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PHARMACOLOGY

Using Population Pharmacokinetic Modeling and Monte Carlo Simulations To Determine whether Standard Doses of Piperacillin in Piperacillin-Tazobactam Regimens Are Adequate for the Management of Febrile Neutropenia

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ABSTRACT Changes in the pharmacokinetics of piperacillin in febrile neutropenic patients have been reported to result in suboptimal exposures. This study aimed to develop a population pharmacokinetic model for piperacillin and perform dosing simulation to describe optimal dosing regimens for hematological malignancy patients with febrile neutropenia. Concentration-time data were obtained from previous prospective observational pharmacokinetic and interventional therapeutic drug monitoring studies. Nonparametric population pharmacokinetic analysis and Monte Carlo dosing simulations were performed with the Pmetrics package for R. A two-compartment model, with between-subject variability for clearance (CL), adequately described the data from 37 patients (21 males, age of 59 ± 12 years [means ± standard deviations] and weight of 77 ± 16 kg). Parameter estimates were CL of 18.0 ± 4.8 liters/h, volume of distribution of the central compartment of 14.3 ± 7.3 liters, rate constant for piperacillin distribution from the central to peripheral compartment of 1.40 ± 1.35 h^{-1}, and rate constant for piperacillin distribution from the peripheral to central compartment of 4.99 ± 7.81 h^{-1}. High creatinine clearance (CL_{CR}) was associated with reduced probability of target attainment (PTA). Extended and continuous infusion regimens achieved a high PTA of >90% for an unbound concentration of piperacillin remaining above the MIC ($fT_{>MIC}$) of 50%. Only continuous regimens achieved >90% PTA for 100% $fT_{>MIC}$ when CL_{CR} was high. The cumulative fraction of response (FTA, for fractional target attainment) was suboptimal (<85%) for conventional regimens for both empirical and directed therapy considering 50% and 100% $fT_{>MIC}$. FTA was maximized with prolonged infusions. Overall, changes in piperacillin pharmacokinetics and the consequences on therapeutic dosing requirements appear similar to those observed in intensive care patients. Guidelines should address the altered dosing needs of febrile neutropenic patients exhibiting high CL_{CR} or with known/presumed infections from high-MIC bacteria.

KEYWORDS febrile neutropenia, piperacillin, population pharmacokinetics

Received 10 February 2017 **Returned for modification** 28 May 2017 **Accepted** 30 July 2017

Accepted manuscript posted online 14 August 2017

Citation Sime FB, Hahn U, Warner MS, Tiong IS, Roberts MS, Lipman J, Peake SL, Roberts JA. 2017. Using population pharmacokinetic modeling and Monte Carlo simulations to determine whether standard doses of piperacillin in piperacillin-tazobactam regimens are adequate for the management of febrile neutropenia. Antimicrob Agents Chemother 61:e00311-17. https://doi.org/10.1128/AAC.00311-17.

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Altered antibiotic dosing requirements in febrile neutropenic patients have been documented previously (1–3). Changes in the pharmacokinetics (PK) of hydrophilic antibiotics appear common and can result in low plasma and tissue antibiotic exposure when conventional dosing regimens are used. The drivers for altered PK of antibiotics are thought to be the pathophysiologic phenomena associated with systemic inflammation, including increased cardiac output and organ blood flow and movement of fluid into the interstitial space (3). There are also additional causes of altered PK associated with iatrogenic factors, such as high intravenous fluid loading, a common intervention in patients with hematological malignancies, which can affect drug volume of distribution (4).

In a single-dose pilot study (5), we previously described the altered PK of piperacillin in febrile neutropenic patients with hematological malignancy. We observed markedly altered PK with elevations in volume of distribution as well as clearance leading to suboptimal exposure. This was reflected in a low percentage of the dosing interval for which the unbound concentration of piperacillin remained above the MIC ($fT_{>MIC}$). We observed that 10 (83%) and eight (67%) participants had less than 50% $fT_{>MIC}$ against *Pseudomonas aeruginosa* and *Enterobacteriaceae*, respectively.

Subsequently, we hypothesized that, given the unpredictability of PK alterations, therapeutic drug monitoring (TDM)-guided dose optimization is required to ensure adequate exposure in all patients. Accordingly, we conducted a randomized controlled study to test the utility of piperacillin TDM in febrile neutropenic patients (6). We found that TDM was able to increase the success rate of target attainment from a baseline of 19% to 73%, in contrast to a decrease from 25% to 7% in the control group. Although TDM was able to significantly improve drug exposure, there was a large delay for most patients in achieving therapeutic concentrations, and some patients never achieved the targets. The results of this study highlight the difficulty with empirical prediction of dosing requirements based simply on a measured TDM concentration which may not achieve ideal concentrations until better and quicker real-time TDM is available. To this end, a population pharmacokinetic model that is able to individualize initial dosing based on patient covariate data, e.g., renal function and/or body weight, or that can be used for Bayesian forecasting in combination with TDM would enable more accurate dosing (7). Unfortunately, there is a paucity of such models for piperacillin in adult patients with febrile neutropenia and hematological malignancies.

Therefore, the aim of this work was to develop a population PK model for piperacillin and perform dosing simulations to describe optimized dosing regimens for piperacillin-tazobactam for the treatment of febrile neutropenia.

RESULTS

Demographic and clinical data. Data from 37 patients were used for population PK analysis. Patient demographics and clinical characteristics are presented in Table 1. PK samples during the first dosing interval were available from 12 patients, and steady-state samples during intermittent dosing were available from 25 patients. A total of 184 concentration-time data points were included in the analysis.

Pharmacokinetic model building. The concentration-time data were adequately described by a two-compartment model with linear elimination from the central compartment and linear intercompartmental distribution. Only creatinine clearance (CL_{CR}) resulted in significant reduction in the log likelihood ratio and showed improved model fit as assessed by goodness-of-fit plots. The lowest value of objective function and better goodness-of-fit plots (Fig. 1; see also Fig. S1 and S2 in the supplemental material) were observed when CL_{CR} was normalized to 100 ml/min/1.73 m^2. The final covariate model thus was given by the equation piperacillin clearance = TVCL × (CL_{CR}/100), where TVCL is the typical value of clearance. Parameter estimates for the final covariate model are given in Table 2.

Dosing simulations. The final covariate model was used for Monte Carlo dosing simulations. The PTA during the first 24 h for conventional intermittent dosing regimens of piperacillin for PK/pharmacodynamic (PD) targets of 50% $fT_{>MIC}$ and 100%

TABLE 1 Characteristics of study participants

Characteristic[a]	*n* (%) or median (IQR[b])
Age (yr)	61 (53–66)
Sex	
Male	21 (57)
Female	16 (43)
Body mass index (kg/m^2)	25.7 (23.0–28.1)
Weight (kg)	78 (63–87)
Creatinine clearance (ml/min/1.73 m^2)	94 (71–132)
Albumin (g/liter)	27 (23–28)
Malignancy	
Acute myeloid leukemia	14 (38)
Multiple myeloma	10 (27)
Hodgkin's lymphoma	4 (11)
Non-Hodgkin's lymphoma	4 (11)
Diffuse large B-cell lymphoma	2 (5)
B-lymphoblastic lymphoma	1 (3)
Follicular lymphoma	1 (3)
Primary CNS lymphoma	1 (3)
Positive blood culture	14 (38)
Organisms isolated	
Bacillus cereus	2 (5)
Escherichia coli	1 (3)
Enterobacter cloacae	1 (3)
Enterobacter aerogenes	1 (3)
Klebsiella pneumonia	2 (5)
Pseudomonas aeruginosa	1 (3)
Staphylococcus sp.	3 (8)
Viridans streptococci	3 (8)
Additional antibiotics	
Gentamicin	36 (97)
Vancomycin	4 (11)
Ciprofloxacin	1 (3)
Metronidazole	1 (3)
Trimethoprim-sulfamethoxazole	1 (3)

[a]CNS, central nervous system.
[b]IQR, interquartile range.

$fT_{>MIC}$ at various levels of CL_{CR} are presented in Fig. 2. Similar PTA was observed at steady state (data not shown).The results show that for patients with normal CL_{CR}, the probability of attaining 50% $fT_{>MIC}$ is low even for MIC values as low as 1 to 2 mg/liter. The PTA is very low when CL_{CR} is higher (140 and 160 ml/min/1.73 m^2). PTA for 100% $fT_{>MIC}$ is low even for very low MIC values (0.125 mg/liter) with normal to high CL_{CR} values (>100 ml/min/1.73 m^2). The PTA from prolonged infusion dosing regimens is given in Tables 3 and 4. Generally, extended infusion (EI) and continuous infusion (CI) regimens achieve a high PTA (>90%) for 50% $fT_{>MIC}$, except for MIC values of ≥16 mg/liter in patients with a high CL_{CR}. However, only CI regimens achieve a high PTA for 100% $fT_{>MIC}$ for a wide range of renal function and MIC values.

The fraction of response (FTA, for fractional target attainment) for various dosing regimens of piperacillin against the EUCAST MIC distributions of *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* for the different simulated renal functions (CL_{CR}) is given in Tables 5 and 6. For *E. coli*, the FTA for intermittent dosing regimens was suboptimal (<85%) for both empirical and directed therapy considering 50% and 100% $fT_{>MIC}$, particularly at high CL_{CR}. Both EI and CI regimens achieved high coverage at all CL_{CR} levels for empirical and directed therapy targeting 50% $fT_{>MIC}$. However, only CI achieved optimal FTA for 100% $fT_{>MIC}$ at all CL_{CR} levels. For *K. pneumoniae*, high-dose CI (4.0-g loading dose over 1 h [LD] plus 16.0-g CI) or more

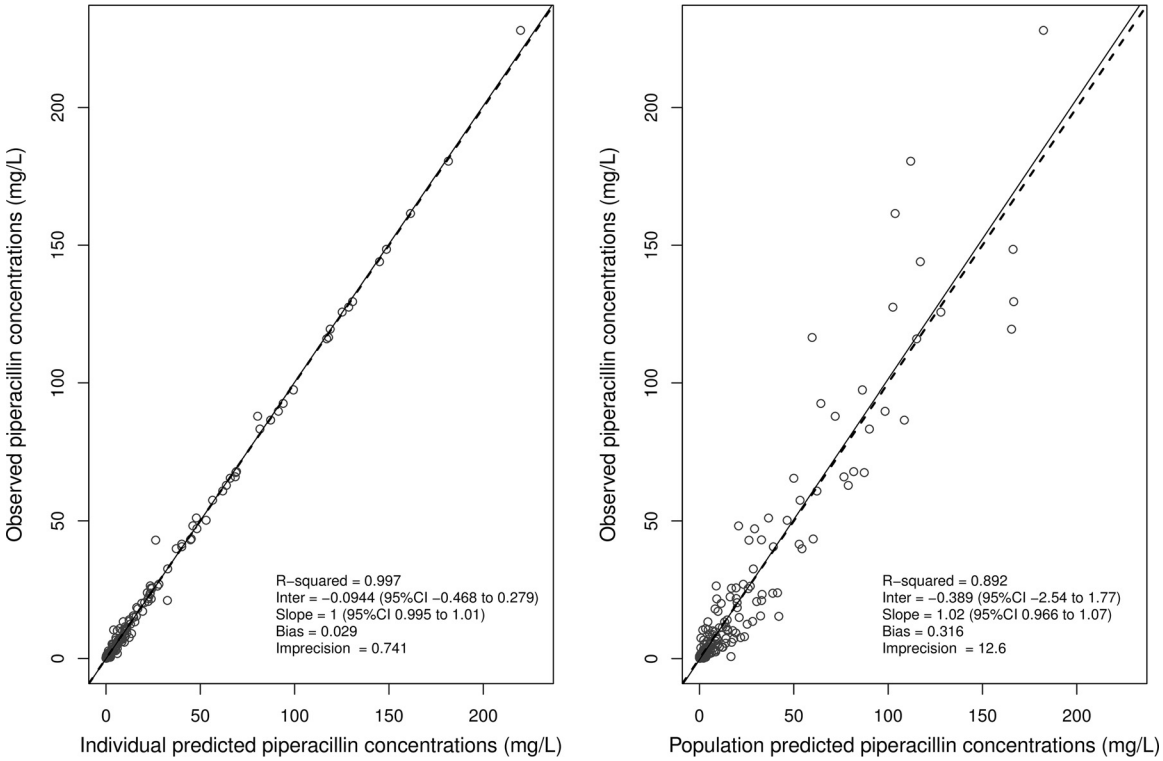

FIG 1 Diagnostic plots for the final covariate model, observed versus individual-predicted (left) and population-predicted (right) concentrations.

frequent EI (4.0 g every 6 h [q6h] with 3-h EI) was required for empirical coverage at 50% and 100% $fT_{>MIC}$. For directed therapy, all of the EI or CI regimens achieved optimal FTA for 50% $fT_{>MIC}$, but only CI regimens achieved optimal FTA for 100% $fT_{>MIC}$. For *P. aeruginosa*, none of the tested dosing regimens achieved optimal FTA for empirical therapy, but for directed therapy, EI regimens and CI regimens (except the 8-g CI) provided good coverage at 50% $fT_{>MIC}$. At 100% $fT_{>MIC}$, only two of the CI regimens (12.0 g and 16.0 g with 4.0-g LD) achieved optimal FTA.

Table 7 presents a comparison of the model-predicted steady-state concentrations (for continuous infusions) and steady-state trough concentrations at 72 h (for extended infusion and intermittent infusion) for a low and high simulated CL_{CR}.

DISCUSSION

Compared to data from healthy volunteers, changes in the pharmacokinetic parameters of piperacillin and other hydrophilic antibiotics have been described in some special patient populations, such as febrile neutropenic patients receiving cancer chemotherapy (1, 3), surgical and medical intensive care unit patients (8), patients with cystic fibrosis (9), and obese patients (10). The change in primary pharmacokinetic

TABLE 2 Estimates of piperacillin pharmacokinetic parameters for the final covariate model

Parameter[a]	Mean (SD)	%CV[b]
CL (liters/h)	18.02 (4.80)	26.63
V (h)	14.30 (7.31)	51.09
Kcp (h^{-1})	1.40 (1.35)	96.28
Kpc (h^{-1})	4.99 (7.81)	156.49

[a]CL, clearance; *V*, volume of distribution of central compartment; Kcp, rate constant for piperacillin distribution from central to peripheral compartment; Kpc, rate constant for piperacillin distribution from peripheral to central compartment.
[b]CV, coefficient of variation.

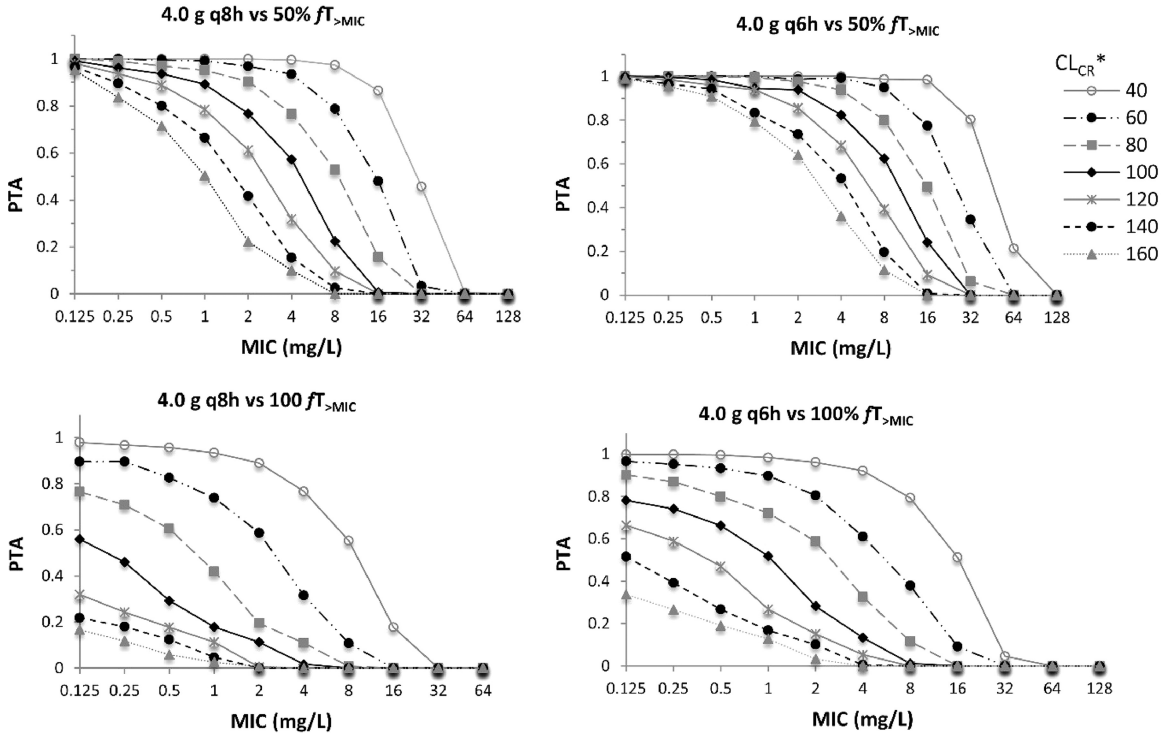

FIG 2 Probability of target attainment for conventional intermittent dosing regimens of piperacillin for PK/PD targets of 50% $fT_{>MIC}$ and 100% $fT_{>MIC}$. CL_{CR}, creatinine clearance in ml/min/1.73 m^2; PTA, probability of target attainment; q8h, every 8 h intermittent infusion; q6h, every 6 h intermittent infusion.

parameters (volume of distribution and clearance) have been attributed to disease-specific physiological perturbances and iatrogenic interventions (1, 11). The estimated mean population central volume of distribution in the current study (14.3 ± 7.3 liters) is comparable with a previously reported population estimate (14.5 ± 6.6 liters) for critically ill patients (12). These values are only slightly higher than reported values for healthy individuals, e.g., 12.7 liters (13) and 10.4 liters (14). However, other population pharmacokinetic analyses have reported significant expansion of the volume of distribution in critically ill and hospitalized patients, e.g., 19.4 liters (15) and 21.7 liters (16), which appears highest in obese critically ill patients (49.0 ± 19.0 liters) (17).

On the other hand, the estimated mean population clearance of piperacillin in this analysis (18.2 ± 4.8 liters/h) is higher than that reported for healthy volunteers (10.1 liters/h [13] and 11.3 liters/h [13]. The increased clearance in this study is consistent with the study cohort which included a substantial proportion of patients with high CL_{CR} (32% of patients had CL_{CR} greater than 120 ml/min/1.73 m^2). Indeed, clearance of piperacillin is highly dependent on the renal function of the study cohort, and this in many ways explains the different reported mean piperacillin clearances in different patient populations. In the critically ill, for instance, clearance could be elevated (e.g., 17.1 liters [18]) or similar/slightly higher (e.g., 13.8 liters/h [15, 16] and 14.0 ± 7.1 liters [17]) or may even be reduced (e.g., 3.6 liters/h [19] and 5.6 ± 3.2 liters/h [12]) compared to healthy volunteers (13). It could be particularly high in those patients with burns and trauma (20). For example, a pharmacokinetic model for burn patients predicts elevated clearance of 16 liters/h for patients when CL_{CR} is 130 ml/min and 20 ml/min when CL_{CR} is 160 ml/min (21). This is comparable to the elevated mean clearance observed in the current study (18.2 ± 4.8 liters/h) and, consistent with other studies, contributes to suboptimal therapeutic exposure from traditional dosing regimens.

Indeed, results of this pharmacometric analysis suggest that commonly employed intermittent piperacillin doses (4.0 g every 6 to 8 h) are highly likely to result in subtherapeutic exposures, particularly when higher-MIC Gram-negative bacteria are

TABLE 3 PTA for alternative prolonged infusion dosing regimens during the first 24 h[a]

Dosing regimen and CL_{CR} (ml/min/1.73 m^2)	PTA for 50% $fT_{>MIC}$ by MIC (mg/liter)								PTA for 100% $fT_{>MIC}$ by MIC (mg/liter)							
	0.125	0.25	0.5	1	2	4	8	16	0.125	0.25	0.5	1	2	4	8	16
4.0-g EI over 4 h q8h																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
60	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−
80	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−
100	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
120	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
140	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
160	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
4.0-g EI over 3 h q6h																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
60	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−
80	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−
100	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−
120	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−
140	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−
160	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
4.0-g LD + 8.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
80	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
100	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
120	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−
140	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	−
160	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	−
4.0-g LD + 12.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
80	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
120	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
140	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
160	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
4.0-g LD + 16.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
80	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
120	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
140	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
160	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−

[a]+, PTA of ≥0.9; −, PTA of <0.9.

targeted in patients with high CL_{CR} (Fig. 2). Although the prevalence of Gram-negative infection in febrile neutropenia is low in the developed world, e.g., 10.7% in a French hematology center (22), in other parts of the world the majority of bacteremia in these patients are attributed to Gram-negative pathogens, e.g., 60.3% in Malaysia (23) and 78.8% in Lebanon (24). Given the relatively high MIC of Gram-negative pathogens, subtherapeutic exposure is highly likely in patients with high CL_{CR}, as observed in this study (Tables 5 to 7). Increased renal elimination of antibiotics, termed augmented renal clearance (ARC), has been described previously for piperacillin and other antibiotics predominantly eliminated by renal excretion (6, 25). In a previous trial of febrile neutropenic patients, we observed that 31% of the study cohort exhibited ARC. This is comparable to other reports for intensive care unit (ICU) patients: 33% by Ruiz et al. (26), 38.7% by Kawano et al. (27), and 28% by Campassi et al. (28). A higher incidence in ICU patients was also reported by other authors, e.g., 55.8% (29) and 65.1% (30). In patients with ARC (commonly defined as CL_{CR} of ≥130 ml/min/1.73 m^2), intermittent dosing regimens of piperacillin are highly likely to result in poor exposure (31). While

TABLE 4 PTA for alternative infusional dosing regimens at pharmacokinetic steady state measured at 48 to 72 h[a]

Dosing regimen and CL_{CR} (ml/min/1.73 m^2)	PTA for 50% $fT_{>MIC}$ by MIC (mg/liter)								PTA for 100% $fT_{>MIC}$ by MIC (mg/liter)							
	0.125	0.25	0.5	1	2	4	8	16	0.125	0.25	0.5	1	2	4	8	16
4.0-g EI over 4 h q8h																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
60	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−
80	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−
100	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
120	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
140	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
160	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−
4.0-g EI over 3 h q6h																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
80	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−
100	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−
120	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−
140	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
160	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
4.0-g LD + 8.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
80	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
100	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
120	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−
140	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	−
160	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	−
4.0-g LD + 12.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
80	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
120	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
140	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
160	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
4.0-g LD + 16.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
80	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
120	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
140	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
160	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−

[a]+, PTA of ≥0.9; −, PTA of <0.9.

this is in agreement with the findings of the current study, our results also suggest that underexposure occurs even in patients without ARC. The FTA of piperacillin-directed therapy at the traditional dosing regimen of 4.0 g every 8 h (q8h) against the common pathogens *E. coli*, *K. pneumoniae*, and *P. aeruginosa* was inadequate (<85%) for CL_{CR} values as low as 100, 80, and 60 ml/min/1.73 m^2, respectively, even for the conservative target 50% $fT_{>MIC}$ (Tables 5 and 6). Similarly, dosing with 4.0 g every 6 h also fails to provide adequate FTA for normal to high CL_{CR} values. Importantly, both intermittent regimens show poor FTA for a wide range of low to high CL_{CR} values if 100% $fT_{>MIC}$ is the desired treatment target (Tables 5 and 6). These findings are consistent with previous observations of altered antibiotic PK in febrile neutropenic patients that result in frequent failure of conventional intermittent dosing regimens to meet PK/PD dosing targets (3). Thus, the use of traditional intermittent dosing regimens of piperacillin-tazobactam in the treatment of febrile neutropenia should be critically reevaluated in clinical studies, particularly if it is to be used as a monotherapy either for directed

TABLE 5 FTA for various dosing regimens of piperacillin against the EUCAST MIC distributions of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* during the first 24 h

Treatment type, PK/PD target (% $fT_{>MIC}$), and dosing regimen	FTA (%) by bacteria and CL_{CR} (ml/min/1.73 m^2)[a]																				
	E. coli							*K. pneumoniae*							*P. aeruginosa*						
	40	60	80	100	120	140	160	40	60	80	100	120	140	160	40	60	80	100	120	140	160
Empirical																					
50																					
4.0 g q8h	96	91	82	72	59	45	31	87	80	69	56	42	29	18	77	64	50	35	22	13	8
4.0 g q6h	97	95	92	86	80	69	61	89	86	81	73	64	53	44	82	75	65	54	43	32	24
4.0 g q8h, 4-h EI	97	96	96	95	94	94	93	90	88	87	86	84	84	83	83	79	77	70	71	68	67
4.0 g q6h, 3-h EI	97	97	96	96	96	95	95	90	90	88	88	87	87	85	84	82	79	78	77	76	73
4.0-g LD + 8.0-g CI	96	95	94	94	93	92	91	88	87	85	83	82	80	78	80	77	71	68	66	60	56
4.0-g LD + 12.0-g CI	97	96	96	95	94	94	93	90	88	88	86	85	84	83	83	80	77	75	71	69	67
4.0-g LD + 16.0-g CI	97	97	96	96	95	95	94	91	90	88	88	87	86	85	85	83	79	78	77	73	71
100																					
4.0 g q8h	82	56	26	12	5	2	2	69	40	16	7	2	1	1	50	22	8	3	1	0	0
4.0 g q6h	90	75	56	34	18	11	7	80	60	40	21	11	6	3	64	40	22	10	5	2	1
4.0 g q8h, 4-h EI	91	79	61	39	21	12	7	80	64	44	24	12	7	4	63	43	24	11	5	2	1
4.0 g q6h, 3-h EI	94	89	78	64	49	33	21	85	77	63	48	33	20	12	72	59	42	27	15	9	5
4.0-g LD + 8.0-g CI	96	95	94	93	93	91	91	88	87	84	83	82	79	77	78	76	70	67	64	58	55
4.0-g LD + 12.0-g CI	96	96	96	95	94	94	93	89	88	88	86	84	84	83	81	78	77	73	70	68	67
4.0-g LD + 16.0-g CI	96	96	96	96	95	94	94	89	89	88	88	87	85	84	81	80	78	77	76	72	70
Directed																					
50																					
4.0 g q8h	100	97	89	78	64	48	33	100	94	83	68	51	35	22	97	84	65	45	29	17	11
4.0 g q6h	100	99	97	92	85	74	66	100	99	95	88	77	64	54	99	95	85	71	57	42	31
4.0 g q8h, 4-h EI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	96	92	90	88
4.0 g q6h, 3-h EI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	95
4.0-g LD + 8.0-g CI	100	100	100	100	100	99	98	100	100	100	100	100	97	95	100	100	93	89	87	79	74
4.0-g LD + 12.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	97	93	90	88
4.0-g LD + 16.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	96	93
100																					
4.0 g q8h	88	61	28	13	5	3	2	83	49	20	9	2	1	1	66	28	10	4	1	0	0
4.0 g q6h	96	81	60	36	20	12	7	94	72	49	26	13	8	4	84	52	29	13	6	3	1
4.0 g q8h, 4-h EI	97	85	65	42	23	13	8	95	77	53	29	15	8	4	82	56	31	14	7	3	2
4.0 g q6h, 3-h EI	100	95	84	69	53	36	22	99	92	77	58	40	24	14	94	77	55	36	20	11	6
4.0-g LD + 8.0-g CI	100	100	100	100	100	98	98	100	100	100	100	99	96	94	100	99	92	88	84	75	72
4.0-g LD + 12.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	95	92	89	87
4.0-g LD + 16.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	94	92

[a]Shaded area indicates optimal FTA of greater than or equal to 85%.

therapy against pathogens with higher MIC breakpoints (≥8 mg/liter) or for initial empirical coverage.

On the other hand, in accordance with previous observations (2), the dosing simulations presented in this paper suggest that for optimal piperacillin exposure covering common pathogens isolated from patients with febrile neutropenia (*E. coli*, *K. pneumoniae*, and *P. aeruginosa*), particularly those with higher MICs, prolonged infusion dosing regimens (EI or CI) are necessary. High PTA values for 50% $fT_{>MIC}$ were observed for EI regimens (Tables 3 and 4) with high FTA against susceptible strains of *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. Similar results were observed with CI regimens, except that low-dose (8-g) CI may result in underexposure against *P. aeruginosa* when patients have high CL_{CR} (≥140 ml/min/1.73 m^2) (Tables 5 and 6). These findings are in accordance with previous studies which reported that EI or CI regimens achieve better PK/PD exposure for the time-dependent beta-lactam antibiotics, including piperacillin (32–34).

However, the current PK analysis shows that despite the high PTA for EI or CI regimens within the susceptible MIC range, the FTA for empirical therapy, especially against the MIC distribution of *P. aeruginosa*, was very poor across the wide range of simulated CL_{CR} (Tables 5 and 6). Therefore, monotherapy with piperacillin-tazobactam even with prolonged infusion is unlikely to provide consistent empirical coverage against *P. aeruginosa*. Similarly for *K. pneumoniae*, CI may not provide empirical coverage in those patients with high CL_{CR}, even at the maximum recommended total

TABLE 6 Steady-state FTA for various dosing regimens of piperacillin against the EUCAST MIC distributions of *E. coli*, *K. pneumoniae*, and *P. aeruginosa*

Treatment type, PK/PD target (% $fT_{>MIC}$), and dosing regimen	FTA (%) by bacteria and CL_{CR} (ml/min/1.73 m^2)[a]																				
	E. coli							*K. pneumoniae*							*P. aeruginosa*						
	40	60	80	100	120	140	160	40	60	80	100	120	140	160	40	60	80	100	120	140	160
Empirical																					
50																					
4.0 g q8h	96	90	81	69	56	41	29	87	79	67	52	40	27	18	77	63	47	32	21	12	8
4.0 g q6h	97	95	92	87	80	71	61	90	86	81	74	65	54	44	83	75	66	55	44	33	24
4.0 g q8h, 4-h EI	97	96	95	94	94	93	93	90	88	87	85	84	83	82	83	79	77	72	69	68	64
4.0 g q6h, 3-h EI	97	97	96	96	95	94	94	90	89	88	87	86	85	84	84	82	79	77	74	71	69
4.0-g LD + 8.0-g CI	96	95	94	93	93	92	91	88	87	84	83	82	79	78	79	76	70	68	65	59	56
4.0-g LD + 12.0-g CI	97	96	96	95	94	94	93	90	88	87	86	84	84	83	83	79	77	73	70	68	67
4.0-g LD + 16.0-g CI	97	97	96	96	95	95	94	90	90	88	88	87	87	84	84	82	79	78	76	76	70
100																					
4.0 g q8h	81	56	29	14	7	4	2	68	41	18	9	4	2	1	50	24	9	3	2	1	1
4.0 g q6h	91	77	58	35	19	11	7	81	63	42	22	12	7	3	67	44	23	10	5	2	1
4.0 g q8h, 4-h EI	92	78	59	40	23	14	9	81	64	44	26	14	8	4	67	45	25	12	6	3	2
4.0 g q6h, 3-h EI	95	89	79	65	50	34	22	87	78	64	48	33	21	13	76	61	44	28	16	9	5
4.0-g LD + 8.0-g CI	96	95	94	93	92	91	91	88	86	84	83	81	78	77	79	75	70	67	62	57	55
4.0-g LD + 12.0-g CI	97	96	96	94	94	94	93	90	88	87	85	84	83	83	83	79	77	72	70	68	66
4.0-g LD + 16.0-g CI	97	97	96	96	95	94	94	90	89	88	88	86	85	84	84	82	79	77	75	71	70
Directed																					
50																					
4.0 g q8h	100	96	87	74	60	44	32	99	93	81	64	48	32	22	97	83	62	42	28	16	11
4.0 g q6h	100	99	97	92	85	77	66	100	99	95	88	78	66	54	100	96	86	73	57	43	31
4.0 g q8h, 4-h EI	100	100	100	100	100	100	99	100	100	100	100	100	100	99	100	100	100	94	91	89	84
4.0 g q6h, 3-h EI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	96	93	91
4.0-g LD + 8.0-g CI	100	100	100	100	100	100	98	100	100	100	100	99	96	95	100	99	92	89	86	77	73
4.0-g LD + 12.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	96	92	90	88
4.0-g LD + 16.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	99	92
100																					
4.0 g q8h	87	60	31	15	8	4	2	81	50	22	11	5	2	2	66	31	12	5	2	1	1
4.0 g q6h	96	83	62	38	20	12	7	94	76	51	27	14	8	4	87	58	30	14	7	3	2
4.0 g q8h, 4-h EI	97	84	64	43	25	15	9	95	77	53	32	17	10	5	86	58	33	16	8	4	2
4.0 g q6h, 3-h EI	100	95	84	70	53	36	23	99	92	77	59	41	25	15	96	80	57	37	21	12	7
4.0-g LD + 8.0-g CI	100	100	100	100	99	98	98	100	100	100	100	98	95	94	100	97	92	88	81	75	71
4.0-g LD + 12.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	95	92	89	87
4.0-g LD + 16.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	97	93	91

[a]Shaded area indicates optimal FTA of greater than or equal to 85%.

daily doses. Although some guidelines suggest routine combination of piperacillin-tazobactam with an aminoglycoside (e.g., gentamicin), other guidelines still recommend monotherapy with conventional intermittent dosing regimens of piperacillin-tazobactam as a first-line empirical therapy for febrile neutropenia (35, 36). When culture results are available and the susceptibility of the pathogen is known, directed therapy with EI or CI regimens of piperacillin-tazobactam monotherapy could provide adequate exposure against high-MIC pathogens in the susceptible range if the conservative target of 50% $fT_{>MIC}$ is considered the optimal target. However, there is as yet no clear data on which PK/PD target is optimal for beta-lactams in general, although for the immunocompromised febrile neutropenic patients, studies suggested a more aggressive 100% $fT_{>MIC}$ is prudent. For the higher exposure of 100% $fT_{>MIC}$, results of this study suggest CI is necessary to cover for high-MIC pathogens. FTA was optimal (≥85%) only for the CI and was suboptimal both for intermittent and EI regimens when 100% $fT_{>MIC}$ was targeted (Tables 5 and 6). Given that most beta-lactams share similar PK properties, these findings also highlight that for all beta-lactams, CI may be necessary in neutropenic patients with ARC when exposure at 100% $fT_{>MIC}$ is considered to maximize outcomes.

On the other hand, in patients with low creatinine clearance, CI regimens may result in high sustained steady-state concentrations (Table 7; see also Fig. S3 in the supplemental material). Although piperacillin and the beta-lactams in general have a wide

TABLE 7 Comparison of model-predicted steady-state concentrations for low and high creatinine clearance

CL_{CR} (ml/min/1.73 m^2) and simulated dosing regimen	Model-predicted Css[a]		
	Median (mg/liters)	IQR (mg/liters)	Maximum Css/trough (mg/liters)
40			
4.0 g q8h	14.2	6.1–22.8	68.9
4.0 g q6h	28	16.5–42.7	87.2
4.0 g q8h, 4-h EI	25.8	5.0–39.8	74.8
4.0 g q6h, 3-h EI	43.1	13.1–62.3	107.5
4.0-g LD + 8.0-g CI	56.3	34.1–56.3	88.2
4.0-g LD + 12.0-g CI	67.8	51.2–84.3	132.0
4.0-g LD + 16.0-g CI	88.3	67.7–112.1	172.2
140			
4.0 g q8h	0.1	BLOQ of −0.4	10.6
4.0 g q6h	0.4	0.1–1	15.8
4.0 g q8h, 4-h EI	0.591556	0.2–1.3	11.3
4.0 g q6h, 3-h EI	1.803293	0.7–3.3	16.9
4.0-g LD + 8.0-g CI	12.91229	10.8–16.1	25.6
4.0-g LD + 12.0-g CI	19.36153	16.1–24.2	38.1
4.0-g LD + 16.0-g CI	25.25549	21.3–32.0	49.5

[a]Data for continuous infusion regimens are for steady-state concentration (Css) between 48 and 72 h and trough concentrations at 72 h for intermittent and extended infusion regimens. BLOQ, below the limit of quantification of the assay method for the model data (<0.1 mg/liter).

safety margin, very high concentrations remain a concern due to potential neurotoxicity (37). Nevertheless, there is a lack of clearly defined cutoffs for steady-state concentrations that mark the risk of toxicity. Centers that perform beta-lactam TDM use an arbitrary cutoff of 6 to 10 times the MIC to denote concentrations above which greater effectiveness is unlikely, rather than where toxicity is more likely (i.e., toxicity is likely to be related to a concentration threshold rather than a concentration/MIC ratio) (38). Considering the EUCAST breakpoints for *Enterobacteriaceae* (8 mg/liter) and *P. aeruginosa* (16 mg/liter), this would mean concentrations as high as 80 mg/liter and 160 mg/liter, respectively. Steady-state concentrations predicted for the CI regimens when CL_{CR} is 40 ml/min/1.73 m^2 were generally within this range (Table 7). However, low-dose intermittent infusions (e.g., 4.5 g piperacillin-tazobactam every 8 hours) may be safe and provide adequate exposure in patients with low CR_{CL} (Tables 3 to 7).

This study has several limitations. First, only total concentrations of piperacillin were available for modeling, and plasma protein binding was assumed to be similar in all patients (30%). Of note, however, patients in the study cohort did not exhibit high variability in albumin concentrations except for a slight hypoalbuminemia (5, 6). Further, a protein binding study by Wong et al. (39) showed that 30% binding is a reasonable assumption for piperacillin. Second, CL_{CR} was calculated using the Cockcroft–Gault formula or the Jelliffe equation and was not directly measured. Mathematical equations generally provide poor estimates at extremes of CL_{CR} and may not be optimal for accurate dosing, although they are commonly used clinically (40). Third, the current analysis provides only the effect of different dosing regimens on PK/PD exposure and not clinical outcome.

Conclusions. The traditional intermittent dosing regimens of piperacillin-tazobactam are unlikely to provide adequate exposure for empirical management of febrile neutropenia. Subtherapeutic exposure is highly likely if Gram-negative pathogens with susceptibility close to clinical breakpoints are causative of the underlying infection. Patients with ARC are particularly vulnerable to underexposure even with the use of EI or CI regimens. Directed therapy with EI or CI regimens are highly likely to achieve adequate exposure in the majority of patients. At least for patients at high risk of subtherapeutic exposure (presence of high-MIC pathogens and/or ARC), guidelines should consider the altered dosing requirements of piperacillin-tazobactam. We suggest the use of EI or CI regi-

mens unless TDM is performed to confirm appropriateness of exposures from intermittent regimens, particularly when used alone as a monotherapy.

MATERIALS AND METHODS

Patients and study setting. Patient data were retrieved from a previously described prospective observational PK study (5) and a prospective interventional TDM study (6). The study population and settings were similar in both studies and included febrile neutropenic patients aged ≥18 years and undergoing treatment for hematological malignancies at The Queen Elizabeth Hospital (TQEH) in Adelaide, Australia. Febrile neutropenia was defined as the presence of a single oral temperature of ≥38.4°C (101°F) or a temperature of ≥38.0°C (100.4°F) for 1 h, with a neutrophil count of <500 cells/mm^3 or a count of <1,000 cells/mm^3 with a predicted decrease to <500 cells/mm^3 (41). Ethics approval was granted from local institutional human research ethics committees (HREC/13/TQEHLMH/301; HREC/12/TQEHLMH/157).

Population pharmacokinetic modeling. Piperacillin concentration-time data after intermittent dosing of piperacillin-tazobactam in the aforementioned studies (5, 6) were included in the population PK analysis. For patients who participated in both studies, only data from the prospective PK study with more frequent sampling was used. All included patients received 4.5 g piperacillin-tazobactam every 8 h. For 12 patients receiving intensive serial blood sampling, the concentration-time data were collected after the first dose: first sample at the end of line flushing (45 min) and then at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, and 7 h after the start of infusion, with a final sample just before the second dose (7.8 h). For the remaining 25 patients, blood samples were collected at steady state. Available data were included from mid-dose intervals and/or trough samples collected after the third dose (20 h and 23.8 h), sixth dose (44 h and 47.8 h), and ninth dose (71.8 h).

An R package for nonparametric adaptive grid algorithms, Pmetrics version 1.5.0, was used for pharmacometric analysis. A stepwise approach was followed in the model-building process: (i) determination of the structural base model, (ii) selection of the best-fit statistical error model, (iii) development of covariate model, and (iv) model evaluation.

Determination of the structural base model. Different structural models, based on one, two, or three compartments, were fitted to the concentration-time data. The elimination of piperacillin from the central compartment and intercompartmental distribution were modeled as linear processes.

Selection of statistical error models. Both the additive and multiplicative error models available in the Pmetrics package were tested. The multiplicative error model takes the form of Error = SD × γ, where SD is standard deviations of observations and γ is the process noise associated with observations. The additive error model is given by Error = $(SD^2 + \lambda^2)^{0.5}$. The SD was further modeled by a second-degree polynomial function, beginning with coefficients deduced from assay data and further iterative optimization based on model diagnostics.

Development of covariate model. Available clinical covariates were assessed for biological plausibility and subsequently evaluated in the covariate analysis. Selected covariates that were tested on the structural model parameters (volume[s] of distribution and clearance) include age, sex, weight, and creatinine clearance (calculated by the Cockcroft-Gault formula if renal function was stable or the Jelliffe equation if not; expressed in ml/min/1.73 m^2). A standard covariate evaluation algorithm was followed through forward addition and backward elimination in a stepwise fashion.

Model evaluation. Diagnostic plots and statistical examination through objective function values were used for comparison and selection of models. Diagnostic plots included scatter plots of observed concentrations versus predicted concentrations, scatter plots of residuals versus predicted concentrations, scatter plots of residuals versus time, a histogram of residuals with a test of normality (D'Agostino test), and visual predictive checks. The log-likelihood ratio test for the nested model, Akaike information criterion (AIC), and Bayesian information criterion (BIC) were each examined. In addition, model bias and imprecision were examined to discriminate between models. Model bias in Pmetrics is defined as the mean weighted error of predicted minus observed concentrations, $\sum$(predicted-observed/standard deviation)/*N*, and imprecision is defined as the bias-adjusted, mean weighted squared error of predicted minus observed concentration, i.e., $|\sum[(\text{predicted-observed})^2/(\text{standard deviation})^2]/N| - |\sum(\text{predicted-observed})/\text{standard deviations}/N|$, where *N* is the number of observations/predictions.

Dosing simulations. Monte Carlo simulations (n = 1,000) were performed to determine the probability of target attainment (PTA) for different dosing regimens and renal function (CL_{CR}) for PK/PD targets of 50% and 100% $fT_{>MIC}$ and 30% plasma protein binding (39). The dosing regimens were simulated up to steady state from 0 to 72 h for CL_{CR} of 40, 60, 80, 100, 120, 140, and 160 ml/min/1.73 m^2 and included 4.0-g intermittent infusion (II) over 30 min q8h, 4.0-g II over 30 min q6h, 4.0-g extended infusion (EI) over 4 h q8h, 4.0-g EI over 3 h q6h, 4.0-g loading dose over 1 h (LD) plus 8.0-g continuous infusion (CI), 4.0-g LD plus 12-g CI, and 4.0-g LD plus 16.0-g CI. PTA was determined at two stages of therapy, during the first 24 h and at steady state from 48 h to 72 h.

The fractional target attainment (FTA), during the first 24 h and at steady state from 48 h to 72 h, was calculated for *Escherichia coli*, *Klebsiella pneumoniae*, and *P. aeruginosa* based on the MIC distribution of the European Committee for Antimicrobial Susceptibility and Testing (EUCAST) database (available at www.eucast.org). FTA describes the proportion of the bacterial population for which the selected PK/pharmacodynamics (PD) target is attained given the Monte Carlo simulation and the MIC distribution. FTA was calculated both for empirical therapy, i.e., considering all of the categories of the entire MIC distribution, and for directed therapy, i.e., considering those categories of MIC distribution within the susceptibility range defined by clinical breakpoints (8 mg/liter for *Enterobacteriaceae* and 16 mg/liter for *P. aeruginosa*). Doses were considered optimal if the FTA was greater than 85%.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.00311-17.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

ACKNOWLEDGMENTS

F.B.S. acknowledges funding from a University of Queensland Postdoctoral Fellowship. J.A.R. recognizes funding from the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP1099452) and a Practitioner Fellowship (APP1117065).

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