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Balancing the scales: achieving the optimal beta-lactam to beta-lactamase inhibitor ratio with continuous infusion piperacillin/tazobactam against extended spectrum beta-lactamase producing *Enterobacterales*

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ABSTRACT Piperacillin/tazobactam (TZP) is administered intravenously in a fixed ratio (8:1) with the potential for inadequate tazobactam exposure to ensure piperacillin activity against *Enterobacterales*. Adult patients receiving continuous infusion (CI) of TZP and therapeutic drug monitoring (TDM) of both agents were evaluated. Demographic variables and other pertinent laboratory data were collected retrospectively. A population pharmacokinetic approach was used to select the best kidney function model predictive of TZP clearance (CL). The probability of target attainment (PTA), cumulative fraction of response (CFR) and the ratio between piperacillin and tazobactam were computed to identify optimal dosage regimens by continuous infusion across kidney function. This study included 257 critically ill patients (79.3% male) with intra-abdominal, bloodstream, and hospital-acquired pneumonia infections in 89.5% as the primary indication. The median (min-max range) age, body weight, and estimated glomerular filtration rate (eGFR) were 66 (23–93) years, 75 (39–310) kg, and 79.2 (6.4–234) mL/min, respectively. Doses of up to 22.5 g/day were used to optimize TZP based on TDM. The 2021 chronic kidney disease epidemiology equation in mL/min best modeled TZP CL. The ratio of piperacillin:tazobactam increased from 6:1 to 10:1 between an eGFR of <20 mL/min and >120 mL/min. At conventional doses, the PTA is below 90% when eGFR is ≥100 mL/min. Daily doses of 18 g/day and 22.5 g/day by CI are expected to achieve a >80% CFR when eGFR is 100–120 mL/min and >120–160 mL/min, respectively. Inadequate piperacillin and tazobactam exposure is likely in patients with eGFR ≥ 100 mL/min. Dose regimen adjustments informed by TDM should be evaluated in this specific population.

KEYWORDS beta-lactamases, beta-lactams, clinical therapeutics, *Enterobacteriaceae*, pharmacokinetics, pharmacodynamics

Piperacillin/tazobactam (TZP) is one of the top five intravenous antibiotics used in hospitals in the United States (1). The dosage of TZP is typically 3.375 g every 6 h infused over 30 min for most indications with a higher dose of 4.5 g every 6 h infused over 30 min for nosocomial pneumonia (2). Recently, a revision to the TZP susceptibility breakpoints for *Enterobacterales* was put forth by the Clinical Laboratory Standards Institute (CLSI) that lowered the susceptibility threshold and includes a susceptible-dose dependent (S-DD) category of 16 mg/L for piperacillin (PIP) in the presence of 4 mg/L tazobactam (TAZ) (3). Reliance on an extended infusion (EI) of TZP over 50% of the dosing interval has been used to justify this S-DD category. The evidence for this pharmacodynamic target was deemed insufficient by the Food and Drug Administration to accept CLSI's S-DD category but sufficient to accept the susceptibility criteria of 8 mg/L

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for PIP in the presence of 4 mg/L of TAZ. As reflected in these assessments, a ratio of 4:1 and 2:1 exists with the CLSI S-DD and susceptibility criteria for PIP:TAZ. Alternatively ensuring that TAZ concentrations exceed 4 mg/L is considered a reasonable systemic concentration threshold (C_T) based on animal and *in vitro* models (4, 5).

The TZP drug product is formulated based on a fixed ratio of 8 parts PIP to 1 part TAZ (2). Once administered intravenously, the clearance (CL) of these compounds is dependent on the glomerular filtration rate (GFR) and kidney tubular secretion with the recovery of 65%–70% of the drugs as the unchanged form in urine (2). Uniquely, PIP inhibits the kidney tubular secretion of TAZ (6). The relevance is that kidney function plays an integral role in dose administration considerations and at present is only used to select lower doses of TZP when kidney function, evaluated by estimated GFR (eGFR) is ≤40 mL/min. The impact of the alternate scenario, when kidney function is augmented (eGFR > 120 mL/min) on the TZP profile, has not been well characterized. Recent drug product approvals for antibiotics like cefiderocol (7) and sulbactam-durlobactam (8) have verified the need for higher antibiotic dose regimens when eGFR exceeds 120 mL/min and 130 mL/min, respectively. These developments raise fundamental concerns for antibiotics like TZP that simultaneously require optimal exposures of two drugs across the full expected clinical range of kidney function. Importantly, how does the ratio of TZP change with kidney function and are there thresholds where clinical dose intervention may be necessary? This question is harder to answer in the United States because routine therapeutic drug monitoring (TDM) is not performed for these agents. Also, one approach to measure kidney clearance is by continuous infusion (CI) and measurement of probe molecule concentrations at steady state. A principle is applied to measure the GFR using an exogenous molecule like inulin. Using the same principle, we leverage CI TZP data from patients undergoing routine TDM for both compounds, a practice that is routine within some institutions in Italy (9). Our objective was to understand how the ratio of the two drug components changes and whether dose adjustments may be necessary in certain groups of patients across the expected adult kidney function range.

MATERIALS AND METHODS

Study design

The study was approved by the local Ethics Committee. Signed informed consent was waived due to the retrospective nature of this investigation, in accordance with the national legislation and the institutional requirements. Adult patients who were consecutively admitted to both the general and post-transplant intensive care units of the IRCCS Azienda Ospedaliero—Universitaria di Bologna, Italy, in the period April 2021 to April 2023 and who were treated empirically with TZP for suspected Gram-negative infections were included in this study.

Standard initial dosing regimens of TZP at the IRCCS Azienda Ospedaliero—Universtaria di Bologna, Italy, were a loading dose of 9 g infused over 1 h and followed immediately by a CI maintenance dose of 18 g/day for eGFR > 40 mL/min, of 13.5 g/day for eGFR of 20–40 mL/min, and of 9 g/day for eGFR < 20 mL/min. After 48–72 h of treatment initiation, patients underwent real-time TDM coupled with clinical pharmacology consultation for exposure optimization (9). At each TDM assessment, a single blood sample was collected for measuring steady-state plasma concentrations of PIP (Css_{PIP}) and TAZ (Css_{TAZ}). Total Css_{PIP} and Css_{TAZ} were measured by means of a liquid chromatography-tandem mass spectrometry commercially available method (Chromsystems Instruments & Chemicals GmbH, Munich, Germany), with a lower limit of quantification of 1 mg/L and 0.5 mg/L for PIP and TAZ, respectively. TDM-based TZP dosing adjustments were provided whenever needed for attaining the so-called optimal joint pharmacokinetic/pharmacodynamic (PK/PD) target of TZP for empirical treatment. The joint PK/PD target of TZP was defined as optimal for empirical treatment when both the $fCss/MIC_{BP}$ ratio of PIP was ≥4 (where MIC_{BP} is the EUCAST and the CLSI clinical breakpoint for TZP against susceptible *Enterobacterales*, namely 8 mg/L) and the $fCss/C_T$ ratio of TAZ was ≥1

(where C_T was the fixed target TAZ concentration used by the EUCAST and the CLSI for *in vitro* standard susceptibility testing of TZP, namely 4 mg/L). The joint PK/PD target of TZP was defined as quasi-optimal or sub-optimal for empirical treatment if only one or none of the two thresholds were attained, respectively. We also quantified the incidence of cases achieving a Css_{PIP} > 157.2 mg/L, a value that has recently been linked to a higher probability of neurotoxicity with TZP (10).

The following demographic and clinical data were retrieved from archived patient clinical records: age, gender, body weight, height, serum creatinine, TZP posology, Css_{PIP} and Css_{TAZ}, type and site of infection, and bacterial isolates (whenever identified). Css_{PIP} to Css_{TAZ} ratios were calculated (PIP:TAZ ratio) and distributed according to seven different classes of eGFR calculated by means of the non-race-based chronic kidney disease epidemiology (CKD-EPI) equation (11).

Population pharmacokinetic modeling

TZP plasma concentrations were analyzed using non-linear mixed effects modeling using the stochastic approximation expectation minimization algorithm through the Monolix software (version 2023R1; Lixoft, Antony, France). As all subjects received TZP by 24 h CI, mono-compartmental system analysis was adequate to simultaneously model the pharmacokinetics of both PIP and TAZ (Fig. S1). First of all, a linear model parameterized with zero order administration and two drug components for CL from the central compartment, one for PIP (CL_{PIP}) and the other for TAZ (CL_{TAZ}), was built. The distribution volume of the central compartment was fixed to 15 L for both PIP and TAZ based on the product label central tendency value (2). Exploratory analyses (Fig. S2) suggested that CL_{TAZ} was influenced by Css_{PIP}. As a consequence, CL_{TAZ} was evaluated as linear and non-linear functions of CL_{PIP} and Css_{PIP} by seven different mathematical functions. The structural models are detailed in Table S1.

All individual parameters were considered to be log-normally distributed. Several error models (additive, proportional, or combined additive and proportional error model) were tested for residual variability. The effect of covariates such as age, body weight, and eGFR, was evaluated. Covariate selection was made according to a forward/backward process. In the forward step, the inclusion of a covariate in the model was based on the result of Pearson's correlation test between each covariate and the random effect of the estimated pharmacokinetic parameter. In the backward step, the Wald test was used to test whether any covariate could be removed from the full covariate model.

Model selection and validation

Comparisons of the performances of the models were evaluated by calculating the Akaike information criteria (AIC). A decrease of at least 2 points in the AIC was used for model discrimination. The adequacy of different models was also assessed by considering the goodness of fit of the observed versus predicted concentrations, the relative standard error (RSE) of the estimated pharmacokinetic parameters, the distribution of the individual weighted residuals, and the nonparametric distributional errors. Visual predictive check showing the time course of the 10th, the 50th, and the 90th percentiles of observed data overlaid to the corresponding 90% prediction intervals was used for internal validation.

Monte Carlo simulation

Monte Carlo simulations (n = 1,000 subjects) were executed using the final population pharmacokinetic model using Simulx 2023R1 (Lixoft, Antony, France) to generate different TZP concentration-time profiles associated with different dosing regimens adjusted for classes of eGFR and administered by 24 h CI.

The simulated TZP dosing regimens were 2.25 and 4.5 g by 24 h CI for eGFR of 20-40 mL/min, 6.75 and 9 g 24 h CI for eGFR of 20-80 mL/min, 13.5 g 24 h CI for eGFR of 60-80 mL/min and 18 g 24 h CI for eGFR of 80-180 mL/min. We also tested an intensified regimen of 22.5 g 24 h CI for eGFR of 100-180 mL/min.

The probability of target attainment (PTA) of the joint PK/PD target of TZP was calculated by using the free fractions (*f*) of PIP and TAZ concentrations that were set at 70% based on plasma protein binding being reported as 30% (2). The joint PK/PD target of TZP was considered optimal for empirical treatment against the *Enterobacterales* whenever the PTA for both the *f*Css/MIC_{BP} ratio of PIP ≥4 and the *f*Css/C_T ratio of TAZ ≥1 were ≥90%. The joint PK/PD target of TZP was considered quasi-optimal whenever PTA was ≥90% for only one of the two thresholds, and sub-optimal whenever PTA was <90% for both of the two thresholds.

The PTAs of optimal, quasi-optimal, and sub-optimal joint PK/PD target of TZP were calculated also against the CLSI S-DD category for *Enterobacterales* by substituting the MIC_{BP} with the MIC value of 16 mg/L, which is used for defining this category ($MIC_{S\text{-}DD}$). We quantified the probability of achieving a Css_{PIP} > 157.2 mg/L, which has been associated with the development of neurotoxicity (10). In addition, we determined the cumulative fraction of response (CFR) based on the MIC distribution of a large collection of *Escherichia coli* clinical isolates from sentinel hospitals across Canada (12).

RESULTS

A total of 257 critically ill patients were evaluated contributing 506 Css_{PIP} and Css_{TAZ} for this analysis. Patients' demographic and clinical characteristics are reported in Table 1. Median (min-max range) age, weight, and eGFR were 66 years (23–93), 75 kg (39–310), and 79.2 mL/min (6.4–234), respectively. Intra-abdominal, bloodstream, and hospital-acquired pneumonia infections accounted for the vast majority of TZP indications (89.5%, 230/257). TDM was assessed first after a median of 3 days interquartile range (IQR 2–4). The median (range) Css_{PIP} and Css_{TAZ} were 71.2 (12.6–423) mg/L and 9.4 (2.0–66.6) mg/L, respectively. A total of 54 patients had 67 observed Css_{PIP} values >157.2 mg/L but no neurotoxicity events were explicitly noted in their medical records. Figure 1 shows the observed distributions of the PIP:TAZ ratios across the different classes of eGFR. Median (IQR) observed PIP:TAZ ratio increased proportionally across different classes of kidney function, from a minimum of 5.8 (4.8–7.05) for eGFR ≤ 20 mL/min up to a maximum of 10.1 (8.6–11.3) for eGFR > 120 mL/min ($P < 0.001$).

Table S2 provides the stepwise comparison of the seven alternate structural models based on independent and dependent (linear, power, Emax, Sigmoidal) functions of

TABLE 1 Demographics and clinical characteristics ($n = 257$)[a]

Age (years)	66 (23–93)
Gender (M/F)	177/80
Weight (kg)	75 (39–310)
BSA (m^2)	1.9 (1.3–3.9)
Creatinine (mg/dL)	1.04 (0.23–8.84)
eGFR (mL/min)	79.2 (6.4–234)
Type of infection	
Intra-abdominal infections	95 (36.9)
Bloodstream infections	75 (29.2)
Hospital-acquired pneumonia	60 (23.4)
Skin and soft-tissue infections	12 (4.7)
Urinary tract infections	8 (3.1)
Bone and joint infections	5 (1.9)
Febrile neutropenia	2 (0.8)
Piperacillin/tazobactam treatment	
Median dose (g/day)	18.0 (2.25–22.5)
Piperacillin Css (mg/L)	71.2 (12.6–423.0)
Tazobactam Css (mg/L)	9.4 (2.0–66.6)
No. of TDM assessment per patient	2 (1–7)

[a]Data are presented as median (min-max) for continuous variables and as number (%) for dichotomous variables. BSA: body surface area and Css: steady-state concentration.

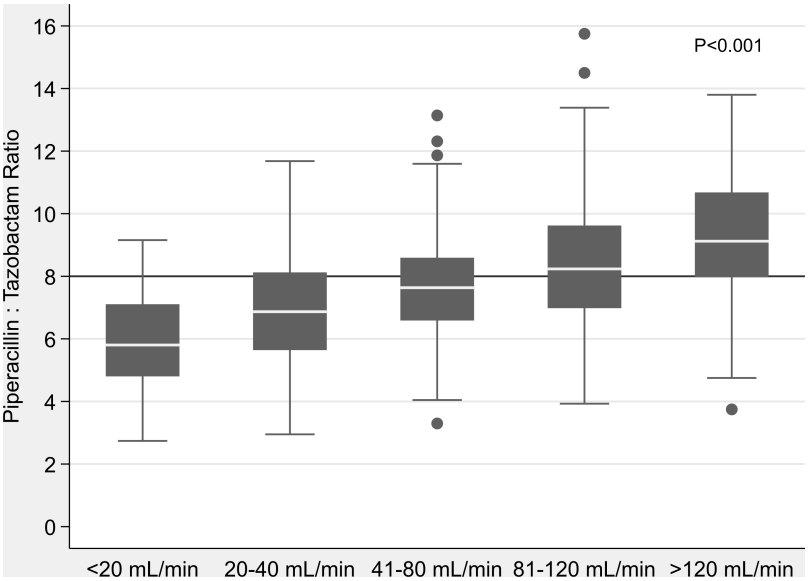

FIG 1 Box and whisker plot (5th and 95th percentiles) of observed piperacillin/tazobactam concentration ratio across different classes of kidney function. The solid line represents the expected value of the concentration ratio based on the 8:1 proportion between piperacillin and tazobactam.

CL_{TAZ} and CL_{PIP}. A one-compartment model including eGFR as a covariate of independent functions of CL_{TAZ} and CL_{PIP} best fits the population pharmacokinetics of TZP (model 1). An Emax model of CL_{TAZ} that included eGFR as a covariate of CL_{PIP} was the next best model and aligned with the observations of lower CL_{TAZ} with increasing Css_{PIP} (Fig. S2), and a comparison is provided in Table S3. While this Emax model was not selected as the final model, Fig. S3 illustrates that an IC_{50} of 29.9 mg/L for Css_{PIP} is associated with a 5.5% reduction in CL_{TAZ} with an inhibition maximum (Imax) of 11% at the highest Css_{PIP} concentrations. As noted, kidney function was the primary covariate of CL_{TAZ} and CL_{PIP}. Comparisons of contemporary kidney function equations are provided in Table S4 and show that eGFR should be in mL/min rather than mL/min/1.73 m^2 and that the 2021 non-race-based CKD-EPI equation performed best. Model diagnostics plots are summarized in Fig. S4 to S7. Given that the distribution volume of the central compartment was fixed to 15 L for both PIP and TAZ, we also performed an analytical solution to the estimation of PIP and TAZ CL based on the rate of infusion/Css value. Figure S8 shows that the individual estimates derived by the final model match a no-model-based analytical solution implying that the typical value for *V* that was selected resulted in CL estimates that were similar to this analytical solution method of estimating CL. The summary of the final population pharmacokinetic mode is reported in l is reported in Table 2.

Table 3 provides the probability estimates for achieving a Css_{PIP} > 157.2 mg/L across eGFR estimates of 20–180 mL/min. The licensed dosing regimens allowed optimal joint PK/PD target of TZP up to the EUCAST/CLSI clinical breakpoint up to eGFR of 80 mL/min if administered by CI (Table 4). The intensified dosing regimen of 22.5 g administered by CI granted optimal joint PK/PD target at eGFR of 100 mL/min, but not at higher eGFR values. In the CLSI S-DD category of 16 mg/L, only quasi-optimal (only for tazobactam) joint PK/PD targets were attainable with the same dosing schedules (Table 5). Table 6 includes the CFR as well as the toxicity risk (TR) estimate (based on Css_{PIP} > 157.2 mg/L) for doses within and above the conventional range. Daily doses of 18 g/day and 22.5 g/day by CI are expected to achieve a >80% CFR when eGFR is 100–120 mL/min and >120–160 mL/min, respectively. Based on the difference between CFR and TR, CI doses of up to 22.5 g are suggested when eGFR > 120 mL/min.

TABLE 2 Summary of the final population pharmacokinetic model[a]

Parameter	Value (%RSE)
Fixed effects	
V_1	15
CL_{PIP}	6.39 (2.92)
β_CL_{PIP}	0.77 (5.43)
CL_{TAZ}	5.89 (2.95)
β_CL_{TAZ}	0.92 (4.47)
V_2	15
F	0.11
SD of the random effects	
ωCL_{PIP}	0.41 (11.6)
ωCL_{TAZ}	0.41 (12.0)
Correlation	
$CL_{PIP}CL_{TAZ}$	0.93 (11.5)
Residual variability	
b (proportional) PIP	0.28 (3.98)
b (proportional) TAZ	0.29 (3.78)

[a]V_1 is the volume of central compartment for piperacillin; CL_{PIP} is piperacillin clearance, β_CL_{PIP} is the coefficient of piperacillin CL as a function of eGFR; CL_{TAZ} is tazobactam clearance, β_CL_{TAZ} is the coefficient of piperacillin CL as a function of eGFR; V_2 is the volume of central compartment for tazobactam; *F* is the fraction of infused drug representative of tazobactam; eGFR is the estimated glomerular filtration rate based on the 2021 chronic kidney disease epidemiology equation; and SD is the standard deviation. The formulas can be represented as follows: $CL_{PIP} = 6.39 \times \left(\frac{eGFR}{60}\right)^{0.77} \times \varepsilon$, $CL_{TAZ} = 5.89 \times \left(\frac{eGFR}{60}\right)^{0.92} \times \varepsilon$, where ε is eta_CL that represents the random effect defining the interindividual variability of CL. It is automatically defined in Monolix as a normal random variable with zero mean and a standard deviation to be estimated. The distribution of Cl is thus defined with two population parameters: Cl_pop (in this case CL_{PIP} and CL_{TAZ}), the typical value of Cl in the population, and omega_Cl, the standard deviation of eta_CL.

DISCUSSION

This study on TZP dosing and TDM provides valuable insights into the complexities of antibiotic administration, especially in patients with augmented renal clearance (ARC). TZP is a frontline antibiotic in the treatment of severe infections, and ensuring adequate concentrations of both PIP and TAZ is crucial for its efficacy. This study's findings shed light on the need for personalized dosing regimens to optimize patient outcomes.

TZP is predominantly eliminated by the kidneys, and the pharmacokinetics of tazobactam is dependent on piperacillin concentrations (13–15). Our results align with these expectations and provide quantitative context to the degree of this interaction. We show that piperacillin reduces tazobactam clearance by up to 11%, and this loss of inhibition is likely in patients with high eGFR where Css_{PIP} <29.9 mg/L is expected. In this regard, the use of EI or CI TZP is a proven strategy to achieve higher PTA than standard II (16) and potentially higher clinical cure rates (17–19). Concerns about the efficacy of

TABLE 3 Probability of achieving a steady-state piperacillin concentration >157.2 mg/L (asssoicated with neurotoxicity) by incremental piperacillin/tazobactam dosages administered by CI across specified values of eGFR

eGFR (mL/min)	Piperacillin/tazobactam dosages (g/day by CI)						
	2.25	4.5	6.75	9	13.5	18	22.5
20	0	0.8	10.3	28.1	64.2	86	94.6
40	0	0.1	0.6	2.1	16.9	37.7	60
60	0	0	0	0.2	6	18	34.7
80	0	0	0	0.1	1.7	6.6	16.6
100	0	0	0	0	0.4	2	7.2
120	0	0	0	0	0.1	0.8	3.7
140	0	0	0	0	0	0.2	1.6
160	0	0	0	0	0	0.1	1.5
180	0	0	0	0	0	0	0.7

TABLE 4 Probability of optimal, quasi-optimal, and sub-optimal joint PK/PD target attainment at day 3 with different dosages of continuous infusion piperacillin/tazobactam by eGFR in relation to the EUCAST clinical breakpoints of *Enterobacterales* of 8 mg/L[a]

eGFR (mL/min)	Piperacillin/tazobactam dosages (g/day by CI)													
	2.25		4.5		6.75		9		13.5		18		22.5[b]	
	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ
20	17.6	35.9	76.2	91.1	95.4	98.7	99.1	99.6	–[c]	–	–	–	–	–
40	0.7	2.5	25.0	38.1	63.4	75.5	84.5	90.3	–	–	–	–	–	–
60	–	–	–	–	36.6	42.4	62.9	69.9	92.2	93.6	–	–	–	–
80	–	–	–	–	17.3	20.2	38.4	43.0	74.7	80.0	94.2	94.9	–	–
100	–	–	–	–	–	–	–	–	–	–	84.1	84.3	94.6	95.2
120	–	–	–	–	–	–	–	–	–	–	78.5	73.4	87.8	87.0
140	–	–	–	–	–	–	–	–	–	–	66.1	60.6	84.5	80.8
160	–	–	–	–	–	–	–	–	–	–	55.3	50.8	76.0	70.5
180	–	–	–	–	–	–	–	–	–	–	50.4	40.3	67.4	61.8

[a]The shaded areas identify optimal (dark gray) and quasi-optimal (light gray) joint PK/PD target attainment.
[b]Intensified CI tested an increased dose of 22.5 g when eGFR ≥ 100 mL/min. A loading dose of 9 g infused over 1 h was used prior to initiation of the CI regimens.
[c]'–' means "Not assessed".

TZP in the treatment of severe infections due to ESBL-producing bacteria have emerged in recent years. In the Merino trial, the 30-day mortality rate of bloodstream infections caused by ESBL-producing bacteria was higher in the TZP arm than in the meropenem arm (12.3% versus 3.7%) (20). While specific beta-lactamases resistant to tazobactam (OXA-48 and ampC) contributed to this difference, issues related to inadequate TZP exposure related to II administration have been raised. Importantly, TZP remains a high-use agent in most institutions in the United States, and II is likely to still be the predominant administration route.

While EI is seen as the middle ground from a clinical implementation perspective, the use of CI should be advocated in our opinion for TZP in the treatment of severe infections in critically ill patients or those with ARC (21). Patients with ARC, characterized by an eGFR ≥ 120 mL/min, present a unique challenge. Prior research has shown that these patients may experience sub-optimal antibiotic exposure due to rapid drug clearance, potentially compromising treatment efficacy (21–24). The findings suggest the need for a more intensified dosing regimen by CI to properly deal with this issue.

Our population pharmacokinetic model emphasizes the intricate relationship between PIP concentrations and TAZ clearance. The pharmacokinetics of the two drugs are highly correlated, but PIP inhibits the renal excretion of TAZ (6, 25), especially when high Css_{PIP} is achieved. This interaction highlights the importance of considering both drugs when adjusting dosing regimens. Previous research has also recognized the need

TABLE 5 Probability of optimal, quasi-optimal, and sub-optimal joint PK/PD target attainment at day 3 with different dosages of continuous infusion piperacillin/tazobactam by eGFR in relation to the CLSI S-DD category of *Enterobacterales* of 16 mg/L[a]

eGFR (mL/min)	Piperacillin/tazobactam dosages (g/day by CI)													
	2.25		4.5		6.75		9		13.5		18		22.5[b]	
	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ	PIP	TAZ
20	0.07	35.9	17.6	91.1	48.9	98.7	76.2	99.6	–[c]	–	–	–	–	–
40	0.01	2.5	0.07	38.1	8.7	75.5	25.0	90.3	–	–	–	–	–	–
60	–	–	–	–	1.8	42.4	9.4	69.9	36.6	93.6	–	–	–	–
80	–	–	–	–	0.06	20.2	2.1	43.0	17.3	80.0	42.6	94.9	–	–
100	–	–	–	–	–	–	–	–	–	–	24.4	84.3	45.9	95.2
120	–	–	–	–	–	–	–	–	–	–	18.4	73.4	30.6	87.0
140	–	–	–	–	–	–	–	–	–	–	10.9	60.6	26.1	80.8
160	–	–	–	–	–	–	–	–	–	–	0.57	50.8	17.4	70.5
180	–	–	–	–	–	–	–	–	–	–	0.40	40.3	11.6	61.8

[a]The shaded areas identify optimal (dark gray) and quasi-optimal (light gray) joint PK/PD target attainment.
[b]Intensified CI tested an increased dose of 22.5 g when eGFR ≥ 100 mL/min. A loading dose of 9 g infused over 1 h was used prior to initiation of the CI regimens.
[c]'–' means "Not assessed".

TABLE 6 CFR, TR, and the difference between these estimates (delta) with different dosages of continuous infusion piperacillin/tazobactam by eGFR

eGFR (mL/min)	Dose (g)	CFR (%)[a]	TR (%)[b]	Delta (CFR–TR)
20	6.75	87.1	10.3	77
	9	90.5	28.1	62
40	9	82.8	2.1	81
	13.5	90	16.9	73
60	13.5	85.3	6	79
	18	88.9	18	71
80	18	86.2	6.6	80
100	18	82.7	2	81
	22.5	86.6	7.2	79
120	18	81	0.8	80
	22.5	83.9	3.7	80
140	18	78.1	0.2	78
	22.5	82.9	1.6	81
160	18	75.3	0.1	75
	22.5	80.6	1.5	79
180	18	73.6	0	74
	22.5	78.4	0.7	78

[a]CFR is the cumulative fraction of response based on the probability of target attainment at MIC distributions of ESBL-producing *Escherichia coli* (12).
[b]TR is the toxicity-risk potential based on probability of a steady-state piperacillin concentration >157.2 mg/L that has been associated with neurotoxicity (10).

for such an integrated approach (26) to ensure that both PIP and TAZ maintain therapeutic concentrations, especially in patients with ARC.

Furthermore, the Monte Carlo simulations in this study align with earlier investigations that revealed the limitations of standard TZP dosing. While the CI of TZP may adequately maintain PIP concentrations above susceptibility breakpoints, it may fall short in achieving optimal TAZ exposure in patients with ARC (27). These findings have practical implications for clinicians, urging them to tailor TZP dosing strategies to individual patient characteristics, particularly kidney function. We also show that the estimation of kidney function using the most contemporary approach is the 2021 CKD-EPI equation that eliminated race as a factor. Our analyses unequivocally show that the unit of reporting these values should be in mL/min rather than mL/min/1.73 m^2, in line with US FDA recommendations.

While kidney function estimation is useful, it is important to acknowledge that 40% of the interindividual variability in clearance remains unexplained for TZP with the inclusion of this parameter. TDM is, therefore, a crucial tool to optimize empiric antibiotic dosing, especially in critically ill patients (28). Prior studies have demonstrated the benefits of real-time TDM, enabling clinicians to make informed dose adjustments to achieve desired PK/PD targets (29). This approach ensures that both PIP and TAZ concentrations remain within the therapeutic window, enhancing the likelihood of clinical success while minimizing the risk of resistance and toxicity.

There are several counter-points and limitations to our work that deserve attention. Firstly, we measured total rather than free concentrations. While free concentration measurement would be ideal, it is not practical or feasible to perform that measurement routinely in TDM practice. We also measured concentrations at steady state that precluded generation of a volume of distribution estimate. We relied on a fixed estimate of volume of distribution that allowed for a reasonable estimation of clearance but restricted our simulations to CI regimens only. Another point of contention is the target concentrations selected to qualify the joint PKPD targets for TZP. Some argue that targeting an $fCss_{PIP} > 1\times$ minimum inhibitory concentration (MIC) to be sufficient (rather than 4× MIC) and that $fCss_{TAZ} \geq 4$ mg/L to be overly aggressive. A recent randomized controlled trial targeted $fCss_{PIP} > 4\times$ MIC, which is consistent with our clinical practice

(30). We empirically target Css_{PIP} values of 32–64 mg/L because we are treating critically ill patients, considering that we are measuring total rather than free concentrations, accounting for the risk of having 1–2 dilution variability in the MIC, and expecting tissue concentrations such as pulmonary penetration of Css_{PIP} to be ~50% of plasma concentrations (31). Empirically targeting a Css_{PIP} of 1× MIC or 8 mg/L would provide a very limited margin of safety when considering all of these variables. Likewise, some argue that it is not necessary to sustain Css_{TAZ} for 100% of the dosing interval and that the threshold is dependent on the degree of beta-lactamase expression (4). Prior work that identified this relationship used laboratory-derived strains expressing one type of beta-lactamase. That research group demonstrated that it is not possible to model these relationships when multiple strains with different beta-lactamase expression profiles were tested (32). They did identify a simple relationship that the Css_{TAZ} threshold was 0.5 times the ceftolozane MIC (32). If that relationship translates to piperacillin then the Css_{TAZ} threshold would be 4 mg/L for a piperacillin MIC of 8 mg/L. Abodakpi et al. constructed an Emax model using four ESBL-producing *Enterobacterales* strains based on the log_2 piperacillin MIC. The IC_{50} for tazobactam was identified to be 2.6, 1.36, 35.3, and 2.71 mg/L, respectively for each of these strains, with near maximal effect around 8 mg/L for two of these strains (33). There is no consensus statement on the optimal Css_{TAZ} threshold, the FDA in their rationale for TZP breakpoints specifically cited, "CLSI's rationale does not specify tazobactam PK/PD targets nor includes tazobactam PK/PD target attainment analyses to demonstrate that tazobactam exposure will be sufficiently high to drive piperacillin efficacy with the dosing regimens noted for the proposed breakpoints (34)." Given these uncertainties, reliance on Css_{TAZ} 4 mg/L as the threshold is a reasonable benchmark that we applied since it is used as the *in vitro* standard. We tested this assumption in a recent prospective study carried out among 35 patients having a documented secondary blood stream infection (BSI) caused by ESBL-producing *Enterobacterales* and specific pre-defined inclusion criteria (namely absence of septic shock at onset; favorable clinical evolution in the first 48 h after starting treatment; low-intermediate risk primary infection source) (35). The findings showed that real-time TDM-guided attainment of this aggressive joint PK/PD target of CI piperacillin–tazobactam monotherapy, by granting microbiological eradication in the vast majority of cases (32/35; 94.1%), may represent an effective carbapenem-sparing strategy for treating non-severe ESBL-producing *Enterobacterales* secondary BSIs (35). Future consensus will address whether lower Css_{PIP} and Css_{TAZ} could support the consideration of lower dosing recommendations than those identified by our analyses.

In conclusion, this study's results build upon prior research in the field of TZP dosing and TDM. This work emphasizes the intricate interplay between piperacillin and tazobactam pharmacokinetics, particularly in patients with ARC. The lessons from previous studies underscore the complexity of antibiotic dosing and the critical role of personalized treatment regimens. By integrating TDM and model-informed precision dosing into clinical practice and considering individual patient characteristics, healthcare providers can enhance the precision of antibiotic dosing, ultimately improving outcomes for patients with severe infections. Future research should continue to explore these nuances and refine dosing recommendations to advance patient care.

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ADDITIONAL FILES

The following material is available online.

Supplemental Material

Fig S1 to S8, Tables S1 to S4 (AAC01404-23-s0001.pdf). Modeling strategy and rationale, iterative model building decision points, interpretations and diagnostics.

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