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Therapeutic Drug Monitoring-guided dosing of continuous piperacillin/tazobactam in critically ill cardiac surgery patients

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Abstract

Purpose:

Critical illness and sepsis are associated with marked pharmacokinetic variability, complicating adequate dosing of β-lactam antibiotics. Data on pharmacokinetic/pharmacodynamic (PK/PD) target attainment and therapeutic drug monitoring (TDM) of piperacillin/tazobactam (TZP), a widely used β-lactam antibiotic, in cardiac surgical patients remain limited. This study evaluated PK/PD target attainment during continuous TZP infusion combined with daily TDM in a cardiac surgical intensive care unit (ICU).

Methods:

This single-center retrospective observational study included ICU patients receiving continuous TZP infusion with daily TDM. The PK/PD target was defined as 100% fT > 4× minimum inhibitory concentration (MIC) of *Pseudomonas aeruginosa* (≥ 64 mg/L), with concentrations of 32–<64 mg/L considered clinically acceptable ('near-target exposure'). Overexposure was defined as concentrations > 100 mg/L. Target attainment and potential risk factors for non-attainment, including renal and cardiac failure, were analysed.

Results:

Among 105 patients, initial target attainment was only 27.6%, while 43.8% were overexposed. Overexposure was frequent in patients with severely impaired renal function (80.0%), whereas normal or augmented renal clearance predominantly resulted in near target exposure (57.1% and 81.8%, respectively). Most patients requiring extracorporeal organ support were overexposed during the initial therapy. Across all patients, TDM-guided dose adjustments increased target attainment to 50.0% and reduced overexposure to 12.9%.

Conclusions:

Standardized continuous TZP infusion did not ensure adequate target attainment in cardiac surgical ICU patients. Early and repeated TDM improved target attainment and reduced overexposure, particularly in patients with impaired renal function and extracorporeal organ support. Nevertheless, limited overall target attainment supports the need for more individualized dosing strategies.

Introduction

Despite advances in modern intensive care medicine and the development of minimally invasive surgical techniques, infectious complications remain a major challenge for critically ill patients. Numerous studies have demonstrated that infections are among the leading causes of morbidity and mortality in intensive care units (ICUs), with hospital mortality rates significantly increased in patients with severe infections or sepsis [1, 2]. Timely use of appropriate antimicrobial agents is an indispensable component

of adequate intensive care for the immediate and targeted treatment of critically ill patients [3]. Piperacillin (PIP), combined with the β-lactamase inhibitor tazobactam, is a widely used and well-established broad-spectrum hydrophilic antibiotic with time-dependent bactericidal activity [4]. Commonly employed for the empirical treatment of severe infections, its efficacy depends on the percentage of time during which the unbound (free; f) concentration exceeds the minimum inhibitory concentration (fT > MIC) [5]. In a survey investigating antimicrobial dosing strategies in German ICUs, PIP was identified as the most frequently used antibiotic [6].

Several studies in patients in the ICU have demonstrated substantial variability in antibiotic serum concentrations, especially for hydrophilic agents such as PIP, resulting in an increased risk of therapeutic failure [7, 8]. Altered pathophysiology, including changes in volume of distribution, capillary leak, and organ dysfunction, contributes substantially to the considerable pharmacokinetic variability of β-lactam antibiotics, potentially resulting in inadequate drug exposure [9–11]. Subtherapeutic concentrations increase the risk of therapeutic failure and the development of antimicrobial resistance, whereas excessive exposure risks drug-related toxicity [12, 13]. In cardiac surgical ICUs, patient- and treatment-related variability is amplified by specific circumstances. Increased rates of acute kidney injury (AKI), renal replacement therapy (RRT), and mechanical circulatory support (MCS) [14], as well as augmented renal clearance (ARC), increased volume of distribution, and antibiotic sequestration in the extracorporeal circuit are major concerns [15].

Several strategies have been developed to address these issues. Continuous infusion of β-lactam antibiotics, as opposed to intermittent dosing, may result in improved PK/PD target attainment, better clinical outcomes, and reduced hospital mortality [16–18]. Additionally, therapeutic drug monitoring (TDM), which involves measuring drug concentrations and adjusting doses accordingly, is increasingly being applied to optimize antimicrobial exposure and minimize toxicity [19].

A standard operating procedure (SOP) integrating continuous PIP infusion with TDM-guided dose adjustment was established for the first time in the cardiac surgical ICU at LMU University Hospital, LMU Munich, in September 2023. Previous clinical studies have investigated the impact of TDM of β-lactam antibiotics and PK/PD models in different cohorts of critically ill patients, but not specifically in patients who underwent cardiac surgery [19–21]. This study aimed to evaluate target attainment rates during continuous PIP infusion combined with TDM-guided dose adjustment in a cardiac surgical ICU setting.

Methods

Study design and study population

This study was a single-center, retrospective analysis conducted in a cardiac surgical intensive care unit at LMU University Hospital, LMU Munich, Germany. Data were collected from medical records between September 2023 and November 2024. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, LMU Munich (approval number 25–0361). The study was performed in accordance

with the ethical standards of the Declaration of Helsinki. Patient consent was waived because this study was conducted as a retrospective observational analysis in compliance with all applicable national and regional regulations, as well as relevant ethical and legal standards. Patient data were anonymized before analysis to ensure patient confidentiality.

The indication for treatment, selection of the antibiotic, dosage, and duration of treatment were determined according to the clinical judgment of the treating physicians. Inclusion criteria were cardiac surgery necessitating postoperative intensive care and treatment with TZP including TDM. Patients who had already been transferred to a regular ward and required readmission to the ICU due to an acute illness or for cardiac emergency surgery were also included.

Antibiotic treatment protocol

The institutional SOP developed by the antibiotic stewardship team recommended a loading dose of piperacillin (4 g) with tazobactam (0.5 g) administered as a short infusion over 30 min, followed by a continuous infusion of 18 g TZP over 24 h via a central venous catheter. In patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 20 mL/min/1.73 m²), a reduced daily dose of 13.5 g TZP was recommended. Although the fixed-dose combination of piperacillin and tazobactam was administered, laboratory analyses were restricted to piperacillin (PIP). Accordingly, all reported concentrations and PK/PD parameters refer to PIP only.

Therapeutic drug monitoring and laboratory analysis

The PK/PD target was set to 100% fT > 4× minimum inhibitory concentration (MIC) of the causative pathogen. For empirical therapy, target attainment was assessed using the *Pseudomonas aeruginosa* susceptibility breakpoint (MIC_{PSA} = 16 mg/L), resulting in a total steady-state PIP target concentration of ≥ 64 mg/L, in accordance with the clinical breakpoints recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [22]. Concentrations of 32–<64 mg/L, corresponding to 2–4× MIC_{PSA}, were classified as near-target exposure and considered clinically acceptable in routine practice, particularly in presumed or probable infections with more susceptible pathogens. Overexposure was defined as concentrations > 100 mg/L based on evidence associating supratherapeutic PIP exposure with increased 28-day mortality [23]. Accordingly, the therapeutic range comprised concentrations of 32–100 mg/L, whereas concentrations < 32 mg/L were classified as underexposure.

Blood samples for laboratory analysis and TDM were collected at 6:00 a.m. during routine daily procedures and dispatched within 30 min to the Institute of Laboratory Medicine. Laboratory analyses for TDM were performed from Monday to Saturday, whereas samples collected on Sundays and public holidays were analysed on the next working day. Total plasma concentrations of piperacillin were quantified by liquid chromatography–tandem mass spectrometry (LC-MS/MS), with a laboratory turnaround time of approximately 8 h from sample receipt to electronic reporting of the results. Total

plasma concentrations were used for TDM without correction for the relatively low protein binding of piperacillin (approximately 20–30%). The lower limit of quantification (LLOQ) of the piperacillin assay was 0.5 mg/L until February 2024 and 1.75 mg/L thereafter.

Extracorporeal organ support in critically ill patients

For patients requiring MCS, the following devices were used: veno-arterial extracorporeal life support (ECLS) (Sorin SCPC®), a left ventricular microaxial pump (Abiomed Impella CP®), an intra-aortic balloon pump (Getinge Cardiosave Hybrid®), a ventricular assist device (Abbott HeartMate III®), and an extracorporeal heart pump (Excor Berlin Heart®). For extracorporeal lung support, veno-venous extracorporeal membrane oxygenation (ECMO) (Getinge Rotaflow 2®) was employed. Devices for continuous and intermittent renal replacement therapy included the Fresenius Medical Care Multifiltrate and the Fresenius Genius 90®.

Data management and statistical analysis

A fully digital patient data management system (QCare, Fa Health Information Management GmbH, Bad Homburg, Germany) was employed for the continuous monitoring, recording, and storage of data on vital signs, ventilatory parameters, the use of extracorporeal support devices, and medication administration. Additionally, the system recorded the timing of daily dose administration and the precise hourly infusion rate over the entire treatment period. Laboratory parameters such as inflammatory markers, kidney function tests, and disease severity scores (APACHE II and SOFA) were extracted, alongside data on the use and duration of extracorporeal mechanical support. To assess renal function in the context of drug clearance, estimated creatinine clearance (CrCl) was calculated using the Cockcroft–Gault equation based on daily serum creatinine measurements. Data analysis was conducted using R (version 4.5.1) and RStudio (version 2025.05.1 + 513). Target attainment was evaluated by stratifying TDM results into the predefined concentration ranges. Linear and loess regression analyses were performed to detect associations between measured concentrations and covariates. Subgroup analyses stratified by sex, body mass index, renal function, and the use of RRT and MCS were performed to identify risk factors associated with failure to achieve target parameters. To assess differences in PIP concentrations between subgroups, the Shapiro-Wilk test for normality and the Wilcoxon rank-sum test were used, with statistical significance defined as $p \leq 0.05$. Additionally, the timeliness of dose adjustments for patients outside the therapeutic range was evaluated by calculating the time interval between TDM measurement and the subsequent dose adjustment. For a descriptive within-pair analysis of consecutive PIP concentration measurements and corresponding dose adjustments, only the first treatment episode of each patient was considered. Individual patients could contribute multiple consecutive measurement pairs. At least two consecutive, quantifiable TDM measurements were required, and pairs with documented infusion interruptions between measurements were excluded.

Results

Patient and treatment characteristics

The total study population included 105 patients (Table 1), with a median age of 62 years and a sex distribution of 27 (26%) female and 78 (74%) male patients. Median calculated CrCl at treatment initiation was 75 mL/min (IQR: 54–100). The most frequently performed surgery was aortic surgery (n = 40). Other common surgical procedures included combined interventions and assist device surgery (n = 15, each), valvular surgery (n = 14), heart transplantation (n = 12) and bypass surgery (n = 8).

Overall, 442 piperacillin concentrations were available, corresponding to a median of 4 (IQR: 2–6) TDM measurements per patient and therapy episode. A loading dose was administered in 88% of cases, followed by a median cumulative PIP dose of 18.7 g (IQR: 15.8–19.6) within the first 24 h (including loading doses). The median time from treatment initiation to the first TDM measurement was 22 h (IQR: 20–34). Six samples were reported as “>100 mg/L” and therefore classified as overexposure but not included in quantitative analyses. No sample was below the LLOQ. Among patients with PIP concentrations outside the therapeutic range (< 32 mg/L or > 100 mg/L), dose adjustments were performed within 24 h in 49.1% of cases and after more than 24 h in 28.4%, while no adjustment was made in 22.4%. TDM measurements on Sundays and public holidays were excluded from this analysis because laboratory analyses were not routinely performed on these days.

Table 1
Patient and treatment characteristics

Parameter[1,2]	n = 105
Female	27 (26%)
Male	78 (74%)
Age [years]	62 (54–70) [15–82]
Weight [kg]	82 (72–95) [48–146]
BMI [kg/m²]	26.6 (24.2–30.0) [18.0–45.8]
Albumin [g/dL]	3.20 (2.90–3.40) [2.00–4.10]
Serum creatinine [mg/dL]	1.20 (0.90–1.50) [0.40–5.30]
CrCl (Cockcroft-Gault) [mL/min]	75 (54–100) [16–226]
CRP [mg/L]	65 (23–125) [1–254]
APACHE II score	24 (17–29) [7–46]
SOFA score[3]	11.5 (8.5–14.0) [1.0–20.0]
RRT	25 (24%)
MCS	25 (24%)
TDM measurements [n]	442
TDM measurements per episode [n]	4 (2–6) [1–12]
Loading dose administered	92 (88%)
Median time between start and first TDM measurement [h]	22 (20–34) [8–64]

[1]n (%); median (IQR) [min–max]

[2]Patient characteristics are reported at the time of the initial PIP dose. If laboratory data were not available at that specific time point, the earliest available scores and laboratory data were reported.

[3]No SOFA score was available for one patient.

BMI, body mass index; CrCl, creatinine clearance; CRP, C-reactive protein; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; RRT, renal replacement therapy; MCS, mechanical circulatory support; TDM, therapeutic drug monitoring

During the observation period, 25/105 patients received RRT due to renal failure (Table 2). To maintain hemodynamic and respiratory stability, MCS was required in 25/105 patients. Of these patients, 8/25 required RRT and MCS at the same time, due to concurrent cardiovascular and renal failure.

Table 2
Overview of the extracorporeal organ support modalities

Type of extracorporeal organ support	*Patients (n_{total}=105)*[1]
Any MCS type	25 (24%)
ECLS	17 (16%)
LVAD	6 (6%)
Impella	4 (4%)
ECMO	4 (4%)
IABP	1 (1%)
Any RRT type	25 (24%)
CVVHD	24 (23%)
Hemodialysis (Sustained low-efficiency dialysis)	9 (9%)

[1] *Data are presented as number of patients and proportion (%) of the study population (n = 105). For some patients, more than one device was used during treatment period resulting in higher total numbers and percentages, when summarized.*

MCS = mechanical circulatory support; ECLS = extracorporeal life support; LVAD = left ventricular assist device; ECMO = extracorporeal membrane oxygenation; IABP = intraaortic ballon pump; RRT = renal replacement therapy; CVVHD = continuous veno-venous hemodialysis

Longitudinal PIP exposure during repeated TDM with dose adjustment

At the first TDM measurement, the median PIP concentration was 73 mg/L (IQR: 56–108). Target concentrations of 64–100 mg/L were achieved in 29 (27.6%) patients, while 28 (26.7%) showed near-target exposure of 32–<64 mg/L. Overexposure occurred in 46 (43.8%) patients, while underexposure was uncommon (1.9%).

PIP exposure changed progressively during repeated TDM, as shown in Fig. 1. Target attainment increased from 33.9% at sampling points 2–3 to 50.0% at aggregated sampling points 6–13, while overexposure decreased to 12.9%. The number of patients contributing to the analysis declined with successive TDM measurements, reflecting shorter treatment duration and discontinuation of further TDM.

To assess the response to TDM-guided dose adjustments, 317 pairs of consecutive PIP concentration measurements from 92 of 105 patients were analyzed according to the dosing decision following the preceding TDM measurement (Table 3). Individual patients could contribute multiple consecutive measurement pairs. Dose increases were associated with an increase in median PIP concentration from

48.5 mg/L (IQR 39.1–53.9) to 59.4 mg/L (IQR 52.6–69.8), corresponding to a median within-pair change of 25.8% (IQR 8.9–71.7). Conversely, dose reductions were associated with a decrease from 116 mg/L (IQR 106.5–146.5) to 84.0 mg/L (IQR 65.7–111.0), with a median within-pair change of − 25.2% (IQR − 43.7 to − 16.4). Nevertheless, the upper quartile of follow-up concentrations remained above the overexposure threshold of 100 mg/L. Without dose adjustment, PIP concentrations remained relatively stable (median change − 4.0%).

Table 3
Changes in PIP concentrations between consecutive TDM measurements according to dose adjustment

Dose adjustment	Pairs, n	Patients, n[1]	Index PIP[2]	Follow-up PIP[2]	PIP change, %[3]
Dose increase	22	21	48.5 (39.1–53.9)	59.4 (52.6–69.8)	+ 25.8 (+ 8.9 to + 71.7)
Dose reduction	47	38	116.0 (106.5–146.5)	84.0 (65.7–111.0)	−25.2 (−43.7 to − 16.4)
No change	248	88	73.5 (57.4–97.7)	68.4 (55.6–91.7)	−4.0 (−16.8 to + 9.7)

[1] Patients could contribute multiple paired measurements, including pairs across different dose adjustment categories.

[2] Median [mg/L] (IQR). Index PIP refers to the piperacillin concentration preceding dose adjustment and follow-up PIP to the concentration at the subsequent TDM measurement.

[3] Median (%) (IQR). PIP change was calculated as the percentage change from index to follow-up PIP for each paired measurement

PIP, piperacillin; TDM, therapeutic drug monitoring

PIP exposure and TDM during extracorporeal organ support

Patients receiving extracorporeal organ support also showed substantial variability in initial PIP exposure. Overexposure was frequent among patients receiving RRT (82.4%, n = 17) or MCS (70.8%, n = 24) at the time of the first TDM measurement, whereas target attainment was less common (5.9% and 25.0%, respectively).

During repeated TDM among patients receiving extracorporeal organ support at any time, PIP exposure changed progressively, as shown in Fig. 2. Overexposure declined from 46.7% at sampling points 2–3 to 15.9% in aggregated samples 6–13 in patients receiving RRT and from 39.5% to 14.3% in those receiving MCS. Concurrently, target attainment increased to 52.3% and 54.3%, respectively.

Initial target attainment according to clinical characteristics

Women showed slightly higher PIP concentrations (105 mg/L vs. 83 mg/L, p = 0.085) and a higher rate of overexposure than men (63.0% vs. 37.2%), while target attainment was comparable. However, women (26%, 27/105) were markedly underrepresented in the study population. Patients with normal body weight were more frequently overexposed (53.8%) compared to patients with higher BMI and obesity (41.0% and 30.8%, respectively). A linear regression model indicated that elevated BMI values were weakly associated with lower PIP serum concentrations (R^2=0.16).

Initial PIP exposure varied markedly according to renal function, as shown in Fig. 3. Among patients without RRT before or at the first TDM measurement, overexposure occurred in 57.1% to 80% of patients with moderate and severe renal impairment (estimated creatinine clearance (Cockcroft Gault) (CrCl) < 60 mL/min and < 30 mL/min, respectively) and declined to 7.1% with normalization of renal function (CrCl 90–<130 mL/min). In patients with moderate renal impairment (CrCl 30–<60 mL/min), target exposure was 34.3%, while near-target exposure accounted for 8.6%. Target attainment predominated in patients with mild renal impairment (47.8%; CrCl 60–<90 mL/min), whereas near-target exposure increased from 26.1% in this group to 57.1% in patients with normal renal function and 81.8% in those with augmented renal function (CrCl > 130 mL/min). With increasing renal function, shifting of PIP exposure to lower target concentrations occurred. Loess regression analysis indicated an association between increasing renal impairment and higher PIP concentrations, although considerable interindividual variability was observed.

Discussion

This retrospective single-center analysis of standardized continuous PIP infusion combined with TDM demonstrated progressive improvement in PK/PD target attainment and marked reduction in overexposure over the course of therapy. However, initial antibiotic exposure was highly variable, with frequent overexposure, particularly in patients with impaired renal function, heart failure, and extracorporeal organ support.

Our findings support and extend previous observations of substantial variability in β-lactam pharmacokinetics after treatment initiation among critically ill patients, making proper target attainment challenging [8, 21, 24]. In their prospective observational study, Dhaese et al. demonstrated considerable variability in β-lactam exposure, with only 37.1% of patients achieving the predefined target range of 64–160 mg/L [25]. In a retrospective analysis, Richter et al. reported a target attainment rate of 34.3% at the first TDM measurement, using a predefined PK/PD target range of 33–64 mg/L [19]. When accounting for differences in PK/PD target ranges and considering concentrations of 65–99 mg/L as moderately elevated, the overall distribution of PIP exposure was broadly comparable between the studies. However, overexposure was more frequent in our cohort than in that of Richter et al. (43.8% vs. 30.2%). Previous studies assessing target attainment showed considerable heterogeneity in predefined PK/PD targets,

ranging from pathogen-specific MICs to multiples thereof, while the underlying target remained unspecified in some studies [8, 19, 26]. Median cumulative doses ranged from 12 to 23 g across studies [19, 21], highlighting that target attainment depends on both the administered dose and the selected target, with more stringent targets increasing the risk of non-attainment.

Cardiac surgery-associated acute kidney injury (AKI) affects approximately 20–30% of patients [27, 28], making renal function an important determinant of β-lactam PK/PD target attainment [29]. Given that PIP is hydrophilic and primarily eliminated via the kidneys, impaired renal function may result in increased drug exposure. Despite daily monitoring of renal function, overexposure remained common, particularly with a creatinine clearance < 60 mL/min, possibly related to the absence of graded dose adjustments as applied by Dhaese et al. [25]. Conversely, augmented renal clearance (ARC), characterized by enhanced drug elimination, is a frequent cause of subtherapeutic β-lactam levels and may be observed in younger cardiac surgical patients without cardiac dysfunction [30]. Accordingly, underexposure occurred only with normal or augmented renal clearance, supporting previous reports of PK/PD target non-attainment with standard dosing regimens [31, 32]. These findings emphasize the need for renal function-based dose adjustment.

In our study, 82.4% of patients requiring RRT were initially overexposed. Similarly, a meta-analysis by Mohd et al. reported substantial PK variability during RRT, with overexposure rates ranging from 10% to 67% [33]. Model-based simulations by Roberts et al. showed that dosing requirements depend on urine output, RRT intensity, and duration, as well as the predefined PK/PD target, with recommended doses of 10–12 g/24 h for higher targets (i.e., 100%fT > 2–4×MIC_{PSA}) at moderate RRT intensity [34]. Although the higher dose used in our study may partly reflect the more stringent PK/PD target, the high rate of overexposure suggests that current dose adjustment strategies during RRT may not consistently prevent excessive drug exposure.

To maintain organ perfusion and prevent further organ damage, postoperative heart failure may require MCS, which can further alter pharmacokinetics in critically ill cardiac surgery patients [15]. In our cohort, overexposure was frequent among patients receiving MCS. In contrast, Kühn et al. reported substantial β-lactam underexposure during ECMO and RRT [35], whereas Bouglé et al. found a more than twofold higher rate of overexposure in MCS patients without RRT [14]. These conflicting findings suggest that overexposure may be driven by underlying factors, such as renal impairment, rather than MCS itself. This uncertainty further supports the role of TDM in this heterogeneous population. However, effective TDM requires timely dose adjustments following target non-attainment, which were not always implemented promptly in our study.

The analysis of consecutive TDM measurements showed that PIP concentrations changed in the expected direction following TDM-guided dose modification. However, dosing decisions were based on preceding PIP concentrations and pharmacokinetic determinants may also have changed between consecutive measurements. Nevertheless, overexposure persisted in a proportion of patients despite

dose reduction, suggesting that conventional dose adjustments may not consistently achieve the optimal β-lactam exposure supporting the need for more individualized dosing strategies.

Limitations of the study

Several limitations should be acknowledged. The single-center design limits causal inference and generalizability. As data were retrospectively collected during routine clinical care without a predefined study protocol, unmeasured factors may have introduced residual confounding and selection bias. Clinical outcomes were not assessed, precluding conclusions on the clinical impact of PK/PD target attainment. Subgroup findings remain exploratory and hypothesis-generating. The independent contribution of potential determinants of PIP exposure was not assessed, as pharmacokinetics in this population are influenced by multiple, interrelated factors, including renal function and extracorporeal organ support. Consequently, the observed associations and concentration changes following dose adjustment cannot be attributed to individual factors independently. Further studies using population pharmacokinetic modelling may help to disentangle the contributions of multiple clinical factors and better characterize inter- and intraindividual pharmacokinetic variability. As individual MIC values were not consistently available, target attainment was based on a conservative PK/PD target of 4× the EUCAST susceptibility breakpoint for *P. aeruginosa*. Exposure was assessed using measured total piperacillin concentrations rather than the unbound fraction, which may have affected target classification. Concentrations of 2–4×MIC_{PSA} were classified as near-target exposure and considered clinically acceptable in many cases, substantially increasing the proportion classified as having acceptable exposure when combined with the target range. Thus, target attainment strongly depends on the selected PK/PD thresholds and should be interpreted accordingly. Finally, structured pharmacological guidance was not routinely integrated into the TDM process.

Implications for clinical practice and future research

Taken together, standardized continuous infusion combined with TDM improved PK/PD target attainment, although substantial variability and persistent non-attainment of optimal β-lactam exposure remained despite dose adjustments, consistent with previous findings [23]. Model-informed precision dosing (MIPD), integrating pharmacokinetic models, patient-specific data, and TDM, may provide a more individualized approach. Greppmair et al. reported a theoretical PIP target attainment of up to 80.6% using Bayesian forecasting with two TDM samples [36], while Schatz et al. achieved approximately 90% with multi-model strategies [37]. By enabling individualized initial dosing and Bayesian forecasting, MIPD may allow earlier and more precise optimization than reactive TDM alone, particularly during the first 24–72 h of therapy when physiological fluctuations are most pronounced.

Antimicrobial stewardship programs (ASPs) can further support individualized antibiotic dosing. The international A-TEAMICU survey reported stewardship rounds in 63% of ICUs and antimicrobial TDM in 61%, with established ASPs being significantly associated with TDM use [38]. Moreover, Gatti et al. demonstrated that multidisciplinary expert clinical pharmacological advice (ECPA) improved the

timeliness and clinical utility of antimicrobial TDM, thereby supporting individualized dose optimization in critically ill patients [39].

Conclusion

Our findings revealed variable and frequently excessive initial PIP exposure, underscoring the limitations of standardized, one-size-fits-all continuous dosing strategies. TDM was associated with progressive improvement in target attainment throughout therapy and a marked reduction in overexposure. However, TDM alone remains a largely reactive strategy and cannot fully address the pronounced interindividual variability observed in critically ill cardiac surgery patients. Future dosing strategies should therefore move toward more individualized approaches. Integrating MIPD, TDM-guided dose adaptation, and structured pharmacological support may enable earlier and more precise dose optimization in this complex population.

Declarations

Ethics approval

The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, LMU Munich (approval number 25-0361).

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to data protection regulations but may be made available from the corresponding author upon reasonable and justified request.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Author contributions

TD and UL conceptualized and designed the study. TD performed the literature search and review, extracted the data, and drafted and revised the manuscript. SB contributed to data curation, statistical analysis, and drafting of the manuscript. UL contributed to visualization, supervision, review and editing of the manuscript. JK contributed to investigation, review and editing of the manuscript. MP contributed to data interpretation, review and editing. DW, DJ and NL reviewed and edited the manuscript for intellectual content. All authors read the final version of the manuscript and approved its submission.

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Figures

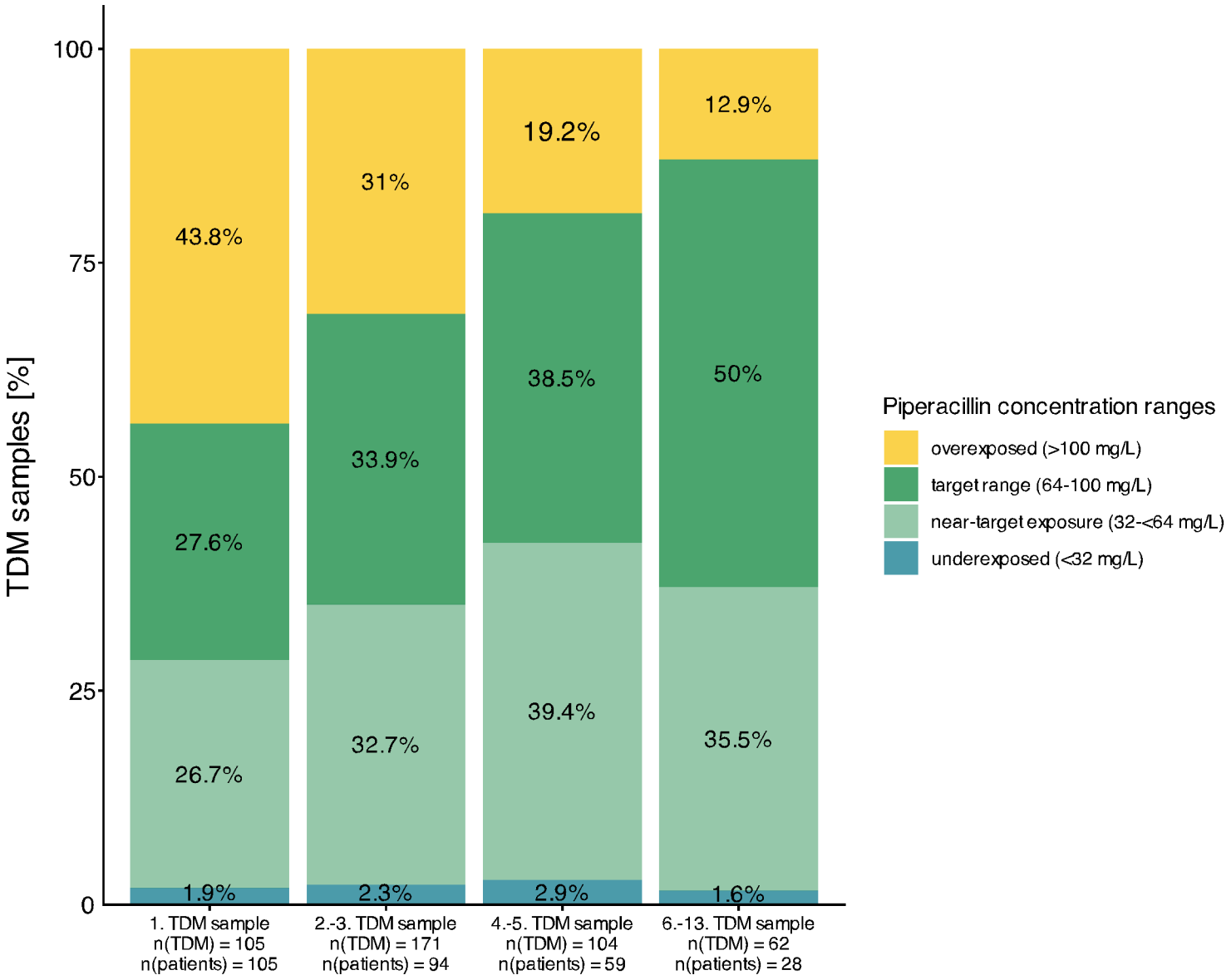


Figure 1

Longitudinal changes in piperacillin concentration ranges across consecutive TDM measurements. Bars represent the percentage of measurements within each exposure category. Consecutive TDM samples were numbered according to their sequential order within each patient, with later samples aggregated as indicated. The numbers of TDM samples and corresponding patients are provided for each sampling point

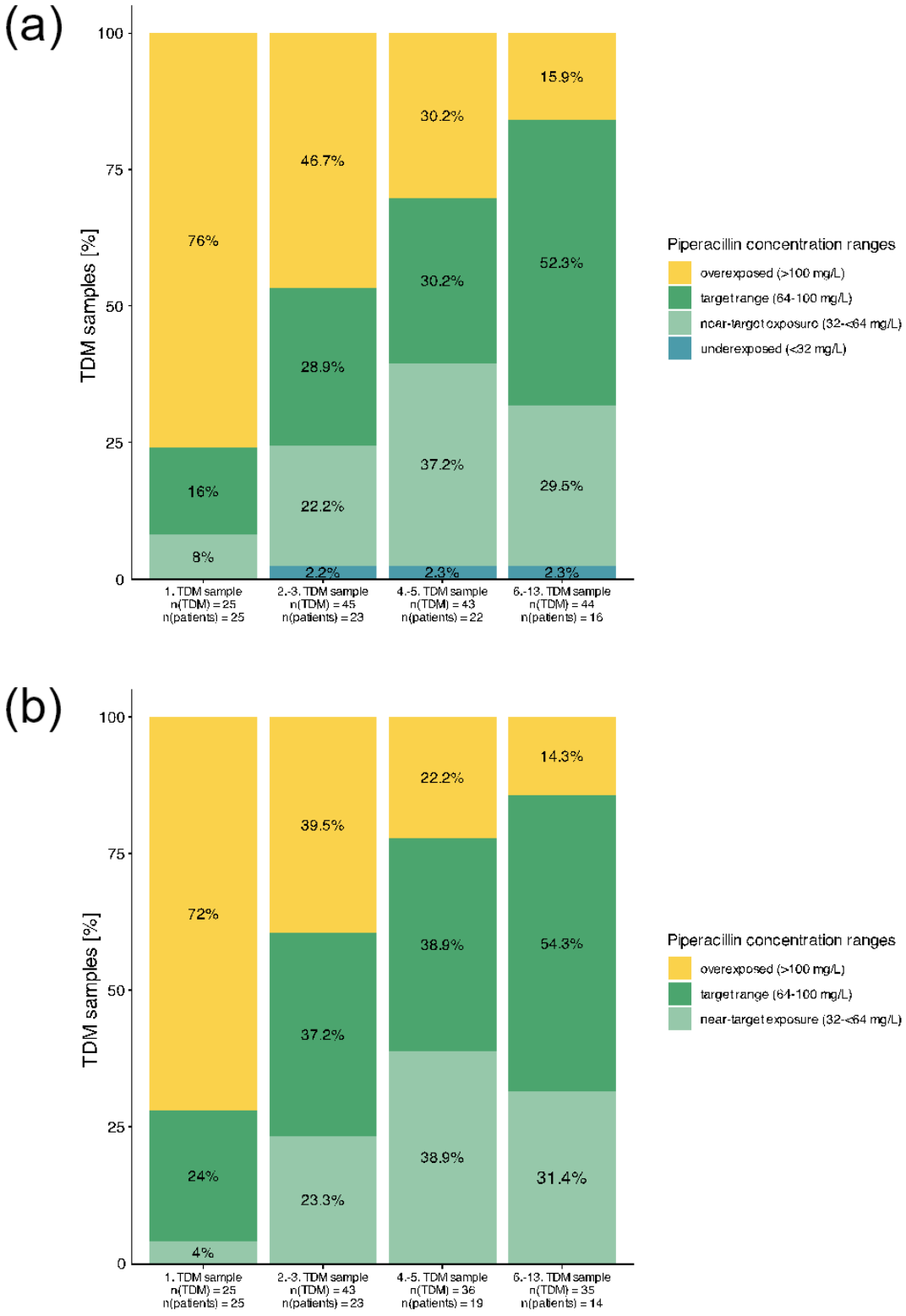


Figure 2

Longitudinal changes in piperacillin concentration ranges across consecutive TDM measurements in patients receiving extracorporeal organ support. (a) Patients receiving renal replacement therapy (RRT) and (b) mechanical circulatory support (MCS) at any time during the observation period. Later TDM samples were aggregated as indicated. The numbers of TDM samples and corresponding patients are provided for each sampling point

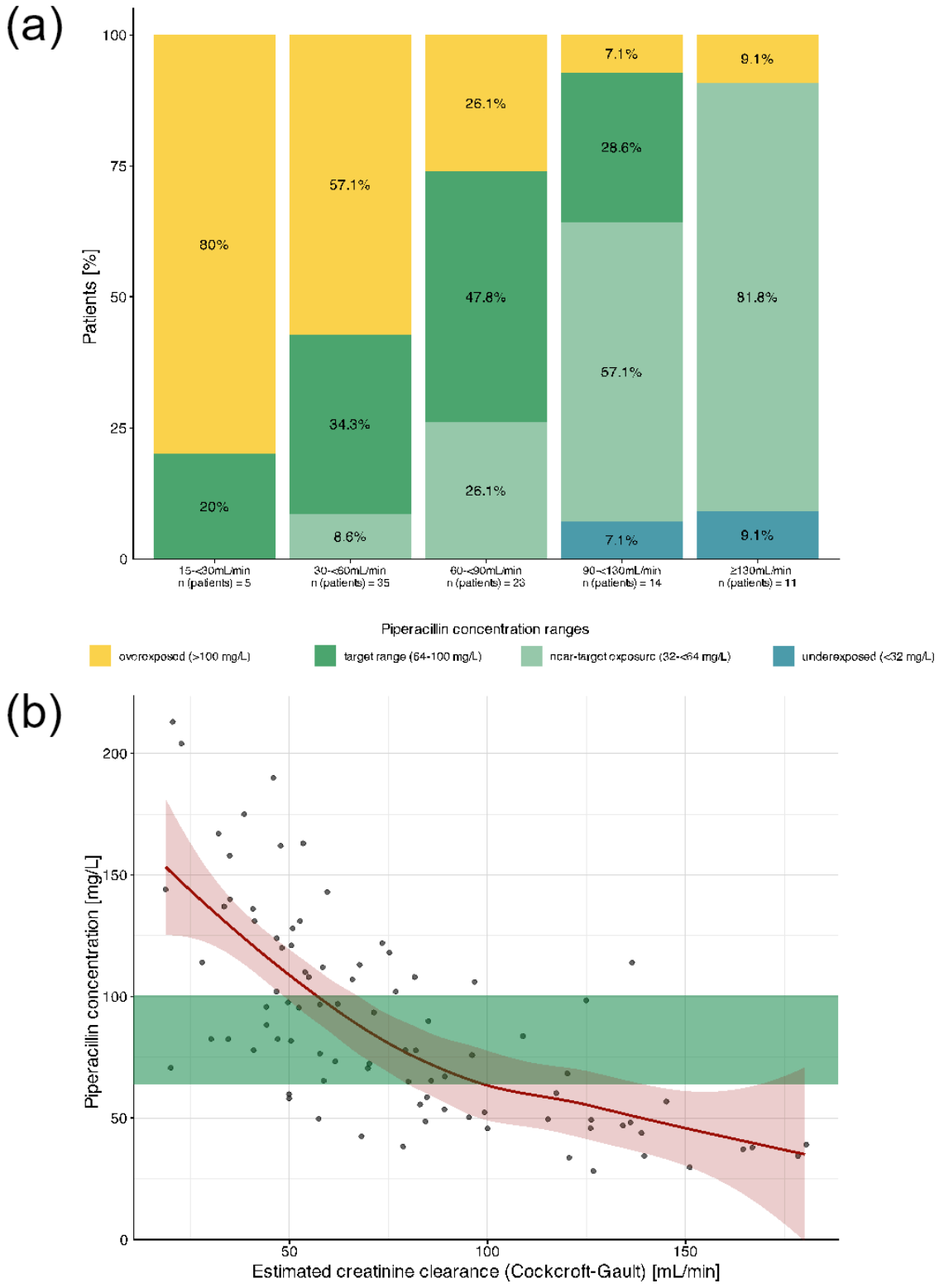


Figure 3

Association between renal function and piperacillin concentrations at initial TDM. (a) Distribution of piperacillin concentration ranges across estimated creatinine clearance (Cockcroft-Gault) categories (n = number of patients). (b) Individual piperacillin concentrations plotted against creatinine clearance (Cockcroft-Gault). The solid line represents the LOESS regression curve, with the shaded area indicating the 95% confidence interval, and the green band the predefined PK/PD target range (64–100 mg/L)