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ORIGINAL

Meropenem and piperacillin/tazobactam optimised dosing regimens for critically ill patients receiving renal replacement therapy

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Abstract

Purpose: Optimal dosing of meropenem and piperacillin/tazobactam in critically ill patients receiving renal replacement therapy (RRT) is uncertain due to variable pharmacokinetics. We aimed to develop generalisable optimised dosing recommendations for these antibiotics.

Methods: Prospective, multinational pharmacokinetic study including patients requiring various forms of RRT. Independent population PK models were developed, externally validated and applied to perform Monte Carlo dosing simulations using Monolix and Simulx. We calculated the probability that these dosing regimens achieved standard and high therapeutic unbound antibiotic concentrations over 100% of the dosing interval for the treatment of Enterobacterales and *Pseudomonas aeruginosa*.

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Results: We enrolled 300 patients from 22 intensive care units across 12 countries receiving continuous veno-venous haemodialysis (13.0%), haemofiltration (23.3%), haemodiafiltration (48.4%) or sustained low-efficiency dialysis (15.3%). Models were developed using data from 234 patients (8322 samples) and validated with 66 additional patients (560 samples). Predictive performance was high, with mean prediction errors of − 5.2% for meropenem and − 16.9% for piperacillin. Dosing simulations showed that meropenem and piperacillin/tazobactam dosing requirements were dependent on urine output and RRT intensity and duration ($p < 0.05$). In all scenarios, extended/continuous infusions led to a better achievement of effective concentrations with lower daily doses compared to short infusion. Dosing nomograms were developed to inform dosing for different RRT settings, urine outputs, and target concentrations.

Conclusion: RRT intensity and duration and urine output determine meropenem and piperacillin/tazobactam dosing requirements in critically ill patients receiving RRT. Extended/continuous infusions facilitate the attainment of effective concentrations.

Keywords: Critically ill patients, Meropenem, Piperacillin/tazobactam, Renal replacement therapy, Pharmacokinetics, Dosing nomograms

Introduction

Infection-associated severe acute kidney injury (AKI) requiring renal replacement therapy (RRT) is a serious complication of sepsis and septic shock [1–3], with associated mortality rates up to 50% higher than those observed in non-septic patients with AKI [1, 2]. In this context, early and appropriate antibiotic therapy is crucial [4]. However, compelling evidence indicates that optimal antibiotic concentrations are not achieved during treatment in approximately 25–40% of cases due to difficult-to-predict pharmacokinetics (PK) [5–7]. Due to such variable PK, universal dosing recommendations for antibiotics during RRT have not been defined, making these patients one of the most challenging groups for antibiotic therapy optimisation.

Meropenem and piperacillin/tazobactam are amongst the most prescribed antibiotics in the intensive care unit (ICU) [8]. As beta-lactams, their efficacy is related to the percentage of time over a dosing interval that the unbound (free) concentration is maintained above the minimum inhibitory concentration (MIC) of the infecting bacteria (% $fT_{>MIC}$) [9]. For the treatment of severe infections in critically ill patients, a 100% $fT_{>MIC}$ is generally recommended for efficacy [10]. Moreover, emerging pre-clinical data suggest that maintaining even higher concentrations (e.g., 4×MIC) may suppress the emergence of bacterial resistance and may be necessary for treating certain infections [11] albeit with an increased risk of toxicity. Nonetheless, associated dosing regimens are undefined.

We aimed to describe the PK of meropenem and piperacillin/tazobactam and their sources of variability in critically ill patients with AKI receiving RRT. With this information, we sought to develop generalisable optimised dosing nomograms that also minimise the likelihood of drug-associated toxicity.

Take-home message

The results of this large international pharmacokinetic study show that meropenem and piperacillin/tazobactam dosing in critically ill patients receiving RRT is dependent on the target concentration chosen and on the main pharmacokinetic determinants in this population, namely RRT intensity, 24 h urine output, and RRT duration in the case of SLED. In most clinical scenarios, extended/continuous infusions facilitate the achievement of effective antibiotic concentrations.

Methods

The Sampling Antibiotics in Renal Replacement Therapy (SMARRT) study was an international, prospective, observational PK study that originally included critically ill patients with AKI requiring renal replacement therapy (RRT) from 29 ICUs across 14 countries over the period December 2011–March 2017 [Australian and New Zealand Clinical Trial Registry (ACTRN12613000241730)]. The study was approved at the lead site by the Royal Brisbane and Woman's Hospital Human Ethics Research Committee (HREC/13/QRBW/1), and all participating sites obtained individual ethics approval. The detailed protocol and the clinical results describing variability of RRT practise and observed antibiotic concentrations have been published elsewhere [5, 7].

Adult critically ill patients receiving meropenem or piperacillin/tazobactam and with severe AKI [12] requiring RRT with continuous veno-venous haemofiltration (CVVHF), haemodialysis (CVVHD) or haemodiafiltration (CVVHDF), or intermittent sustained low-efficiency dialysis (SLED) for an expected duration of at least 4 days were included in the study [7]. All patients or their authorised representative gave written informed consent. Due to slow recruitment, additional patient data were included from contemporary PK studies at participating sites with similar entry criteria and data collection methods [13–20].

Antibiotic dosing, data collection, plasma sampling, and bioanalysis

Antibiotic dosing and RRT settings were at the discretion of the clinical team. Demographic and clinical data were collected at inclusion and on the days of sampling, that was performed over one or two dosing occasions accounting for the initial and maintenance phases of therapy. Plasma from pre- and post-filter RRT ports and effluent fluid samples were obtained following a rich sampling strategy. Meropenem, piperacillin, and tazobactam total and unbound concentrations were measured using a validated ultra-high performance liquid chromatography with tandem mass spectrometry method [21]. A detailed description of sample collection and bioanalysis is provided in the electronic supplementary material.

Pharmacokinetic analyses

Population PK analyses and validation were performed using the non-linear mixed effects modelling software Monolix 2024R1 (Lixoft SAS, Antony, France) [22]. Briefly, a population PK model was developed for each drug to integrate pre- and post-filter plasma and effluent concentrations as described by Broeker et al. [23]. In the models, drug clearance (CL) was defined as the sum of non-RRT-mediated CL (CL_{body}) and RRT-mediated CL (CL_{RRT}). During the statistical analysis, the covariates that clinically and significantly explained the variability in CL and volume of distribution (V) were included. Internal validation of the models was based on goodness-of-fit (GOF) plots, a prediction-corrected visual predictive check (pc-VPC), and non-parametric bootstrapping ($n = 1000$) [24, 25]. The predictive performance of the PK models was assessed using additional data from patients receiving the four RRT modalities, that came primarily from non-SMARRT-funded studies allowing as well for evaluation of the model's performance on slightly different patients, centres, and study designs. Bias and precision of the population predicted pre-filter concentrations were assessed by the mean prediction error (MPE) and mean absolute prediction error (MAPE), respectively [26]. Values < 30% were considered acceptable, and those < 20% were considered optimal [27]. Modified Bland–Altman plots were also built [28]. A detailed data analysis description is provided in the electronic supplementary material.

Monte Carlo simulations and probability of target attainment for efficacy and toxicity

Monte Carlo initial and steady-state dosing simulations were performed with the final covariate models using the Simulx 204R1 (Lixoft SAS) simulation software. For meropenem and piperacillin, the pharmacokinetic/pharmacodynamic (PK/PD) target was set taking into account (1) a standard efficacy target against Gram-negative bacilli (i.e., global 100% $fT_{>MIC}$ and 4 × MIC for Enterobacterales) [5, 10, 11, 29]; and a higher efficacy target (4 × MIC for global empirical treatment and for directed treatment of *P. aeruginosa*) and (2) toxicity thresholds described in the literature [30, 31], i.e., unbound trough concentrations or in the case of continuous infusion, unbound average steady-state concentrations of ≥ 45 mg/L and ≥ 160 mg/L for meropenem and piperacillin, respectively. Therefore, for each dosing regimen, we calculated the probability of target attainment for a range of unbound trough/average steady-state concentrations considering that the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints and epidemiological cut-off values (ECOFF) for *Pseudomonas aeruginosa* are 2 mg/L for meropenem and 16 mg/L for piperacillin in combination with tazobactam [32]. For tazobactam, the efficacy PK/PD target was defined as maintaining unbound concentrations above a concentration threshold for a percentage of time during the dosing interval, that has been described to be ≥ 85% $fT_{>2mg/L}$ in combination with piperacillin in in vitro models with Gram-negative bacteria producers of extended-spectrum beta-lactamases [33]. A toxic concentration threshold has not been described for tazobactam; instead, we chose the most conservative toxicity concentration for piperacillin that has been reported with the two drugs in co-administration [31]. The minimum desired probability of target attainment was defined as ≥ 90%.

From these results, a dosing nomogram was developed for each drug, considering (1) a standard trough/average steady-state concentration target of ≥ 2 mg/L for meropenem and ≥ 16 mg/L for piperacillin/tazobactam (global 100% $fT_{>MIC}$ and 4 × MIC for Enterobacterales) and (2) a higher target of ≥ 4–8 mg/L for meropenem and ≥ 32–64 mg/L for piperacillin/tazobactam (empirical treatment and 4 × MIC for *P. aeruginosa*). The recommended dosing regimens provided the highest likelihood of achieving effective and non-toxic concentrations during the first 24 h and at steady state.

Results

Across 22 ICU from 12 countries, 300 patients treated with meropenem or piperacillin/tazobactam were enrolled. From these patients, 179 patients were enrolled in the SMARRT study and 121 belonged to similar PK studies [13–20]. Most of the patients were male, with a mean age of 61.1 years, had respiratory or intra-abdominal infections, and were intubated (79.3%) and receiving vasopressors (70%) on the days of the study. Overall, the most prescribed RRT modality was

CVVHDF (48.3%). The median antibiotic daily dose was 3 g for meropenem and 12/1.5 g for piperacillin/tazobactam; in 67% of the cases, these drugs were prescribed as short infusions (<1 h) and in 33% as extended/continuous infusions. Trough concentrations were below the clinical breakpoints for meropenem and piperacillin (2 and 16 mg/L, respectively) in 1.3% of the cases for meropenem and in 4% of the cases for piperacillin. Conversely, 18.5% of the patients receiving meropenem had concentrations above 20 mg/L (10×clinical breakpoint) and 1.5% above 45 mg/L (specified toxicity threshold). For piperacillin, 11% of the patients had concentrations >160 mg/L (10×clinical breakpoint and specified toxicity breakpoint). Clinical and demographic characteristics are detailed in Table 1 and electronic supplementary Tables A–C.

Population PK modelling

Overall, the models were built with 1551 unbound plasma pre-filter, 1231 unbound plasma post-filter and 557 effluent concentrations from the patients receiving meropenem, 1266 total plasma pre-filter (101 unbound), 884 total plasma post-filter (100 unbound) and 371 effluent concentrations from the patients receiving piperacillin and, of those, 883 total plasma pre-filter (88 unbound), 836 total plasma post-filter (85 unbound), and 369 effluent tazobactam concentrations. In total, 8322 samples were collected.

For the three drugs, the structural model that best described pre-filter plasma concentrations over time was a two-compartment model with linear elimination from the central compartment. The final models included RRT intensity (calculated as dialysate + replacement fluid flow rates) and urine output as covariates that significantly incremented CL_{RRT} and CL_{body}, respectively, and explained their variability ($p < 0.05$ for all covariates). In addition, the use of SLED modality also explained variability in CL_{RRT} for meropenem. The final models are summarised in the electronic supplementary Tables D–F.

The models were internally valid (electronic supplementary Tables D–F and electronic supplementary Figures A–F) demonstrating stability. External validation was performed with additional 177 plasma pre-filter and 40 plasma post-filter concentrations from 36 individuals [13, 20] for meropenem and 210 plasma pre-filter and 133 plasma post-filter concentrations from 30 individuals [15, 18, 20] for piperacillin (additional 560 concentrations). For both drugs, patients receiving continuous RRT had higher illness severity scores, were more frequently on vasopressors and mechanical ventilation, and, in the case of meropenem, received lower RRT intensities. Conversely, patients receiving SLED were outpatients with end-stage chronic kidney disease and intermittent dialysis requirement, and the total intensity used was significantly higher (Table 1) [20]. In spite of these important clinical differences between development and validation datasets, the results of the external validation were the following: MPE was − 5.2% (95% CI − 6.8 to − 3.6) and MAPE was 25.8% (22.1% to 29.6%) for meropenem and MPE was − 16.9% (− 22.0% to − 11.7%) and MAPE was 29.1% (22.5% to 35.7%) for piperacillin. These data support the models' predictive power, with MPE < 20% for both drugs. The modified Bland–Altman plots are consistent with these results (electronic supplementary Figures G and H).

Dosing simulations

Monte Carlo first 24-h- and steady-state-dosing simulations were performed for dosing different short, extended, and continuous infusion regimens that reflected usual practise in the ICU [5]. An initial full loading dose administered in a 30-min short infusion was always simulated for the first 24 h of therapy, as recommended by the Surviving Sepsis campaign guidelines [34]. Different RRT intensities, durations (for SLED) and urine outputs (oligoanuria or urine output ≥500 mL/24 h for meropenem, and anuria or urine output ≥100 mL/24 h for piperacillin and tazobactam as the thresholds identified during model development) were tested in the simulations. The probabilities of target attainment for each dosing regimen at steady state are detailed in the electronic supplementary Tables G–Q.

Our simulations consistently show that meropenem and piperacillin/tazobactam dosing requirements are strongly dependent on RRT intensity, urine output, and, in the case of SLED, RRT duration. For all the scenarios, extended/continuous infusions (after a full initial loading dose if therapy with meropenem or piperacillin/tazobactam is being initiated) are more likely to achieve effective unbound concentrations for empirically treating Enterobacterales and *P. aeruginosa* compared to equivalents dose given as a short 30-min infusion. This is especially important for patients with higher CL, i.e., those receiving RRT with higher intensities, longer SLED sessions, and/or with urine outputs ≥100–500 mL/24 h. Where higher unbound concentrations are targeted (4×MIC), continuous infusion provides the highest likelihood of effective and safe dosing. Conversely, for treating bacteria with lower MICs, short 30-min infusions had similar target attainment to extended/continuous infusions.

Tables 2 and 3 provide the dosing nomograms for meropenem and piperacillin/tazobactam for standard and high targets stratified by modality, intensity, and urine output. The recommended doses are the ones that optimise effective concentrations and minimise the risk

Table 1 Demographical and clinical characteristics of the patients receiving meropenem and piperacillin/tazobactam included in the model development and model validation datasets

Variable	Meropenem		Piperacillin/tazobactam	
	Model development dataset ($n = 128$)	Model validation dataset ($n = 36$)	Model development dataset ($n = 106$)	Model validation dataset ($n = 30$)
Sex (females (%))	38 (29.9%)	18 (50.0%)	37 (34.9%)	18 (60.0%)
Age (years)	60.1 (SD = 14.4)	65.8 (SD = 12.1)	62.3 (SD = 15.3)	55.4 (SD = 16.4)
Height (cm)	170.2 (SD = 11.0)	167.2 (9.7)	169.2 (SD = 12.9)	162.9 (SD = 10.7)
Weight (kg)	85.0 (SD = 25.3)	79.5 (SD = 17.5)	83.2 (SD = 26.9)	78.8 (SD = 15.5)
Body mass index (kg/m^2)	30.1 (SD = 12.7)	28.5 (SD = 6.8)	29.7 (SD = 13.6)	29.7 (SD = 3.8)
APACHE II score at admission	25.1 (SD = 7.1)	26.5 (SD = 9.5)	25.3 (SD = 8.9)	32.5 (29–35.3)
Primary source of infection (number of episodes)[a]				Not available
Respiratory	55	7	56	Not available
Abdominal	42	13	39	Not available
Urinary tract	25	2	14	Not available
Skin and soft tissue	20	0	9	Not available
Central venous catheter-related	5	2	2	Not available
Central nervous system	0	2	1	Not available
Bone and joint	1	0	3	Not available
Cardiac	2	0	0	Not available
Others/Unknown	10	4	8	Not available
With concomitant blood-stream infection	33	10	31	Not available
Clinical and analytical variables (on the day of sampling occasion 1)				
SOFA score	8.5 (SD = 4.0)	11.7 (SD = 4.0)[d]	8.9 (SD = 4.5)	14.5 (11.5–16)[d]
Use of vasopressors	102 (79.7%)	28 (93.3%)[d]	80 (75.5%)	Not available
Mechanical ventilation	96 (75.6%)	30 (100%)[d]	88 (83.0%)	24 (100%)[d]
Urine output (mL/24 h)[b]	50 (5–500)	212 (0–325)	68 (14–204)	Not available
Urine output 100–499 mL/24 h (%)	10 (7.8%)	9 (25%)	26 (24.5%)	Not available
Urine output ≥ 500 mL/24 h (%)[b]	39 (30.5%)	5 (13.9%)	7 (6.6%)	Not available
Serum creatinine (µmol/L)	211.5 (144.0–355.0)	267.0 (210.4–433.3)	227.0 (148.0–321.0)	289.5 (171.5–395.5)[d]
Serum bilirubin (µmol/L)	34.2 (14.0–66.0)	Not available	40.5 (18.0–78.7)	29.9 (15.1–58.8)[d]
Serum albumin (g/L)	24 (21–28)	22 (18–25)[d]	25 (20–29)	26 (23–33)[d]
Haematocrit (%)	26.1 (SD = 3.0)	Not available	27.7 (SD = 5.1)	28.0 (27.0 29.8)
Days of study antibiotic previous to first sampling	1 (0–2)	2 (1–2)[d]	1 (1–2)	3 (2.8–4.3)[d]
Antibiotic daily dosing on the day of the study (g)	3 (3–3)	2.5 (2–3)[d]	12 (12–16) piperacillin 1.5 (1.5–2) tazobactam	9 (9–12)[d] piperacillin 1..1 (1.1–1.5)[d] tazobactam
Antibiotic pre-filter trough/steady-state concentration on the day of the study (mg/L)	10.9 (7.4–16.6)	13.2 (8.9–20.0)	78.5 (50.3–115.1) piperacillin 11.1 (7.3–14.3) tazobactam	71.4 (36.2–93.9) piperacillin
RRT parameters				
RRT modality				
CVVHF	27 (21.1%)	4 (11.1%)	23 (21.7%)	16 (53.3%)
CVVHD	22 (17.2%)	1 (2.8%)	16 (15.1%)	0 (0%)
CVVHDF	54 (42.2%)	25 (69.4%)	58 (54.7%)	8 (26.7%)
SLED	25 (19.5%)	6 (16.7%)	9 (8.5%)	6 (20.0%)

Table 1 (continued)

Variable	Meropenem		Piperacillin/tazobactam	
	Model development dataset ($n = 128$)	Model validation dataset ($n = 36$)	Model development dataset ($n = 106$)	Model validation dataset ($n = 30$)
Filter membrane type				
Acrylonitrile and sodium methallyl sulfonate	42 (32.8%)	29 (80.6%)	56 (52.8%)	8 (26.7%)
Polyethersulfone	46 (35.9%)	0 (0%)	28 (26.5%)	16 (53.3%)
Polysulfone	35 (27.3%)	6 (16.6%)	21 (19.8%)	6 (20.0%)
Blend of polyarylethersulfone, polyvinylpyrrolidone, polyamide	0 (0%)	1 (2.8%)	0 (0%)	0 (0%)
Polyarylethysulfone	2 (1.7%)	0 (0%)	1 (0.9%)	0 (0%)
Other	3 (2.3%)	0 (0%)	0 (0%)	0 (0%)
Filter surface				
0.6 m^2	0 (0%)	0 (0%)	1 (0.94%)	0 (0%)
0.9 m^2	19 (15.2%)	20 (55.6%)	27 (25.5%)	0 (0%)
1 m^2	9 (7.2%)	0 (0%)	12 (11.3%)	8 (26.7%)
1.2 m^2	0 (0%)	0 (0%)	2 (1.9%)	16 (53.3%)
1.3 m^2	4 (3.2%)	0 (0%)	1 (0.94%)	0 (0%)
1.4 m^2	39 (31.2%)	6 (16.6%)	26 (24.5%)	6 (20.0%)
1.5 m^2	14 (11.2%)	9 (25.0%)	17 (16.0%)	0 (0%)
1.8 m^2	30 (24.0%)	0 (0%)	17 (16.0%)	0 (0%)
1.9 m^2	10 (8.0%)	1 (2.8%)	3 (2.8%)	0 (0%)
Unknown	3	0 (0%)	0 (0%)	0 (0%)
Blood flow rate for SLED (mL/min)	228 (182–263)	250 (220–250)	200 (200–200)	250 (220–250)
Dialysate flow rate for SLED (mL/h)	14,600 (12,000–16,200)	18,000 (18,000–18,000)	12,000 (12,000–12,000)	18,000 (18,000–18,000)
Blood flow rate for CRRT (mL/min)	180 (145–200)	200 (180–245)	180 (150–200)	200 (200–200)
Dialysate flow rate for CVVHD and CVVHDF (mL/h)	1500 (1000–2000)	900 (800–1200)	1500 (1000–2000)	No available
Replacement fluid rate for CVVHF and CVVHDF (mL/h)	2350 (2000–3000)	1800 (1050–1900)	1900 (1200–2080)	No available
RRT intensity for CRRT (mL/h)[c]	3500 (3000–4000)	2350 (1875–2650)	2300 (2000–3000)	2000 (2000–3022.5)
Duration for SLED (min)	314 (301–369)	240 (240–240)	360 (360–390)	240 (240–240)
ICU mortality	44 (34.4%)	14 (46.7%)[d]	49 (46.3%)	Not available
28-days mortality	50 (39.1%)	Not available	53 (50.0%)	Not available

Continuous variables are summarised as mean [standard deviation (SD)] or as median [quartile 1 (Q1)–quartile 3 (Q3)] as appropriated. Discrete variables are described as absolute count [*n*, percentage (%)]

APACHE II score acute physiology and chronic health evaluation II score, *SOFA score* sepsis-related organ failure assessment score, *RRT* renal replacement therapy, *CRRT* continuous renal replacement therapy, *CVVHF* continuous veno-venous haemofiltration, *CVVHD* continuous veno-venous haemodialysis, *CVVHDF* continuous veno-venous haemodiafiltration, *SLED* sustained low-efficiency dialysis; *N/A* non-applicable

[a] The count of source of infection is higher than the number of patients included, because some patients had > 1 infectious episodes during their ICU stay treated with meropenem

[b] When these data were not available as a continuous covariate, it was interpolated as a binary covariate from a punctuation < 3 for the urine subsection of the SOFA score on the day of sampling

[c] RRT intensity calculated as dialysate flow rate + replacement fluid flow rate

[d] These statistics only consider critically ill patients, i.e., excluding the patients from reference [20]

of toxic concentrations. Figure 1 schematises the dosing decision-making algorithm.

Discussion

We present the results of the largest prospective multicentre study of meropenem and piperacillin/tazobactam PK in critically ill patients with AKI receiving the most prescribed RRT modalities in the ICU [2, 8, 35]. Our main findings are that meropenem, piperacillin, and tazobactam PK are highly variable and dependent on RRT intensity, urine output, and, in the case of SLED, duration of therapy, with the same factors determining dosing requirements for optimised concentrations. In most clinical scenarios, extended/continuous infusions provided a better attainment of optimal antibiotic trough/average steady-state unbound concentrations (100% $fT_{>MIC}$) compared to the equivalent doses administered as a short 30-min infusion; continuous infusion appeared particularly advantageous when higher concentrations are required (4×MIC for *P. aeruginosa* or for empirical treatment), especially for those patients with clinical characteristics associated with higher drug CL. Our dosing nomograms provide dosing recommendations that maximise the attainment of effective meropenem and piperacillin/tazobactam concentrations (either standard or higher target as required) and also minimise the risk of toxic concentrations.

Optimising beta-lactam dosing in critically ill patients receiving RRT is a major challenge in daily practise. The diversity in RRT modalities, techniques, and settings may have a major effect on the PK of water-soluble drugs like beta-lactams [5, 6], leading to different antibiotic requirements depending on each infection, patient, and RRT treatment [12]. However, existing dosing recommendations are still generic and not robust. Multiple well-designed PK studies have tried to address this clinical question for meropenem and piperacillin/tazobactam, but patient heterogeneity and small sample sizes in single-centre settings have provided insufficient data to generate optimised dosing recommendations [13–16, 18, 36–44]. In this context, the large sample size of our multi-centre study has identified RRT intensity and duration and urine output as the primary factors influencing drug CL, allowing our dosing nomogram to be highly accurate across a wide range of scenarios.

Regarding the influence of RRT settings and modality on CL_{RRT}, higher CL has been associated with diffusive or mixed modalities and higher intensities [17, 39, 41, 42, 45], but their effect on CL_{RRT} had not been sufficiently characterised to develop stratified dosing recommendations. In our patients, who received a broad range of RRT modalities and settings, RRT intensity explained the majority of CL_{RRT} variability for meropenem, piperacillin, and tazobactam. As expected, prescription of longer SLED sessions resulted in higher CL_{RRT}. On the other hand, urine output significantly influenced CL_{body} [13, 19], which is congruent with its role as a clinical predictor of renal function recovery in patients with AKI receiving RRT [12, 46].

Table 2 Meropenem dosing nomogram for a standard steady-state concentration target of ≥ 2 mg/L (global 100% $fT_{>MIC}$ and 4×MIC for Enterobacterales) and higher target of ≥ 4–8 mg/L (empirical treatment and 4×MIC for *P. aeruginosa*), considering a toxicity threshold of 45 mg/L [30] and stratified by RRT modality, intensity and urine output

RRT modality	RRT intensity	Oligoanuria		Urine output ≥ 500 mL/24 h	
		Standard target (steady-state concentration ≥ 2 mg/L)	Higher target (steady-state concentration ≥ 4–8 mg/L)	Standard target (steady-state concentration ≥ 2 mg/L)	Higher target (steady-state concentration ≥ 4–8 mg/L)
For all types of modality, time and settings: If starting treatment, administer a 1 g loading dose over a 30-min short infusion and immediately after initiate the continuous infusion at the recommended daily dose					
Continuous RRT	1.5 L/h 2.5 L/h 3.5 Lh	1 g–1.5 g per day CI	1.5–2 g per day CI 2 g per day CI	1 g–1.5 g per day CI	3 g per day CI
Short SLED (~ 6 h)	9 L/h 12 L/h 15 L/h	1 g–1.5 g per day CI	2 g per day CI 3 g per day CI	1 g–1.5 g per day CI	3 g per day CI
Intermediate SLED (~ 8 h)	9 L/h 12 L/h 15 L/h	1 g–1.5 g per day CI	2 g per day CI 3 g per day CI	1 g–1.5 g per day CI	3 g per day CI
Long SLED (~ 12 h)	9 L/h 12 L/h 15 L/h	1 g–1.5 g per day CI	3 g per day CI	1 g–1.5 g per day CI	3 g per day CI 3–4 g per day CI

RRT: renal replacement therapy, SLED: sustained low-efficiency dialysis, CI: continuous infusion

Table 3 Piperacillin/tazobactam dosing nomogram for a unbound average concentration target of ≥16mg/L (global 100% $fT_{>MIC}$ and 4 × MIC for Enterobacterales) and a higher target of ≥32–64 mg/L (empirical treatment and 4 × MIC for *P. aeruginosa*), considering a toxicity threshold of 160 mg/L [31] and stratified by RRT modality, intensity, and urine output

RRT modality	RRT intensity	Anuria		Urine output ≥ 100 mL/24 h	
		Standard target (steady-state concentration ≥ 16 mg/L)	Higher target (steady-state concentration ≥ 32–64 mg/L)	Standard target (steady-state concentration ≥ 16 mg/L)	Higher target (steady-state concentration ≥ 32–64 mg/L)
For all types of modality, time and settings: If starting treatment, administer a 4 g/0.5 g loading dose over a 30-min short infusion and immediately after initiate the continuous infusion at the recommended daily dose					
Continuous RRT	1.5 L/h	6 g/0.725 g–8 g/1 g per day CI	6 g/0.725 g–8 g/1 g per day CI[a]	6 g/0.725 g–8 g/1 g per day CI	10 g/1.25 g–12 g/1.5 g daily in CI[a]
	2.5 L/h		8 g/1 g–10 g/1.25 g per day CI[a]		
	3.5 L/h				12 g/1.5 g–16 g/2 g per day CI[a]
Short SLED (~6 h)	9 L/h	6 g/0.725 g–8 g/1 g per day CI	8 g/1 g–10 g/1.25 g per day CI[a]	6 g/0.725 g–8 g/1 g per day CI	12 g/1.5 g–16 g/2 g per day CI[a]
	12 L/h		10 g/1.25 g–12 g/1.5 g per day CI[a]		
	15 L/h				
Intermediate SLED (~8 h)	9 L/h	6 g/0.725 g–8 g/1 g per day CI	10 g/1.25 g–12 g/1.5 g per day CI[a]	6 g/0.725 g–8 g/1 g per day CI	12 g/1.5 g–16 g/2 g per day CI[a]
	12 L/h				
	15 L/h		12 g/1.5 g–16 g/2 per day CI[a]		
Long SLED (~ 12 h)	9 L/h	6 g/0.725 g–8 g/1 g per day CI	10 g/1.25 g–12 g/1.5 g per day CI[a]	6 g/0.725 g–8 g/1 g per day CI	12 g/1.5 g–16 g/2 g per day CI[a]
	12 L/h		12 g/1.5 g–16 g/2 g per day CI[a]		
	15 L/h				16 g/2 g per day CI

RRT renal replacement therapy, *SLED* sustained low-efficiency dialysis, *CI* continuous infusion

[a] Based on simulations data, the higher recommended dose will increase the likelihood of attaining the steady-state concentration of ≥ 64 mg/L but can also increment the risk of surpassing the toxicity threshold chosen for piperacillin (> 160 mg/L)

In such difficult-to-predict RRT scenarios, dosing simulations have shown that extended/continuous infusions increased the likelihood of achieving effective concentrations even when an intermittent RRT modality like SLED is used, resulting in lower daily doses and a reduced risk of potentially toxic concentrations compared to the higher doses required for achieving effective concentrations when the drug is administered as a short 30-min infusion. For the most likely patient—anuric on CRRT, prescribed an intensity of 20–25 mL/kg/h (1.5–2 L/h for an 80 kg patient [12])—a daily dose of 2 g meropenem and 8 g/1 g–10 g/1.25 g of piperacillin/tazobactam in continuous infusion would provide optimal concentrations even for the higher targets. However, our patients received notably higher daily doses and, consequently, median trough concentrations were above the higher efficacy targets for the three drugs (Table 1). Considering the results of the present PK analysis, a key message from the SMARRT project is that a significant proportion of patients receiving RRT are at risk of excessive daily dosing. Dosing simulations using these daily doses administered over different infusion times show that they can lead to unnecessarily high concentrations that may even be above the toxicity threshold in up to 10–35% of the cases, especially for piperacillin/tazobactam. However, caution is warranted when considering toxicity risk, as most available evidence that identified a threshold for beta-lactam toxicity is derived from retrospective data that are subject to multiple sources of bias. Consequently, the clinical significance of the proposed toxicity thresholds remains uncertain.

The strengths of this research are its multi-centre design and the rich PK sampling that has led to the development and validation of robust population PK models for each drug. Furthermore, dosing recommendations consider standard versus high concentration targets for efficacy as well as toxicity and are based on clinical variables that are easily identifiable at the bedside. Finally, our recommendations align with the current treatment guidelines for septic patients, particularly the Surviving Sepsis Campaign initiative which endorses the use of extended/continuous beta-lactam infusions over short infusions [34]. They are also consistent with the results of the BLING III randomised clinical trial ($n = 7000$ septic patients) and the associated systematic review and meta-analysis that showed better survival and clinical

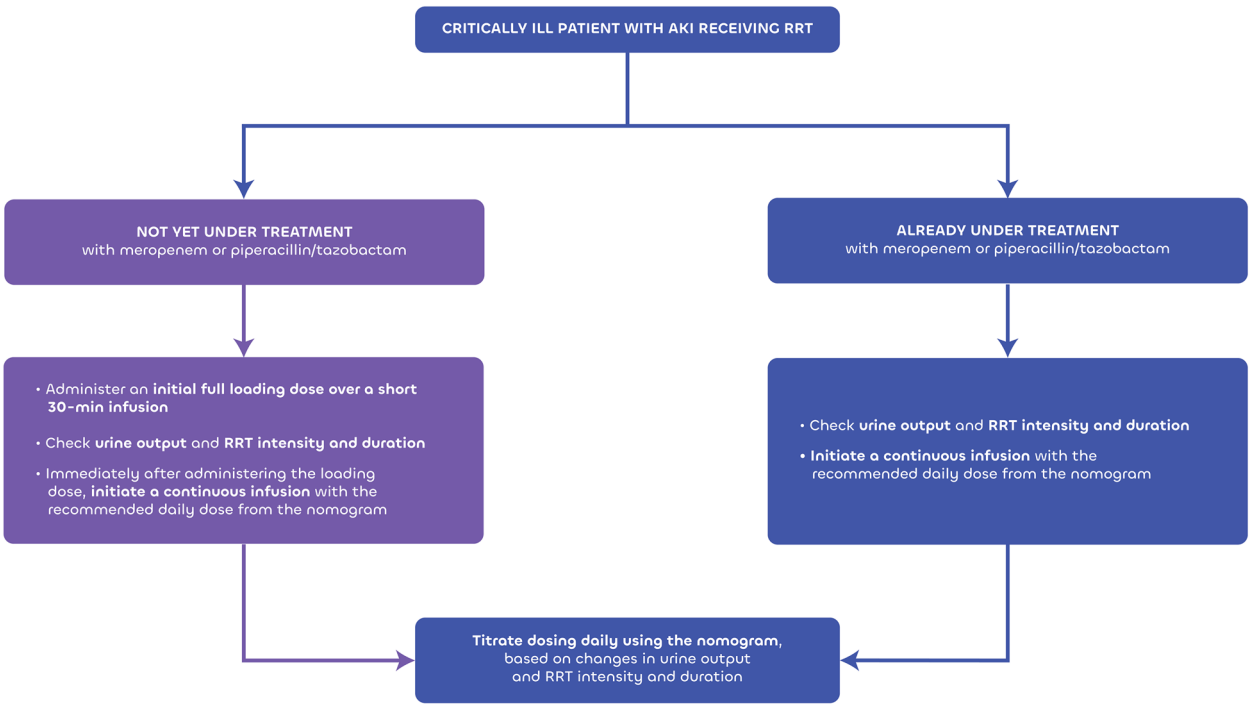

Fig. 1 Schematic algorithm illustrating the dose decision-making process based on the primary determinants of meropenem and piperacillin/tazobactam dosing requirements, using the dosing nomograms

cure rates with extended/continuous beta-lactam infusions, even though only a small proportion of patients received RRT during the study [47, 48]. The study limitations include the fact that the population PK models were developed with data from critically ill patients receiving continuous RRT or SLED, for which dosing recommendations should be extrapolated with caution to patients undergoing other RRT modalities or settings, including those concurrently receiving extracorporeal therapies such as extracorporeal membrane oxygenation. Further, there were limited numbers of patients who were morbidly obese or cachectic critically ill patients, and caution is also advised in these scenarios. Further, our results are based on plasma concentrations, that may not represent infection site PK, especially in the context of haemodynamic instability in patients with septic shock. However, current evidence on organ and tissue distribution suggests that maintaining high trough/average steady-state concentrations in plasma enhances distribution to organs and peripheral tissues [49, 50], for which dosing strategies that optimise plasma exposure may also improve antibiotic distribution at the infection site. Finally, due to the observational nature of our data, the clinical effect of these optimised dosing recommendations is uncertain and should be evaluated in a randomised clinical trial.

In conclusion, this study provides optimised dosing regimens for meropenem and piperacillin/tazobactam in critically ill patients receiving diverse RRT prescriptions. Daily dosing is dependent on the target concentration and the main PK determinants in this population, namely RRT intensity, 24-h urine output, and RRT duration in the case of SLED. As described in the dosing nomogram, extended/continuous infusions facilitate the achievement of optimised antibiotic concentrations in most clinical scenarios, resulting in lower daily doses and a reduced risk of exposure-related toxicity.

Supplementary Information

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Data sharing
Data availability requests should be made to the corresponding author. Each request requires a research proposal with a clear research question and proposed analysis plan. Requests will be considered on an individual basis and will be reviewed by the SMARRT steering committee, as well as relevant human research ethics committees.

Declarations

Conflicts of interest
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Ethics approval
The study was designed and conducted following the declaration of Helsinki guidelines and received ethics approval from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/13/QRBW/1) as the lead site. All other participating sites also obtained individual HREC approval.

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