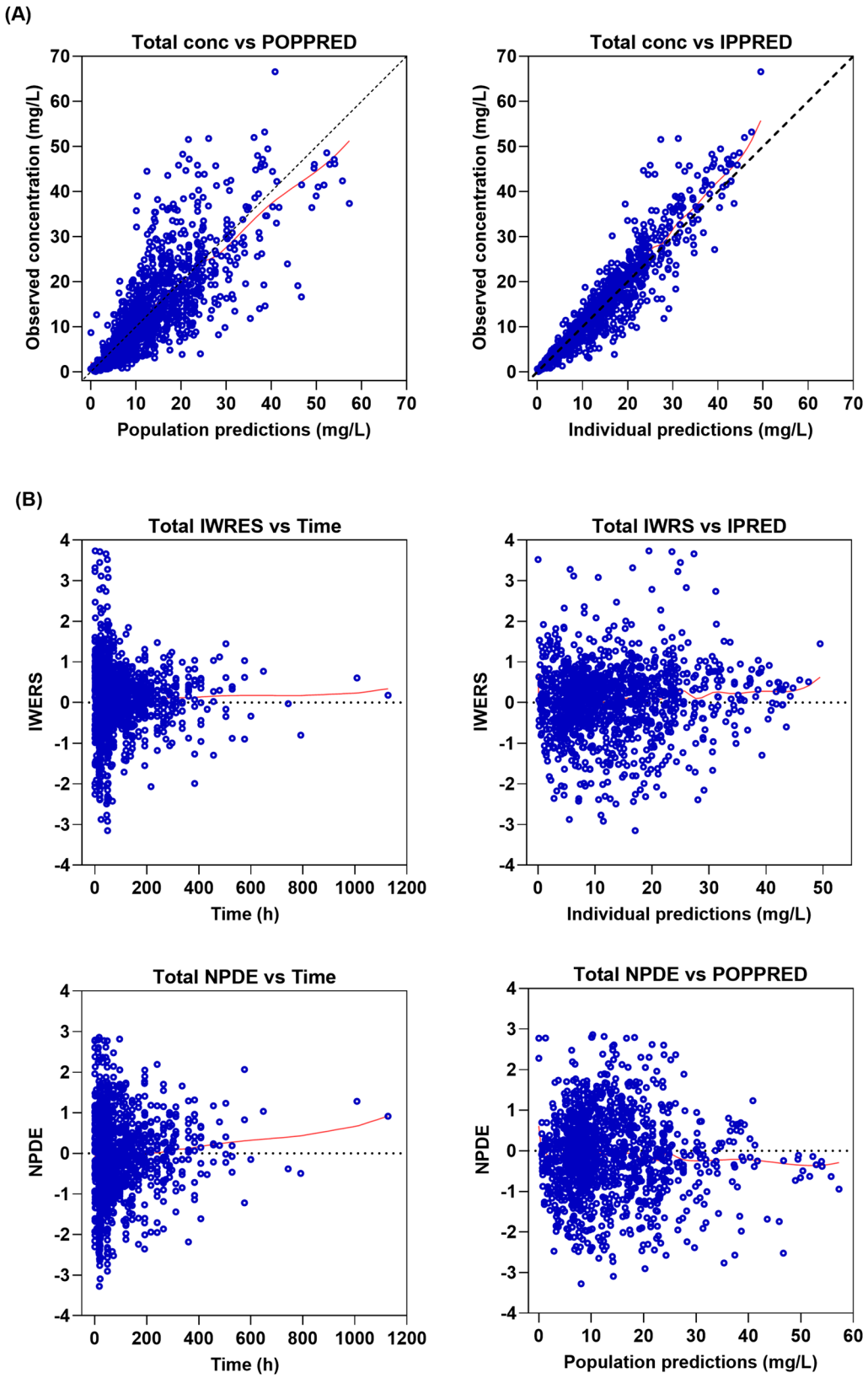

Fig. 3 Goodness of fit (GOF) plots for total tazobactam concentrations. (**A**) Observed versus population or individual predicted concentrations; (**B**) Scatter plots of residuals; IWRES versus time or individual predicted concentrations and NPDE versus time or individual predicted concentrations, IWERS; Individual Weighted Residuals, NPDE, Normalized Prediction Distribution Errors

https://doi.org/10.1186/s13054-026-06321-1

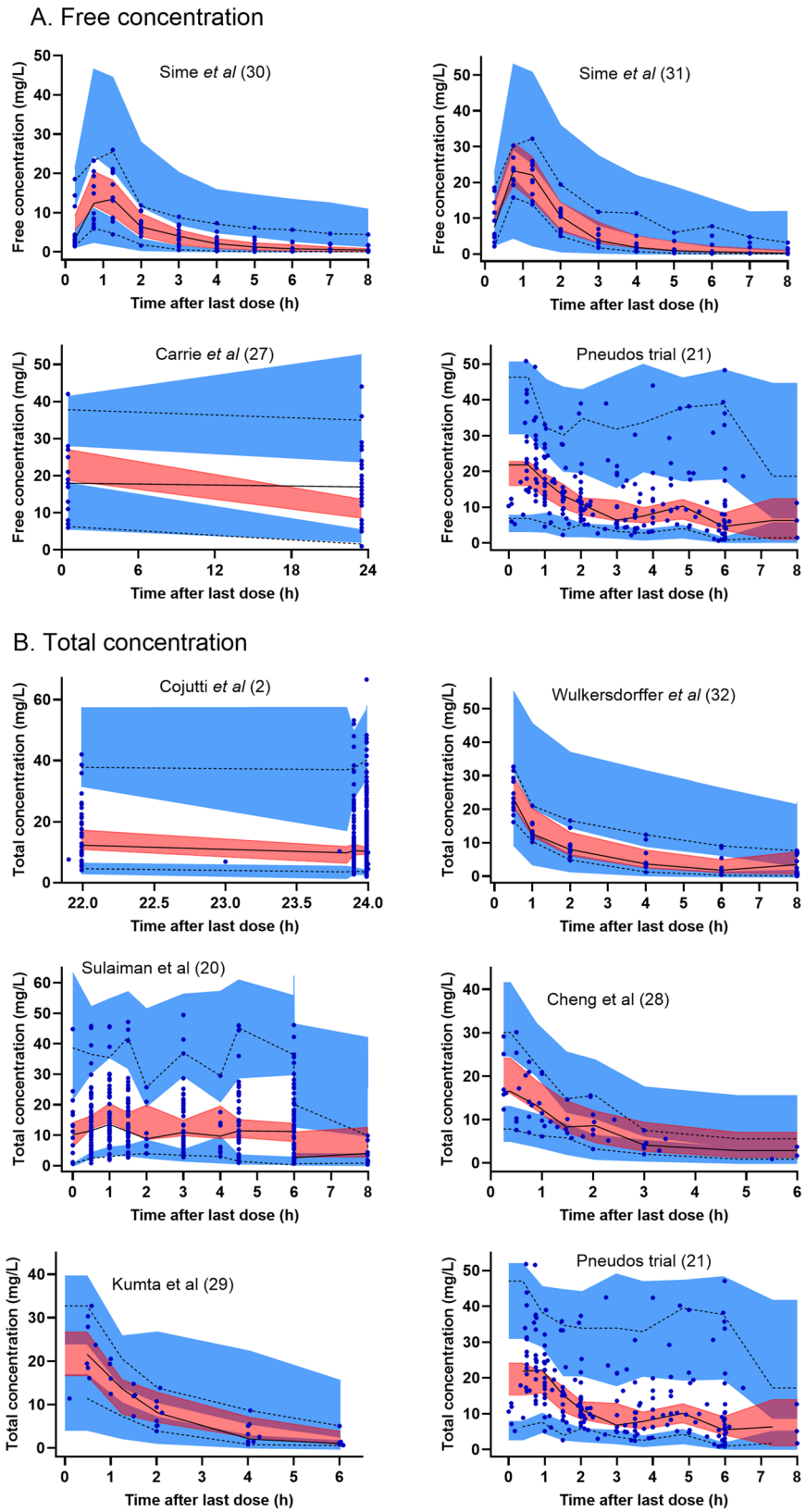

Fig. 4 Visual predictive plots for each of the studies that contributed data for analysis

Table 3 Population parameter estimates from the final model and bootstrap runs

Parameter	Estimate (RSE %)	Bootstrap (N=1000)		
		Median	P2.5	P97.5
Fixed Effects				
CL (L/h)	8.47 (2.64)	8.60	8.06	9.15
Ceftolozane coadministration on CL	0.57 (15.20)	0.57	0.41	0.75
CKD-EPI eGFR effect on CL	0.92 (3.14)	0.92	0.86	0.98
Weight effect on CL	0.67 (11.30)	0.67	0.54	0.81
V1 (L)	16.62 (5.20)	16.81	14.40	20.02
Q (L/h)	12.68 (18.90)	13.05	7.24	25.1
V2 (L)	9.96 (9.31)	10.26	7.41	10.26
fu	0.94 (1.98)	0.93	0.88	0.98
Random effects				
IIV_{CL} (%)	32.53 (6.17)	32	27	38
Residual Error				
$Proportion_{Free}$ (%)	30.0 (3.60)	30.0	25.0	34.0
$Additive_{Total}$ (mg/L)	0.18 (15.60)	0.17	0.003	0.28
$Proportion_{Total}$ (%)	24.0 (3.00)	24.0	21.0	27.0

CL, clearance; V1, central volume of distribution; Q, intercompartmental clearance; V2, peripheral volume of distribution; fu, free fraction; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation for estimating glomerular filtration rate; IIV_{CL}, interindividual variability in clearance expressed as coefficient of variation (CV%); RSE, relative standard error; P2.5 and P97.5, 2.5th and 97.5th percentiles of the bootstrap parameter distribution, respectively. $Proportional_{Free}$, proportional residual error for free concentrations; $Additive_{Total}$ and $Proportional_{Total}$, additive and proportional residual errors for total concentrations, respectively

Table 4 Probability of target attainment for different tazobactam dosing regimens at 48–72 h across varying renal function levels

Coadministered β-lactam	Tazobactam dosing regimen	Tazobactam PTA by renal function and PK/PD targets									
		eGFR = 80 mL/min					eGFR = 140 mL/min				
		20% fT >1 mg/L	50%fT >2 mg/L	85%fT >2 mg/L	100%fT >2 mg/L	100%fT >4 mg/L	20% fT > 1 mg/L	50% fT > 2 mg/L	85%fT >2 mg/L	100%fT >2 mg/L	100%fT >4 mg/L
Combination with Piperacillin	0.5 g q6h, 0.5 h infusion	100	98.4	83.2	75.1	44.6	99.9	80.8	34	26	6.1
	0.5 g q6h, 3 h infusion	100	100	99.1	97.2	79.4	100	99.9	82.2	67.6	29.1
	1.0 g q6h, 0.5 h infusion	100	99.9	95.6	91.1	75.2	99.9	95.7	63.5	51.8	26.3
	1.0 g q6h, 3 h infusion	100	100	100	99.3	95.9	100	100	96	90	65.5
	1.5 g q6 h, 0.5 h infusion	100	100	98.3	97	89.6	100	98.9	78	67.7	43.1
	1.5 g q6h, 3 h infusion	100	100	100	100	98.9	100	100	98.9	96.4	82.1
	2.0 g q6h, 0.5 h infusion	100	100	99.6	98.5	92.6	100	99.6	84.2	77.1	54.8
	2.0 g q6h, 3 h infusion	100	100	100	99.9	99.3	100	100	99.2	97.3	89.3
	2.0 g CI for 24 h with 0.5 g LD	100	100	100	100	99.1	100	99.8	99.8	99.8	86.6
	4.0 g CI for 24 h with 1.0 g LD	100	100	100	100	100	100	100	100	100	99.9
	6.0 g CI for 24 h with 1.5 g LD	100	100	100	100	100	100	100	100	100	100
	8.0 g CI for 24 h with 2.0 g LD	100	100	100	100	100	100	100	100	100	100
Combination with Ceftolozane	0.5 g q8h, 0.5 h infusion	100	58.3	11.7	7	1.6	96.1	13.4	0.6	0.2	0
	0.5 g q8h, 4 h infusion	100	97.3	33.5	20.9	3.4	100	73.7	2.8	1.1	0
	1.0 g q8h, 1 h infusion	100	84.2	31.3	22.3	6.3	99.2	37.3	3.1	1.1	0
	1.0 g q8h, 4 h infusion	100	100	66.5	48.9	19.7	100	99.4	15.7	8.9	1
	1.5 g q8h, 1 h infusion	100	92.2	45.8	35.1	14.8	99.9	54.2	7.3	4.5	0.7
	1.5 g q8h, 4 h infusion	100	100	79.2	64.9	36.4	100	99.9	28.7	15.7	3.8
	2.0 g q8h, 1 h infusion	100	96.7	54.3	44.2	23.8	100	65.1	11.6	7.3	2.2
	2.0 g q8h, 4 h infusion	100	100	85.3	73.5	46.9	100	100	37.6	22.3	8.3
	1.5 g CI for 24 h with 0.5 g LD	99.9	96.8	96.8	96.8	56	99	72.3	72.3	72.3	10.3
	3.0 g CI for 24 h with 1.0 g LD	100	100	100	100	97.8	100	99.4	99.4	99.4	74.9
	4.5 g CI for 24 h with 1.5 g LD	100	100	100	100	99.9	100	100	100	100	95.7
	6.0 g CI for 24 h with 2.0 g LD	100	100	100	100	100	100	100	100	100	99.5

eGFR- estimated Glomerular Filtration Rate, q6h- every six hours, q8h- every eight hours, CI- continuous infusion, LD-Loading dose infused for one hour, grey shade indicates optimal PTA ≥ 90%, white unshaded cell (figures) indicates sub-optimal PTA < 90

Previous studies have not reached consensus on a single PK/PD metric to describe tazobactam's efficacy, leading to multiple proposed PK/PD targets [7, 8]. In this study, five targets were evaluated, representing a range of scenarios from preclinical and clinical studies, with 20% $fT_{>1\ mg/L}$ [24, 25] reflecting low β-lactamase expression, 50–100% $fT_{>2\ mg/L}$ [6] representing intermediate to high β-lactamase expression (mainly in Enterobacterales) and 100% $fT_{>4\ mg/L}$ corresponding to what could be considered an aggressive target based on in vitro susceptibility testing at a fixed tazobactam concentration of 4 mg/L [2, 26]. The conservative 20% $fT_{>1\ mg/L}$ target was met by all regimens across all renal function groups. However, achieving higher targets, 50–100% $fT_{>2\ mg/L}$, is needed to protect companion β-lactams in moderate to high β-lactamase expression [2, 6]. Simulations targeting 100% $fT_{>4\ mg/L}$ showed that standard dosing regimens were inadequate, suggesting that conventional MIC assays in which tazobactam is fixed at 4 mg/L might overestimate activity. Doses two- to four-fold higher (4.0–8.0 g) than currently approved doses would be required to achieve the 100% $fT_{>4\ mg/L}$ target. Collectively, these results underscore the risk of tazobactam underexposure and the need for careful dose optimisation to ensure effective β-lactamase inhibition and improve clinical outcomes in critically ill patients.

Consistent with our findings, previous clinical PK studies show that standard 30 min infusion dosing regimens frequently fail to achieve adequate tazobactam exposure. Even with continuous infusion of currently recommended doses (1.5 and 2 g per day), subtherapeutic tazobactam exposure remains common, particularly in critically ill patients [1, 2]. Observational studies in critically ill populations have further demonstrated that failure to attain aggressive PK/PD targets is associated with increased microbiological failure and poorer early treatment response [9, 33] underscoring the clinical importance of target attainment. Taken together, these findings suggest that tazobactam underexposure may contribute to treatment failure in critically ill patients and in infections caused by β-lactamase-producing organisms.

Clearance of tazobactam is predominantly mediated by glomerular filtration and organic anion transporters 1 and 3(OAT1 and OAT3)-mediated active secretion in the proximal tubule [34]. Accordingly, renal function is expected to be a major determinant of tazobactam PK. Consistent with this, our population PK analysis identified eGFR as a covariate describing altered tazobactam CL, in agreement with a previous study highlighting the importance of incorporating renal function metrics when optimising tazobactam dosing [12]. Furthermore, both piperacillin and tazobactam are substrates of the renal transporters OAT1 and OAT3, resulting in competition for active tubular secretion and a reduction in tazobactam clearance when co-administered with piperacillin [2, 35]. In contrast, ceftolozane does not appreciably interact with these transporters, so tazobactam elimination via active secretion is not inhibited to the same extent [36]. This mechanistic difference suggests that systemic exposure and PTA for tazobactam may be higher when co-administered with piperacillin than with ceftolozane. Consistent with this hypothesis, the tazobactam-to-β-lactam ratio is fourfold higher in the standard ceftolozane/tazobactam formulation than in the standard piperacillin/tazobactam formulation. Our population PK analysis also showed higher PTA for tazobactam when combined with piperacillin than with ceftolozane, either comparing grossly at standard dosing regimens (Table 4) or at equal total daily doses (Supplementary Table S5). Of note, these results should be interpreted cautiously, as only two clinical studies from a single centre contributed data on tazobactam combined with ceftolozane [30, 31], and direct clinical PK comparisons of tazobactam exposure between the two combinations have not been reported. In addition, differences in patient populations, such as severity of illness and renal function, may have contributed to the observed variability, as piperacillin and ceftolozane are typically used in different prescribing contexts.

Like β-lactams, tazobactam exhibits time-dependent activity, meaning its efficacy is closely linked to the duration that plasma concentrations remain above the threshold required to inhibit target β-lactamases [6]. Standard intermittent dosing (0.5–1 h) often results in periods when tazobactam levels fall below this threshold, particularly in critically ill patients with altered PK, increasing the risk of suboptimal β-lactamase inhibition and treatment failure. Continuous infusion of tazobactam optimises β-lactamase inhibition by maximising time-dependent exposure and maintaining plasma concentrations above the threshold concentration. This approach might increase the likelihood of achieving PK/PD targets for maximal patient outcomes and enhance β-lactamase inhibition, thereby improving microbiological and clinical outcomes. In our analysis, continuous infusion of a

standard tazobactam dose (co-administered with piperacillin) achieved PTA ≥ 90% in patients with an eGFR of 80 mL/min, even at 100% $fT_{>4\ mg/L}$ target, whereas patients with an eGFR of 140 mL/min required higher tazobactam doses administered via continuous infusion to meet this target.

However, administering higher doses of currently available β-lactam/tazobactam combinations to achieve optimal tazobactam exposure may increase the risk of β-lactam toxicity unless guided by frequent therapeutic drug monitoring [12, 37], particularly in critically ill patients who may be more susceptible to adverse effects. This highlights a key limitation of existing combination products: the fixed β-lactam-to-tazobactam ratio may not allow sufficient flexibility to optimise tazobactam exposure without exceeding safe β-lactam concentrations. One potential solution is the development of a stand-alone tazobactam formulation or alternative β-lactam/tazobactam combinations with higher tazobactam ratios (e.g., 8:1 → 4:1 or 2:1), thereby allowing flexibility for individualised dose selection that ensures effective β-lactamase inhibition while maintaining safe β-lactam dosing. Such strategies could improve clinical outcomes against high-level β-lactamase-producing organisms and provide more tailored dosing options for critically ill populations.

While our analysis indicates that standard tazobactam dosing regimens often fail to achieve aggressive PK/PD targets, particularly in critically ill patients with eGFR ≥ 140 mL/min, it is important to recognise that PK/PD targets for β-lactamase inhibitors remain a matter of uncertainty and have not been robustly validated in a clinical study. The translation of aggressive PK/PD goals (e.g. 100% $fT_{>4\ mg/L}$) into improved patient outcomes has not been fully established, and variability in β-lactamase expression level further complicates interpretation. Therefore, while the findings in this study provide valuable insights into exposure requirements, they should be considered within the context of the current uncertainty surrounding PK/PD targets.

Limitations of this study should be acknowledged. First, interindividual variability in V1, V2, and Q could not be reliably estimated, likely due to limited sampling during the early distribution phase, a critical period for accurately defining distribution-related parameters [38]. Second, eGFR equations (e.g., CKD-EPI and Cockcroft–Gault) may underestimate tazobactam renal clearance, as renal elimination also involves active tubular secretion. Third, ceftolozane/tazobactam data were derived from only two studies conducted at a single centre, and unfortunately other studies that measured tazobactam concentration when co-administered with ceftolozane are not available for comparison. It is therefore difficult to completely rule out any study-associated confounding factors. However, sensitivity analysis supports the effect of piperacillin on tazobactam clearance compared to ceftolozane, suggesting that the observed difference is unlikely to be explained solely by study-specific factors (Supplementary Figures S1 and S2). Fourth, the PK/PD relationship of tazobactam remains incompletely characterised; therefore, the clinical significance of variability in tazobactam exposure and target attainment remains uncertain. Lastly, the analysis lacks clinical outcome data, preventing a direct assessment of whether achieving tazobactam PK/PD targets translates into improved therapeutic success. Moreover, covariates such as severity scores (APACHE II, SOFA) and laboratory markers (albumin concentrations), which are relevant in critically ill patients, were either not reported or not available for more than half of the study participants, limiting our ability to include these factors in the analysis. Future studies with targeted sampling during the early distribution phase, including covariates relevant to critically ill patients, linking PK/PD target attainment to patient outcomes, and estimating tazobactam renal clearance from measured urine concentrations, are warranted to refine population PK parameters and optimise tazobactam dosing strategies in these patient populations.

Conclusion

Standard intermittent dosing of tazobactam often results in underexposure, particularly in patients with suspected state of ARC or when aggressive PK/PD targets are applied. Underexposure is more pronounced when tazobactam is co-administered with ceftolozane compared with piperacillin. Importantly, tazobactam exposure can be optimised by increasing doses, administering via continuous infusion, or individualised dosing strategies to achieve effective β-lactamase inhibition. These findings support the potential utility of stand-alone tazobactam

formulations or β-lactam/tazobactam combinations with higher tazobactam ratios to improve efficacy against high-level β-lactamase-producing organisms while maintaining safe β-lactam dosing.

Abbreviations

ARC	Augmented Renal Clearance
BSV	Between-Subject Variability
Cfree	Free (unbound) drug concentration
Ctotal	Ctotal – Total drug concentration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	Creatinine Clearance
$\%fT_{>CT}$	Percentage of time that free drug concentration exceeds the β-lactamase inhibition threshold concentration
$\%fT_{>MIC}$	Percentage of time that free drug concentration exceeds the minimum inhibitory concentration
Fu	Fraction of free (unbound) drug in plasma
GFR	Glomerular Filtration Rate
GOF	Goodness-of-Fit
NLME	Non-Linear Mixed-Effects
NPDE	Normalised Prediction Distribution Error
OFV	Objective Function Value
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
PTA	Probability of Target Attainment
RSE	Relative Standard Error
SAEM	Stochastic Approximation Expectation Maximisation
OAT	Organic Anion Transporters
VPC	Visual Predictive Check
WT	Body Weight

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1186/s13054-026-06321-1.

Acknowledgements G. M. A acknowledges funding from the University of Queensland Research Training Programme (RTP) scholarship. F. B S. acknowledges support from the Australian National Health and Medical Research Council (NHMRC) Investigator Grant (APP1197866). J. A. Roberts acknowledges funding from the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP2007007) and an Investigator Grant (APP2009736).

Author contributions Conceptualisation: GMA, JAR and FS; Methodology: GMA, XL and FS; Investigation: JAR, FP, PGC, DB, CC, MZ, MHA, XL and FS; Data curation: GMA, JAR, FP, PGC, DB, CC, MZ, ZTW, MHA, XL and FS; Formal Analysis: GMA, XL and FS; Supervision: JAR and FS; Writing – original draft: GMA; Writing – review & editing: JAR, FP, PGC, DB, CC, MZ, AI, KT, ZTW, RJW, MU, MHA, XL and FS.

Funding None.

Data availability All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interest The authors declare that there is no competing interest related to this work.

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