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ORIGINAL PAPER

Population pharmacokinetics and pharmacodynamics of piperacillin in critically ill patients during the early phase of sepsis

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Abstract

This study aimed to characterize the population pharmacokinetics (PKs) of piperacillin and investigate probability of target attainment (PTA) and cumulative fraction of response (CFR) of various dosage regimens in critically ill patients during the early phase of sepsis. Forty-eight patients treated with piperacillin/tazobactam were recruited. Five blood samples were drawn before and during 0–0.5, 0.5–2, 2–4 and 4–6 or 8 h after administration. Population PKs was analyzed using NONMEM®. The PTA of 90%$fT_{>MIC}$ target and CFR were determined by Monte Carlo simulation. The two compartment model best described the data. Piperacillin clearance (CL) was 5.37 L/h, central volume of distribution (V_1) was 9.35 L, and peripheral volume of distribution was 7.77 L. Creatinine clearance (CL_{Cr}) and mean arterial pressure had a significant effect on CL while adjusted body weight had a significant impact on V_1. Subtherapeutic concentrations can occur during the early phase of sepsis in critically ill patients with normal renal function. The usual dosage regimen, 4 g of piperacillin infused over 0.5 h every 6 h, could not achieve the target for susceptible organisms with MIC 16 mg/L in patients with $CL_{Cr} \geq 60$ mL/min. Our proposed regimen for the patients with CL_{Cr} 60-120 mL/min was an extended 2 h infusion of 4 g of piperacillin every 6 h. Most regimens provided CFR $\geq$ 90% for the *E. coli* infection while there was no dosage regimen achieved a CFR of 90% for the *P. aeruginosa* infection.

Keywords Population pharmacokinetics · Pharmacodynamics · Piperacillin · Critically ill patients · Sepsis · β-Lactams

Introduction

Piperacillin/tazobactam is an extended-spectrum hydrophilic antibiotic used for empirical treatment in critically ill patients with sepsis [1]. Pharmacokinetic (PK) characteristics of piperacillin in healthy subjects are small volume of distribution (V_d); 18.6 L, short half-life; 1.02 h and high proportion of renal clearance; 79.8% [2, 3]. Piperacillin is a time-dependent antibiotic and the percentage of time which free drug concentrations remain above minimum inhibitory concentration (MIC) during a dosing interval (%$fT_{>MIC}$) has been considered to be the best efficacy predictor [4]. Typically, 50% $fT_{>MIC}$ has been required for optimal activity of penicillins [5]. Recently, 75% $fT_{>MIC}$ has been proposed for bactericidal activity of piperacillin [6], however, higher targets (80 to 100% $fT_{>MIC}$) have been recommended for microbiological success, prevention of bacterial regrowth and improved clinical outcomes in patients with serious bacterial infections [7–9].

Sepsis, a life-threatening organ dysfunction condition, remains a major cause of mortality and critical illness [10–12]. The mortality rate in this group of patients ranged between 14 and 45% [9]. Early antibiotic administration in patients with sepsis could reduce the mortality rate [13] but dosing strategies which enhance 100% $fT_{>MIC}$ attainment of piperacillin concentrations in these patients especially for less susceptible pathogens remain a challenging issue. Pathophysiological changes, particularly during the early phase, in these patients (capillary leakage, high cardiac

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output, organ dysfunction) have several significant effects on PK behaviors. Previous studies found that V_d of piperacillin in patients with sepsis were larger than those in healthy volunteers and non-critically ill patients [14–19]. Patients with sepsis might develop renal dysfunction which led to a decrease in piperacillin total clearance (CL) [14, 16, 18, 20, 21]. On the other hand, in the early phase of sepsis, cardiac output is typically increased to improve organ perfusion leading to augmented renal clearance (ARC) with an incidence of 50 to 85% [22]. Therefore CL could be higher in patients with sepsis compared with in healthy volunteers [17–19]. Because of these PK variabilities, subtherapeutic piperacillin concentrations have been found in patients with the first 24 h of sepsis [16, 20, 23].

The aims of this study were to (i) estimate population PK parameters and variabilities, (ii) investigate the probability of target attainment (PTA) of various piperacillin dosing regimens and (iii) explore the cumulative fraction of response (CFR) against pathogens commonly found in critically ill patients during the early phase of sepsis.

Materials and methods

Subjects

This prospective study was conducted at intensive care units in Songklanagarind hospital between March 2014 and March 2017. The inclusion criteria were (i) age $\geq$ 15 years, (ii) treatment with piperacillin/tazobactam, and (iii) sepsis defined according to the third international consensus definitions for sepsis and septic shock (Sepsis-3) [10]. The exclusion criteria were (i) peritoneal dialysis, hemodialysis or continuous renal replacement therapy, (ii) pregnancy, (iii) sepsis more than 24 h and (iv) known or suspected hypersensitivity to piperacillin/tazobactam. The protocol for the study was approved by the ethics committee of Songklanagarind Hospital. Written informed consent was obtained from each subject or a legally acceptable representative before enrollment.

Drugs and chemicals

Piperacillin/tazobactam (Tebranic®) was purchased from Astrazeneca Thailand Ltd. (Bangkok, Thailand). Piperacillin standard powder was purchased from U.S. Pharmacopeial Convention (Rockville, MD, USA) as pure powder. All solvents were of high performance liquid chromatography (HPLC) grade.

Study design and blood sampling

Piperacillin/tazobactam was administered at the physician's discretion at dosage regimens of 2/0.25 or 4/0.5 g every 6 or 8 h as a 30-min infusion. Serial blood samples were collected over one dosing interval within the first 24 h after dosing. Sampling times were optimized using PFIM Interface 4.0 (PFIM group, INSERM and Université Paris Diderot, Paris, France). Blood samples (5 mL) were obtained at the following times; before administration (time 0) and then during 0 to 0.5, 0.5 to 2, 2 to 4 and 4 to 6 or 8 h after administration. All blood samples were added to heparinized tubes and centrifuged at $1000\times g$ for 10 min within 30 min. All samples were stored at − 80 °C and analyzed within 30 days. Demographic and clinical data were collected on the day of blood sampling.

Free piperacillin assay

The free concentrations of piperacillin were determined using a validated HPLC [24] with minor modifications. Briefly, 300 µL of plasma was subjected to ultrafiltration using a Nanosep 10 K device with omega membrane (Pall Corp., Ann Arbor, MI, USA); the device was centrifuged at $10{,}000\times g$ for 15 min at 4 °C. A 30 µL aliquot of the sample was injected into a Nova-Pack C18 column (150 mm × 3.9 mm inside diameter, 4 µm particle size; Waters associates) using an automated injection system (Waters e2695 Plus autosampler; Waters associates, Milford, MA) at 4 °C. Piperacillin was eluted from the column in 7.2 min with a gradient of 20 mM KH_2PO_4 pH 2.4 (buffer A) and acetonitrile (buffer B) (0–7 min 95% A; 7–7.1 min 50% A; 7.1–10 min 95% A), at a flow rate of 1.0 mL/min. The column effluent was monitored at 220 nm with a photodiode array detector (Waters 2996; Waters associates, Milford, MA). Peaks were recorded and integrated with a Waters 746 data module (Waters associates). The lower limit of quantification for piperacillin was 0.25 mg/L. The standard curve was linear over the concentration range of 0.25 to 500 mg/L ($r \geq 0.999$). The intraassay reproducibility values characterized by coefficients of variations (CVs) were ranged from 0.31 to 9.79% and the interassay reproducibility values ranged between 0.80 and 12.81%.

Population PK analysis

The concentration versus time data were analyzed by a nonlinear mixed-effects modeling approach using NONMEM version 7.4.1 (ICON Development Solutions, Ellicott city, MD, USA). The NONMEM runs were executed by PDx-Pop version 5.2 (ICON Development Solutions,

Ellicott city, MD, USA). The piperacillin concentrations were fitted to one-, two- and three-compartment models using subroutines from the NONMEM's library to obtain the most appropriate base model. Estimations of typical parameter value, interindividual variability (IIV) and residual variability (RV) were done using first-order conditional estimation with interaction (FOCEI) [25].

Fourteen covariates were explored including sex, age, total body weight (TBW), ideal body weight (IBW), adjusted body weight (ABW) calculated by IBW + [0.4 × (TBW − IBW)] [26], creatinine clearance (CL_{Cr}) calculated by the Cockcroft-Gault equation for patients with stable renal function or the Jelliffe equation [27] for patient with unstable renal function, mean arterial pressure (MAP), total bilirubin (TBIL), albumin (ALB), acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, total amount of resuscitation fluids per day, use of vasoactive medications, and use of mechanical ventilation. Individual PK parameter estimates from the base model were plotted against covariate values to assess relationships. If a trend between a covariate and a PK parameter had been found and it had been biologically plausible for affecting piperacillin PKs, then that covariate was considered for inclusion in the base model using a stepwise approach. Based on a χ^2 test, a decrease in the objective function value (OFV) of 3.84 units was considered significant ($P < 0.05$) for forward addition step and an increase in the OFV of 6.64 units was considered significant ($P < 0.01$) for backward deletion step to avoid any possible false positives.

Model evaluation was done by visual inspection of diagnostic scatter plots, including observed versus predicted concentrations, conditional weighted residual error versus time and conditional weighted residual error versus predicted concentrations. Validation of the final model was conducted using the bootstrap method (n = 1000 runs) and visual predictive check (VPC) method.

Pharmacodynamic(PD) assessment using Monte Carlo simulation

Monte Carlo simulations using Crystal ball software (Decisioneering Inc., Denver, CO, USA) were performed based on the final model (Eq. (1)) to determine the PTA of 90%fT_{MIC} of the dosing interval for a variety of MICs (0.002 to 512 mg/L).

$$C_t = \frac{k_0(k_{21}-\alpha)(e^{-\alpha T}-1)}{V_1\alpha(\alpha-\beta)}e^{-\alpha(t-T)} + \frac{k_0(\beta-k_{21})(e^{-\beta T}-1)}{V_1\beta(\alpha-\beta)}e^{-\alpha(t-T)} \quad (1)$$

where $\alpha = 0.5(k_{12}+k_{21}+k_{10}+\sqrt{(k_{12}+k_{21}+k_{10})^2-4k_{21}k_{10}})$, $\beta = 0.5(k_{12}+k_{21}+k_{10}-\sqrt{(k_{12}+k_{21}+k_{10})^2-4k_{21}k_{10}})$, C_t is the piperacillin concentration at time t (if $t < T$, substitute T with t), k_0 is the infusion rate, k_{10} is the elimination rate constant from central compartment ($k_{10} = CL/V_1$), k_{12} is the distribution rate constant from central to peripheral compartment ($k_{12} = Q/V_1$), k_{21} is the distribution rate constant from peripheral to central compartment ($k_{21} = Q/V_2$), CL is the clearance, V_1 is the volume of the central compartment, V_2 is the volume of the peripheral compartment, Q is the intercompartmental clearance, T is the time at the end of infusion, α and β are the functions of k_{10}, k_{12} and k_{21}.

Simulated patients (n = 10,000 each) were created in 4 different renal function groups ($CL_{Cr} < 20$, 20 to < 40, 40 to < 60, and 60 to 120 mL/min). CL_{Cr}, in each group were normally distributed assuming median values of other identified significant covariates. Thirty dosage regimens were created based on four dosage regimens (Piperacillin/Tazobactam 2/0.25 or 4/0.5 g every 6 or 8 h). Each dosage regimen was simulated as 0.5, 1, 2, 3, and 4 h infusion, continuous infusion (CI) without loading dose (LD), CI with LD 2/0.25 g and CI with LD 4/0.5 g. Since maximum daily dose is 16/2 g/day, 16/2 g CI would not be given with any LD.

MIC distributions of *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Escherichia coli* from the European Committee for Antimicrobial Susceptibility and Testing (EUCAST) database [28] were used to determine the CFR. The calculation was done by multiplying the PTA at each MIC by the fraction of organisms susceptible at each MIC. Then the summation of those results was the CFR for the respective MIC distribution. The dosage regimen was considered successful if the CFR value was ≥ 90%.

Results

Demographic and clinical data

Forty-eight critically ill patients participated in the study. Total body weight ranged from 38 to 123 kg. Five patients (10.4%) were morbidly obese (BMI ≥ 30 kg/m^2), 16.7% were obese (BMI 25 to 29.9 kg/m^2) and 6.3% were overweight (BMI 23 to 24.9 kg/m^2). Almost all patients received piperacillin/tazobactam 4/0.5 g every 6 h, except for 2 patients who received 4/0.5 g every 8 h and 2 patients who received 4/0.5 g (first dose) then 2/0.25 g every 6 h. Five blood samples were obtained from each patient, except for 3 patients who underwent surgery. A total of 237

Table 1 Demographic and clinical data

Data	Values (N = 48)
Sex (male) (%)	77
Age (years)	60 (49–78)
Total body weight (kg)	56.6 (49.6–69.5)
Ideal body weight (kg)	62.3 (53.8–66.4)
Adjusted body weight (kg)	56.0 (48.1–65.0)
Body mass index (kg/m^2)	21.0 (18.9–25.5)
Pao_2/Fio_2 (mmHg)	234 (142–333)
Platelets ($\times$ 10^3/μL)	185 (125–283)
Total bilirubin (mg/dL)	0.8 (0.4–2.9)
Mean arterial pressure (mmHg)	68 (61–75)
Serum creatinine (mg/dL)	1.1 (0.7–1.5)
Creatinine clearance (mL/min)[a]	54.9 (41.6–86.5)
Acute physiology and chronic health evaluation II score	22 (18–26)
Sequential organ failure assessment score	6 (5–8)
Total amount of resuscitation fluids per day (mL)	1265 (405–2250)
Patients with septic shock (%)	29
The uses of vasoactive medications (%)	33
The uses of mechanical ventilators (%)	60

Data are presented as median (interquartile range) except sex, patients with shock, the uses of mechanical ventilators and vasoactive medications are presented as the percentage of participants

FiO$_2$ Fraction of inspired oxygen, *PaO*$_2$ Partial pressure of oxygen

[a]Creatinine clearance was estimated using the Cockcroft-Gault equation for patients with stable renal function and the Jelliffe equation for patients with unstable renal function

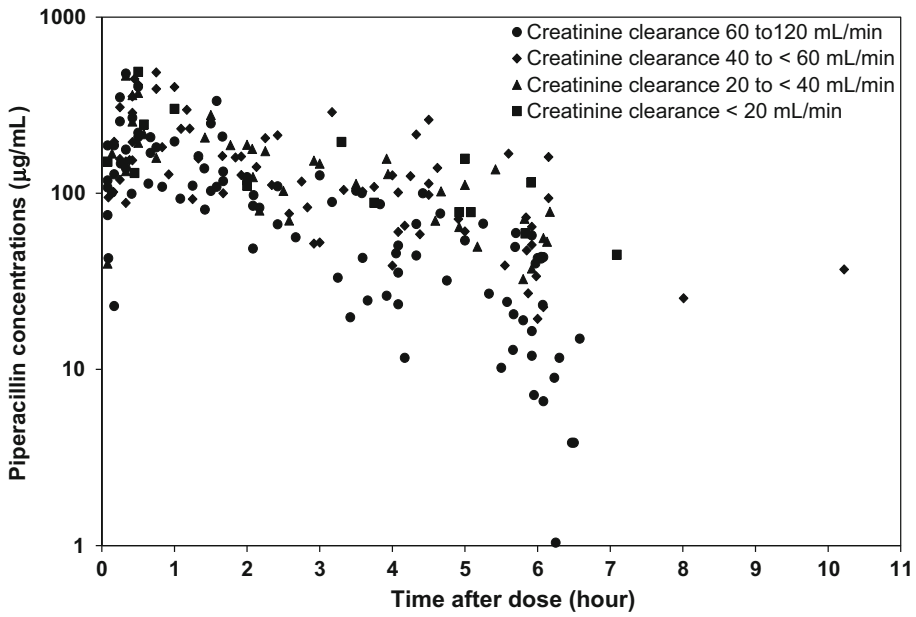

Fig. 1 Piperacillin plasma concentrations (μg/mL) versus time (h) of critically ill patients with sepsis (n = 48)

blood samples were available for the analysis. The demographic and clinical data are shown in Table 1. Most patients had low respiratory function; median of the ratio of partial pressure of oxygen and fraction of inspired oxygen (PaO_2/FiO_2) was 234 mmHg and 60% of patients used mechanical ventilators. In addition, most patients had low cardiovascular function; median of MAP was 68 mmHg. Twenty-seven percent of patients developed septic shock. Most patients had renal impairment; median of CL_{Cr} was 54.9 mL/min.

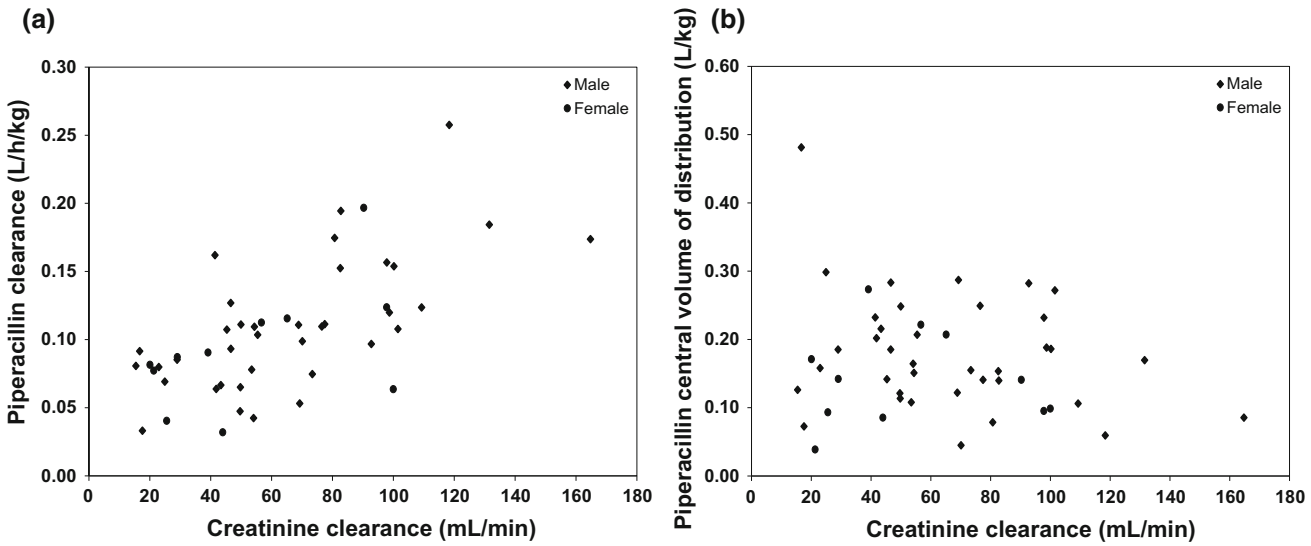

Fig. 2 The plots between individual pharmacokinetic parameters of piperacillin versus creatinine clearance **a** Clearance normalized with total body weight versus creatinine clearance; **b** Central volume of distribution normalized with total body weight versus creatinine clearance

Table 2 Population pharmacokinetic parameter estimates of the final model and bootstrap

Parameter	Description	Estimate	Bootstrap median (95% CI)
Fixed effect			
$TVCL = CL + (\theta_{CLCr} \times (\mathrm{CL_{Cr}} - 55)) + (\theta_{MAP} \times (\mathrm{MAP} - 68))$			
CL (L/h)	Population clearance	5.37	5.34 (4.83–5.87)
θ_{CLCr}	Proportional constant of median-normalized creatinine clearance	0.06	0.06 (0.04–0.08)
θ_{MAP}	Proportional constant of median-normalized mean arterial pressure	0.05	0.05 (0.02–0.08)
$TVV_1 = V_1 + (\theta_{ABW} \times (\mathrm{ABW} - 56))$			
V_1 (L)	Population central volume of distribution	9.35	9.34 (6.69–12.2)
θ_{ABW}	Proportional constant of median-normalized adjusted body weight	0.26	0.26 (0.11–0.43)
V_2 (L)	Population peripheral volume of distribution	7.77	7.78 (5.06–11.3)
Q (L/h)	Population intercompartmental clearance	21.3	22.31 (6.00–47.5)
Random effect (CV %)			
IIV of CL	Interindividual variability for CL	28.5	27.5 (21.1–33.2)
IIV of V_1	Interindividual variability for V_1	55.4	55.3 (36.3–73.3)
RV	Residual variability	22.3	22.1 (17.4–27.1)

TVCL typical values of clearance, TVV_1 typical values of central volume of distribution, *CV* coefficient of variation, *CI* confidence interval

Population PK analysis

Piperacillin concentration–time profiles are depicted in Fig. 1. They were best described by the two-compartment model with first order elimination and a proportional residual variability. The model was significantly improved by the following covariates: $\mathrm{CL_{Cr}}$ and MAP for CL and ABW for central volume of distribution ($\mathrm{V_1}$). $\mathrm{CL_{Cr}}$ tended to have a relation with CL, as shown in Fig. 2a and it decreased the IIV of CL by 11.7%. Both $\mathrm{CL_{Cr}}$ and MAP addition could reduce the IIV of CL by 18% compared with the IIV of the base model. ABW decreased the IIV of $\mathrm{V_1}$ by 8.6%. The final model was represented by Eqs. (2, 3):

$$\mathrm{TVCL} = 5.37 + (0.06 \cdot (\mathrm{CL_{Cr}} - 55)) + (0.05 \cdot (\mathrm{MAP} - 68)) \quad (2)$$

$$\mathrm{TVV_1} = 9.35 + (0.26 \cdot (\mathrm{ABW} - 56)) \quad (3)$$

where TVCL is the typical value of CL, $\mathrm{TVV_1}$ is the typical value of $\mathrm{V_1}$.

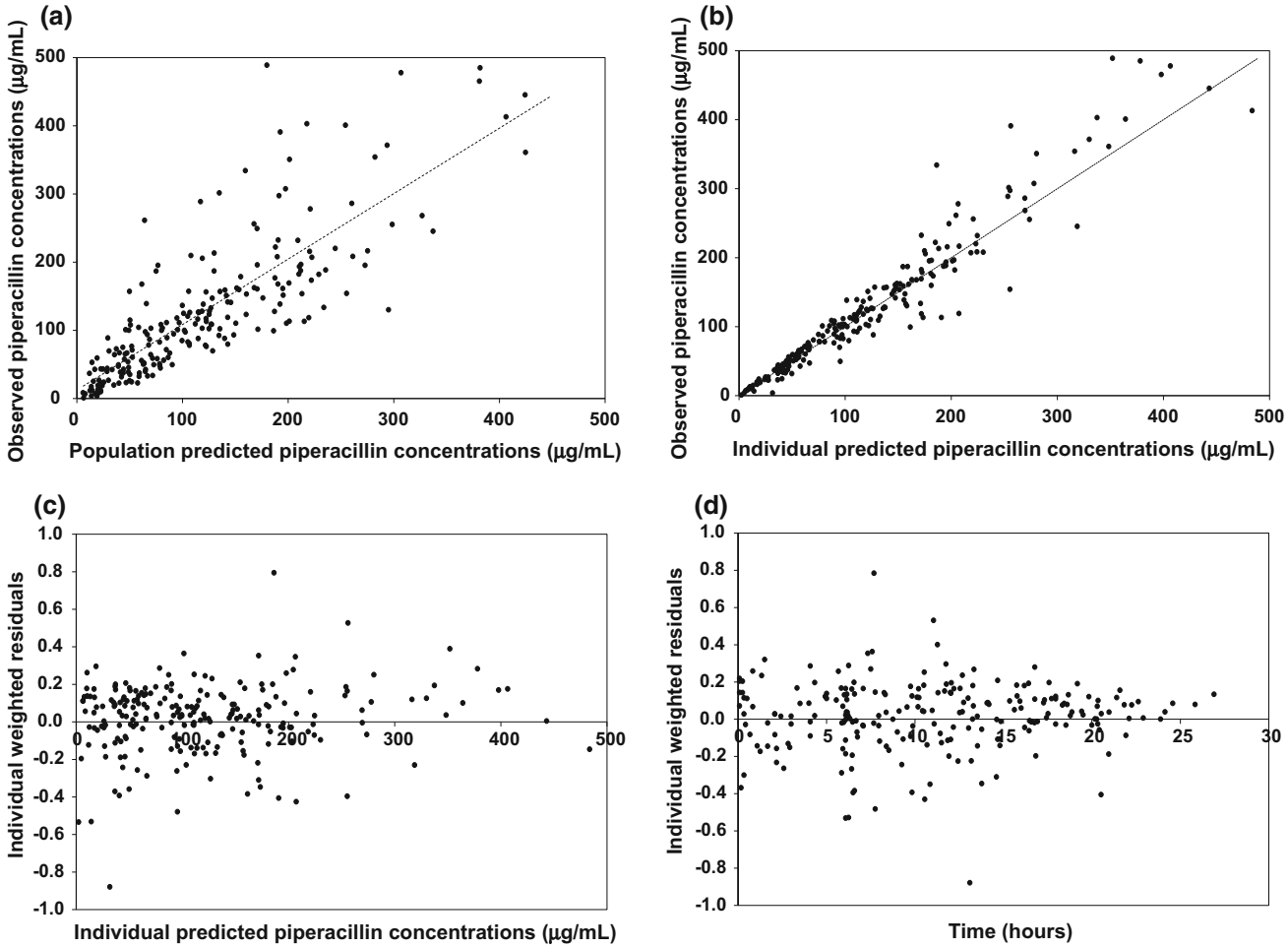

Fig. 3 The goodness-of-fit plots of the final model. **a** Observed versus population predicted piperacillin concentrations; **b** Observed versus individual predicted piperacillin concentrations; **c** Individual weighted residuals versus individual predicted piperacillin concentrations; **d** Individual weighted residuals versus time. Dotted lines represent identity lines

Population PK parameter estimates of the final model are shown in Table 2. The goodness-of-fit plots proved the correctness of the final model, as shown in Fig. 3a to d. All estimates were within the 95% CIs obtained by 1,000 bootstrap runs (Table 2). In addition, the VPC showed that the observed percentiles remained within the 95% CI of corresponding predicted percentiles, as displayed in Fig. 4. These results confirmed that the final model had the sufficient performance to further simulate concentration–time profiles.

PD assessment using Monte Carlo simulation

Population PK parameter estimates and variabilities from the validated final model were used to simulate 10,000 virtual patients for each dosage regimen and renal function. PTA (PK/PD target: 90% $fT_{>MIC}$) versus MIC profiles for the first dose when using 30 different dosage regimens in patients with 4 different renal function groups are depicted in Fig. 5 and Supplementary Material Figs. S1, S2 and S3.

For the least susceptible pathogens (MIC 16 mg/L) in patients with CL_{Cr} 60 to 120 mL/min, two standard regimens; 4 g of piperacillin infused over 0.5 h every 6 h provided PTA of 82% (Fig. 5d) while every 8 h provided PTA of 27% (Fig. 5c). Prolonged infusion increased the PTA, for example, 4 g of piperacillin infused over 2 h every 6 h could provide PTA $\geq$ 90% (Fig. 5d). However, in patients with CL_{Cr} 40 to < 60 mL/min, 4 g of piperacillin infused over 0.5 h every 6 or 8 h could provide PTA $\geq$ 90% (Supplementary Material Fig. S1). In patients with CL_{Cr} 20 to < 40 mL/min, the recommended dosing is 2 g of piperacillin infused over 0.5 h every 6 h, this regimen provided PTA of 100% (Supplementary Material Fig. S2). For patients with CL_{Cr} < 20 mL/min, the recommended dosing is 2 g of piperacillin infused over 0.5 h every 8 h, this regimen also provided PTA of 100% (Supplementary Material Fig. S3).

All dosage regimens were used to investigate CFR for 3 pathogens including *P. aeruginosa, K. pneumoniae,* and *E. coli.* In patients with CL_{Cr} 40 to < 60 and 60 to 120 mL/

min (Table 3, Supplementary Table S1), none of the studied dosage regimens reached CFR ≥ 90% against *P. aeruginosa.* The CI with LD regimens and 4 g of piperacillin every 6 h (only for patients with CL_{Cr} 40 to < 60 mL/min) provided CFR ≥ 90% for the *K. pneumoniae* infection while almost all dosage regimens could achieve CFR ≥ 90% for the *E. coli* infection. In case of patients with CL_{Cr} 20 to < 40 mL/min (Supplementary Table S2), at least 8 g of piperacillin CI with 4 g-LD could reach CFR ≥ 90% against *P. aeruginosa.* The 2 g of piperacillin infused over 0.5 h every 6 h (the recommended dosing) provided nearly 90% CFR (89%) for the *K. pneumoniae* infection. All dosage regimens could achieve CFR ≥ 90% against *E. coli*. For patients with CL_{Cr} < 20 mL/min (Supplementary Table S3), at least 6 g of piperacillin CI with 4 g-LD could reach CFR ≥ 90% against *P. aeruginosa.* The 2 g of piperacillin infused over 0.5 h every 8 h (the recommended dosing) provided nearly 90% CFR (89%) for the *K. pneumoniae* infection. All dosage regimens could achieve CFR ≥ 90% against *E. coli*.

Discussion

Effective piperacillin dosing in patients with the early phase of sepsis is crucial. There are only two previous works which investigated this issue [17, 20]. Obrink-Hansen et al. studied in 15 patients with the first 24 h of septic shock [20] and Roberts et al. studied on Days 1 and 2 of therapy in 16 patients with sepsis and normal renal function [17]. In this study, 48 patients with sepsis (including septic shock) were studied within the first 24 h, either patients with normal or impaired renal function were included to expand the variety of patient characteristics.

Based on the final population PK model, the PK behavior of piperacillin in the early phase of sepsis was best described by the two-compartment model, consistent with two previous studies [17, 20]. The CL could be explained with CL_{Cr} (calculated by the Cockcroft-Gault equation if renal function was stable or the Jelliffe equation if unstable) in this study because it is primarily eliminated by renal clearance, however serum creatinine (S_{Cr}) was found to be a significant covariate in Obrink-Hansen et al. [20]. A critical distinction between two works is renal function of patients; this study recruited both patients with stable and unstable renal function (30% of patients presented acute kidney injury (AKI)) while most patients in Obrink-Hansen et al. had unstable renal function (64% of patients showed AKI). Because the current study estimated CL_{Cr} by using the 2 different equations based on the stability of renal function, CL_{Cr} could explain CL better than S_{Cr}. Interestingly; this study also found that the other significant covariate of CL was MAP, it is used to imply an average blood pressure during a single cardiac cycle [29]. An increase in MAP might associate with increasing blood perfusion to organs including kidney and liver, resulting in rising CL. From the final model, if MAP increases 10 mmHg, CL will raise 0.5 L/h, thus piperacillin dosing increment might be necessary. Mostly, previous studies reported that TBW has been a significant covariate for V_d [21, 30–33]. Differently, in this study, ABW has been found to be the most significant covariate for the V_1 of piperacillin, a hydrophilic drug. The reduction in IIV for ABW addition (8.6%) was slightly greater than TBW addition (7.9%). Although the median and interquartile range values of ABW and TBW were quite similar as shown in Table 1, the maximum value of TBW (123 kg) was much larger than ABW (90 kg). In addition, ABW has been suggested to be a plausible size descriptor for beta-lactams [26, 34]. Although piperacillin dosing in adult patients would not base on ABW, ABW should be considered for dosing particularly in obese patients. A change in ABW of 1 kg is likely to increase the V_1 of 0.26 L, this leads to increased dose consideration, subsequently.

The CL was lower in the present population (5.37 L/h) compared with the result of Robert et al. (17.20 L/h), one possible explanation is the differences in renal function and body size. Most patients in this study had renal impairment (median CL_{Cr} 54.9 mL/min) while Robert et al. [17] included only patients with normal renal function (defined as plasma creatinine < 120 µmol/L). Patients in our study had smaller body size (TBW 57 kg) compared with the Robert's study (TBW 80 kg). In addition, organ functions of patients in our work (median SOFA scores = 6) were

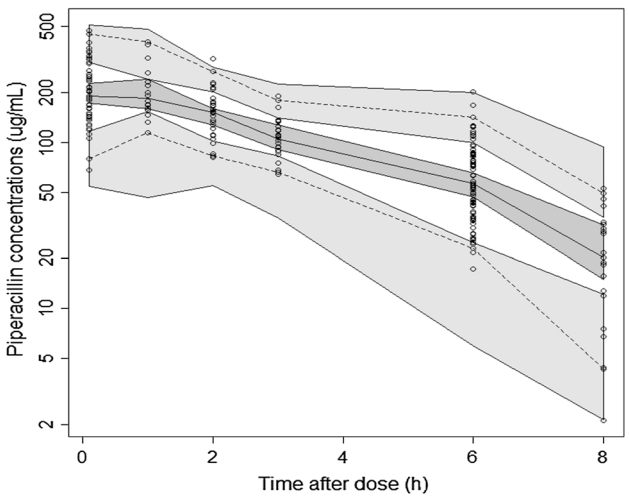

Fig. 4 Visual predictive check of the final model. Individual points represent observed data. Solid line represents 50th percentiles of observed data. Dashed lines represent 5th and 95th percentiles of observed data. The dark gray area represents 95% CI of the 50th percentile of predicted data. The light gray areas represent 95% CI of the 5th and 95th percentiles of predicted data

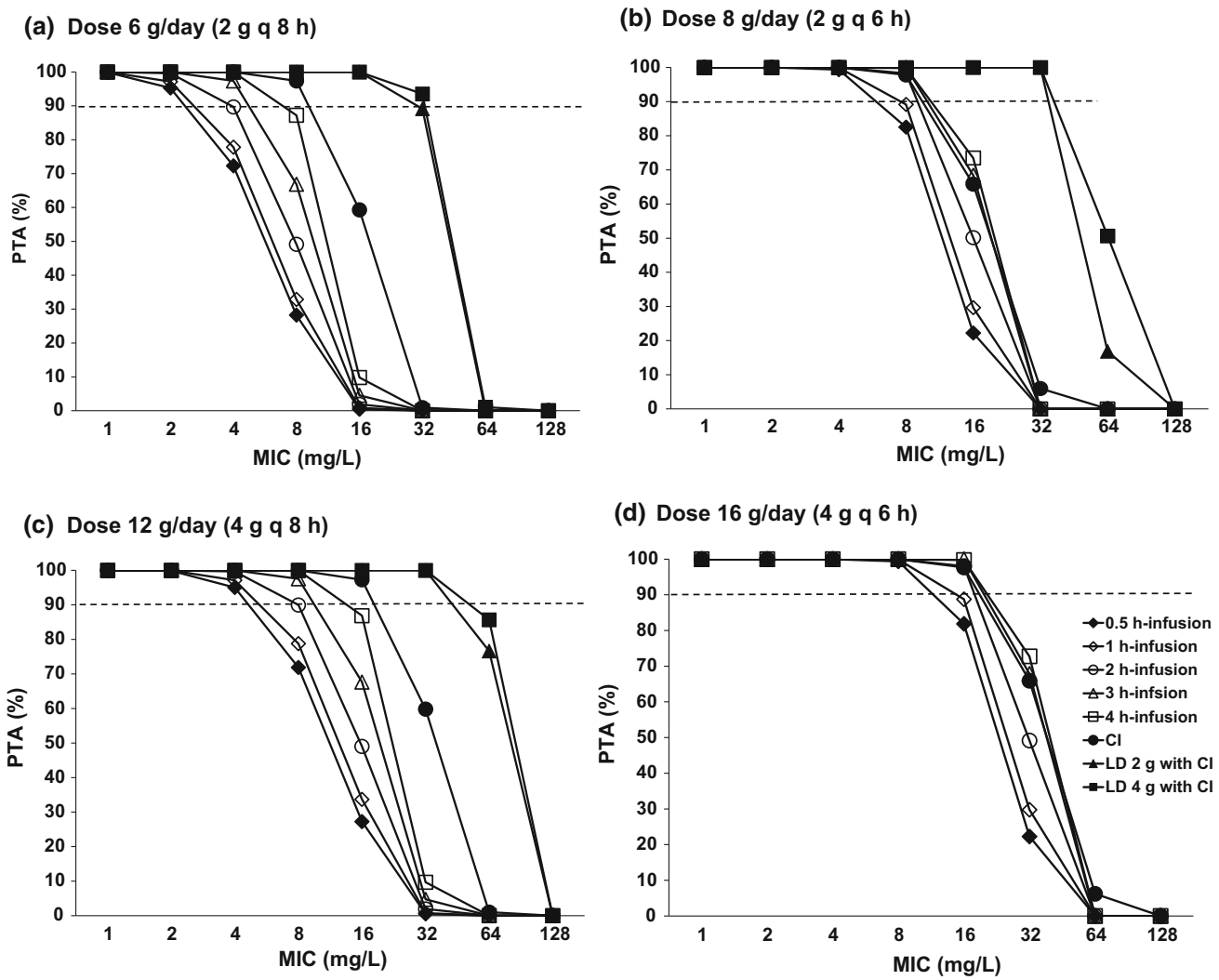

Fig. 5 Probability of target attainment (PTA) versus Minimum inhibitory concentration (MIC) profiles for the first dose in patients with creatinine clearance (CL_{Cr}) 60 to 120 mL/min. The graphs indicate the total administration of **a** 6 g/day; **b** 8 g/day; **c** 12 g/day; **d** 16 g/day. Dashed lines represent the PTA target (≥ 90% of simulated patients reached the 90% $fT_{>MIC}$); *CI* continuous infusion, *LD* loading dose

worse than the study of Robert (median SOFA scores = 3). It should also be mentioned that they included TBW, not CL_{Cr}, in their final model, due to a narrow range of CL_{Cr} in their study. Contrarily, the CL in this study was higher than the result of Obrink-Hansen et al. (3.60 L/h) because most patients in Obrink-Hansen's study presented septic shock and AKI (S_{Cr} 1.9 mg/dL) [20]. The CL is likely to correspond with different levels of patients' renal function. The piperacillin V_d in our population (17.12 L) is smaller than that of Roberts et al. (25.0 L) [17] but V_d normalized to total body weight is quite similar (0.30 vs 0.33 L/kg). This finding suggests that the difference in V_d is probably a result of the difference in body size (median TBW 56.6 vs 75.7 kg). On the other side, the V_d is larger than the result of Obrink-Hansen et al. (11.20 L) [20], the difference in V_d between the present study and Obrink-Hansen et al. may result from the vasopressor therapy. All patients in Obrink-Hansen et al. obtained noradrenaline, while 33% of patients in this study received vasopressor therapy. Vasoactive medications can cause vasoconstriction which may affect drug distribution, subsequently.

Regarding the PK/PD target, an in vitro study found that 75% $fT_{>MIC}$ could provide bactericidal activity of piperacillin [6]. However, higher targets (80 to 100% $fT_{>MIC}$) have been recommended for microbiological success, prevention of bacterial regrowth and improved clinical outcomes in patients with serious bacterial infections [7–9]. From the results of the preliminary analysis pertaining to 90 and 100% $fT_{>MIC}$, 90% $fT_{>MIC}$ was chosen as the target in this study. During the early phase of sepsis, this study found that current dosage regimens; 4 g 30 min-infusion every 6 and 8 h could achieve PTA ≥ 90% (a target of

Table 3 Cumulative fraction of response (CFR) in patients with creatinine clearance 60 to 120 mL/min

Dosage regimens	CFR with the following pathogens (%)		
	P. aeruginosa	*K. pneumoniae*	*E. coli*
Dose 6 g/day			
2 g 0.5 h-inf. q 8 h	43	68	86
2 g 1 h-inf. q 8 h	46	70	87
2 g 2 h-inf. q 8 h	53	75	90
2 g 3 h-inf. q 8 h	59	79	92
2 g 4 h-inf. q 8 h	64	82	93
6 g CI	71	85	94
LD 2 g with 6 g CI	82	89	97
LD 4 g with 6 g CI	82	90	97
Dose 8 g/day			
2 g 0.5 h-inf. q 6 h	64	82	93
2 g 1 h-inf. q 6 h	66	83	93
2 g 2 h-inf. q 6 h	70	85	94
2 g 3 h-inf. q 6 h	73	86	95
2 g 4 h-inf. q 6 h	73	86	95
8 g CI	72	85	95
LD 2 g with 8 g CI	83	90	97
LD 4 g with 8 g CI	85	91	98
Dose 12 g/day			
4 g 0.5 h-inf. q 8 h	61	80	92
4 g 1 h-inf. q 8 h	64	81	93
4 g 2 h-inf. q 8 h	69	84	94
4 g 3 h-inf. q 8 h	73	85	95
4 g 4 h-inf. q 8 h	75	87	95
12 g CI	80	89	96
LD 2 g with 12 g CI	86	91	98
LD 4 g with 12 g CI	86	91	98
Dose 16 g/day			
4 g 0.5 h-inf. q 6 h	75	87	95
4 g 1 h-inf. q 6 h	77	87	96
4 g 2 h-inf. q 6 h	79	88	96
4 g 3 h-inf. q 6 h	80	89	97
4 g 4 h-inf. q 6 h	81	89	97
16 g CI	80	89	97

inf infusion, *LD* loading dose, *CI* continuous infusion

90% $fT_{>MIC}$) at MIC 16 mg/L in patients with CL_{Cr} < 60 mL/min but could not achieved the target in patients with CL_{Cr} 60 to 120 mL/min. Likewise, Obrink-Hansen et al. found that during the early phase of septic shock, 4 g 3 min-infusion every 8 h could not provide PTA ≥ 90% for both targets of 100% $fT_{>MIC}$ and 50% $fT_{>4MIC}$ at MIC 16 mg/L in patients with all groups of plasma creatinine (80, 150, 250 μmoL/L) [20]. Similarly, Robert et al. also reported that during the first dose, 4 g 20 min-infusion every 6 h and 8 h could not provide PTA ≥ 90% (a target of 50% $fT_{>MIC}$) at MIC 16 mg/L in patients with sepsis and normal renal function [17].

To overcome the non-target attainment problem, prolonged infusion has been suggested to increase the PTA. The results of this study show that prolonged infusion could achieve PTA ≥ 90% more than short infusion in patients with CL_{Cr} 40 to 120 mL/min similar to previous studies [17, 20]. However, using every 6 h dosing in patients with CL_{Cr} < 40 mL/min, the 2 and 3 h infusion time provided PTA ≥ 90% while the 4 h infusion time could not achieve PTA ≥ 90%. This finding can imply that the longer infusion time did not show the better benefit to attain the PTA target in patients with CL_{Cr} < 40 mL/min who received every 6 h dosing consistent with the study of Abdul-Aziz et al. They reported that β-lactam exposure is more likely to be adequate in patients with significant renal impairment, regardless of the drug administration method [35]. Moreover, to achieve PTA ≥ 90% at MIC 16 mg/L, this study found that LD 2 or 4 g is necessary for continuous infusion of dose 6 and 8 mg/day, without the LD, these dosage regimens could achieve the target at only MIC 8 mg/L.

Regarding CFR, all dosage regimens provided CFR ≥ 90% for the *E. coli* infection similar to previous studies [36]. When considering the *K. pneumoniae* infection, the CI with LD regimens could be useful options for patients with all renal functions while 4 g of piperacillin every 6 h with all infusion time could be beneficial options for patients with CL_{Cr} < 60 mL/min. Similarly, Alobaid et al., using a target of 50% $fT_{>MIC}$, also found that both short and extended infusion could provide CFR achievement besides continuous infusion [36]. None of the studied dosage regimens provided CFR ≥ 90% againts *P. aeruginosa* in patients with CL_{Cr} 40 to 120 mL/min consistent with previous studies [19, 36]. Udy et al. also found that 4 g 20 min infusion every 6 h could not provide CFR ≥ 90% (both targets of 50% or 100% $fT_{>MIC}$) for *P. aeruginosa* in septic patients with CL_{Cr} 10 to 300 mL/min [19]. Alobaid et al. reported that 4 g every 8 or 6 h (all modes of administration) could not achieve CFR ≥ 90% (50% $fT_{>MIC}$) for *P. aeruginosa* in critically ill patients with CL_{Cr} 30, 50, 150 mL/min [36]. Alternative treatment should be considered to achieve effective treatment. Vojtová et al. documented that combined therapy between piperacillin/tazobactam and amikacin showed the relative safety and usefulness in the treatment of infections caused by *P. aeruginosa* at intensive care unit [37] but such treatment should be carefully used in patients with renal impairment. Another approach proposed is the treatment with carbapenem antibiotics [38]. The limitation of this study should be noted. This study explored the likelihood of target attainment using EUCAST data to improve

generalizability for empirical dosing, although it limits conclusions about sufficiency of drug exposure in any specific patients.

To our knowledge, this was the first prospective study in which piperacillin pharmacokinetics has been investigated in a relatively large number of critically-ill patients during the early phase of sepsis, the vital period for patient survival. The model that best described CL included the covariates CL_{Cr} and MAP. Depending on stability of renal function, we used two different equations to estimate CL_{Cr}. Our results suggested that routine S_{Cr} monitoring should be done in this group of patients to better predict the drug CL and select the appropriate dosage regimen. Piperacillin CL also significantly increased with an increase in MAP, an indicator of vital organ perfusion. We also found that ABW may be beneficial to quantify the influence of body composition on V_1 of piperacillin. Our findings suggested that the usual dosage regimen (4 g of piperacillin infused over 0.5 h every 6 h) could not provide the target attainment for eradication of susceptible pathogens with MIC 16 mg/L in critically ill patients with $CL_{Cr} > 60$ mL/min and normal MAP (> 70 mmHg), a recommended dosing for patients with CL_{Cr} 60 to 120 mL/min would be 4 g of piperacillin infused over 2 h every 6 h.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Prince of Songkla University (EC; 56-501-14-1). The authorized researchers were granted the right to extract the data from the database.

Informed consent Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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