

## Population pharmacokinetics of piperacillin/tazobactam in critically ill Korean patients and the effects of extracorporeal membrane oxygenation

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**Objectives:** To explore extracorporeal membrane oxygenation (ECMO)-related alterations of the pharmacokinetics (PK) of piperacillin/tazobactam and determine an optimal dosage regimen for critically ill adult patients.

**Methods:** Population PK models for piperacillin/tazobactam were developed using a non-linear mixed effect modelling approach. The percentage of time within 24 h for which the free concentration exceeded the MIC at a steady-state ( $50\%fT_{>MIC}$ ,  $100\%fT_{>MIC}$ , and  $100\%fT_{>4\times MIC}$ ) for various combinations of dosage regimens and renal function were explored using Monte-Carlo simulation.

**Results:** A total of 226 plasma samples from 38 patients were used to develop a population PK model. Piperacillin/tazobactam PK was best described by two-compartment models, in which estimated glomerular filtration rate (eGFR), calculated using CKD-EPI equation based on cystatin C level, was a significant covariate for total clearance of each piperacillin and tazobactam. ECMO use decreased the central volume of distribution of both piperacillin and tazobactam in critically ill patients. Patients with *Escherichia coli* or *Klebsiella pneumoniae* infection, but not those with *Pseudomonas aeruginosa* infection, exhibited a PK/pharmacodynamic target attainment >90% when the target is  $50\%fT_{>MIC}$ , as a result of applying the currently recommended dosage regimen. Prolonged or continuous infusion of 16 g/day was required when the treatment goal was  $100\%fT_{>MIC}$  or  $100\%fT_{>4\times MIC}$ , and patients had an eGFR of 130–170 mL/min/1.73 m<sup>2</sup>.

**Conclusions:** ECMO use decreases piperacillin/tazobactam exposure. Prolonged or continuous infusion can achieve the treatment target in critically ill patients, particularly when MIC is above 8 mg/L or when patients have an eGFR of 130–170 mL/min/1.73 m<sup>2</sup>.

### Introduction

Alteration in antimicrobial pharmacokinetics (PK), caused by the pathophysiological conditions of patients in the ICU, are a major factor in failure to achieve the pharmacodynamic (PD) targets for antimicrobials. Therefore, when treating critically ill patients, it is necessary to adjust the antimicrobial dosage regimen in consideration of the patient's condition in order to maximize the therapeutic effect and minimize the occurrence of toxicity and the development of antimicrobial resistance.<sup>1–3</sup> The addition of extracorporeal membrane oxygenation (ECMO) may complicate PK changes in volume of distribution (Vd) and clearance (CL),<sup>4,5</sup>

which highlights the necessity to integrate PK/PD to optimize antibiotic dosage in adult patients on ECMO.<sup>6</sup>

Piperacillin/tazobactam, a commonly used  $\beta$ -lactam/ $\beta$ -lactamase inhibitor and important treatment option for severe infections in critically ill patients, can be prescribed as a carbapenem-sparing alternative.<sup>7–9</sup> Because of substantial risks of nosocomial infection and a high rate of infections caused by MDR organisms, piperacillin/tazobactam may be widely used during ECMO support.<sup>10–12</sup> Altered PK profile of piperacillin/tazobactam during ECMO support can result in insufficient serum concentrations, which can lead to a decreased probability of PK/PD target attainment (PTA) followed by suboptimal clinical

outcomes in critically ill patients.<sup>13–15</sup> In contrast, PK/PD-based optimization of piperacillin/tazobactam dosage may help overcome high inocula of ESBL-producing bacteria.<sup>16</sup> A recent review of ten population PK studies of piperacillin/tazobactam reported high variability in CL and Vd of both drugs in ICU patients undergoing renal replacement therapy or in those with various degrees of renal dysfunction.<sup>17</sup> In that review, the ranges of CL and Vd considered for piperacillin were 3.12–19.9 L/h and 11.2–41.2 L, respectively, and those for tazobactam were 5.10–6.78 L/h and 17.5–76.1 L, respectively.

However, there is a paucity of knowledge about piperacillin/tazobactam PK in patients receiving ECMO and previous studies made no specific dosage recommendations.<sup>15,18–20</sup>

The PK/PD index for piperacillin is the percentage of time during the dosing interval at which the free concentration remains above the MIC ( $\%fT_{>MIC}$ ). For  $\beta$ -lactam antimicrobials, a PK/PD index of 20%–40% is required for bacteriostatic effect and an index of 40%–70% is required for bactericidal effect, as shown in an *in vivo* study.<sup>21</sup> In a recent prospective multinational PK study in critically ill patients, the treatment failure rate was three times higher when the PK/PD index was <50%, and the clinical outcome was significantly better when the PK/PD index was 100% than when it was 50%.<sup>22</sup> A research group recommended a more aggressive target of  $100\%fT_{>4-8 \times MIC}$  to maximize clinical response in critical care patients.<sup>23</sup>

Therefore, we aimed to identify a population PK model of piperacillin/tazobactam that is suitable for critically ill Korean adult patients, including those receiving ECMO, to evaluate the effects of ECMO on piperacillin/tazobactam PK. Moreover, we investigated appropriate dosage regimens of piperacillin/tazobactam via Monte Carlo simulations to predict the standard and aggressive PK/PD indices of  $50\%fT_{>MIC}$ ,  $100\%fT_{>MIC}$ , and  $100\%fT_{>4 \times MIC}$ .

## Materials and methods

### Ethics

The study was approved by the Institutional Review Board of the Hallym University Sacred Heart Hospital (IRB No. 2020-06-015) and was performed in agreement with the Good Clinical Practice and the Declaration of Helsinki. A written informed consent form was signed by each patient's legal representative prior to their participation.

### Patients

This prospective clinical study was conducted in an 840 bed university-affiliated tertiary referral hospital from September 2020 to April 2021 (Hallym University Sacred Heart Hospital, Anyang, South Korea). Clinical indications for piperacillin/tazobactam included nosocomial infections, empirical management of septic shock from an unknown source, and prophylactic administration for patients undergoing ECMO. Patients with a history of penicillin allergy or a positive skin test result for piperacillin were excluded. The demographic characteristics of ECMO and non-ECMO groups were compared. If each group's parameters followed a normal distribution, the independent *t*-test was applied; if they did not, even in one group, the Wilcoxon rank-sum test was applied.

### ECMO apparatus

The ECMO device was the Permanent Life Support (PLS) System (MAQUET, Rastatt, Germany), which consisted of a PLS-i Oxygenator, a ROTAFLOW centrifugal pump, a ROTAFLOW console, and a broad range of HLS

Cannula. The circuit was primed with 1 L of normal saline or plasma solution and the total circuit volume was 500–600 mL.

### Study design

Eligible patients could participate any time after the initiation of piperacillin/tazobactam administration. Enrolled patients received 2000/250 mg, 3000/375 mg, or 4000/500 mg of piperacillin/tazobactam for 30 min every 6 or 8 h via intravenous (IV) infusion. Six blood samples were drawn at the first dosing period following enrolment. The planned sampling times for model development were as follows: (i) immediately before dosing and 0.5, 1, 2, 3, and 6 h after beginning the infusion, for the 6 h interval administration; and (ii) immediately before dosing and 0.5, 1, 2, 4, and 8 h after beginning the infusion, for the 8 h interval administration. Two samples for external evaluation of the final PK model were drawn just before the fourth or fifth dosing for trough level and after the end of the 30 min infusion for peak level.

### Piperacillin/tazobactam assay

Piperacillin/tazobactam plasma concentrations were analysed using an LC/MS/MS assay. The LC system consisted of a prominence LC-20A System (Shimadzu, Japan) and a Gemine C<sub>18</sub> column (Kinetex; Phenomenex, USA) was used. The MS detection was conducted using a hybrid triple quadrupole linear ion trap mass spectrometer (API4000 QTRAP; SCIEX, USA). For piperacillin/tazobactam, the lower limit of quantification (LLOQ) was 0.1 mg/L. The assay results were linear over 0.1–150 mg/L ( $R^2 > 0.99$ ). Piperacillin concentration was determined after analysis by diluting 5-fold to ensure that all samples were within the calibration range because many samples exceeded 150 mg/L, the highest limit of quantification. For piperacillin, the intraday precision and accuracy of the validation concentration range (0.5, 5, and 50 mg/L) analysed using standard samples were 2.25%–2.74% and 94.07%–98.13%, respectively. Inter-day precision and accuracy of the validation concentration range (0.5, 5, and 50 mg/L) were analysed using standard samples for 3 days were 2.60%–6.14% and 98.98%–106.51%, respectively. For tazobactam, intraday precision and accuracy of the validation concentration range (0.5, 5, and 50 mg/L) analysed using standard samples were 1.11%–5.69% and 89.07%–92.87%, respectively. Inter-day precision and accuracy of the validation concentration range (0.5, 5, and 50 mg/L) analysed using standard samples for 3 days were 5.10%–8.49% and 95.83%–106.34%, respectively.

### Population PK analysis

Population PK analysis was conducted using NONMEM software (version 7.5; ICON Development Solutions, USA). A first-order conditional estimation with interaction (FOCE-I) method and Bayesian estimation methods were used to estimate population parameters. The FOCE-I allows interaction between interindividual variability (IIV) of PK parameters and residual unexplained variability (RUV). One-, two-, and three-compartment models were evaluated for structural model building. Drug distribution and elimination processes were assumed to follow first-order kinetics. The PK parameter was defined as  $\theta_i = \theta \times \exp(\eta_i)$ , where  $\theta$  is the typical value of the PK parameter,  $\theta_i$  is an individual PK parameter, and  $\eta_i$  is a normally distributed random variable with the mean of 0 and variance of  $\omega^2$ . Additive, proportional, or additive plus proportional error models were investigated for the RUV, which is a normally distributed random variable with the mean of 0 and variance of  $\sigma^2$ . A power parameter for proportional error was tested to allow for non-linear heteroscedastic variances.

Models were selected based on NONMEM object function value (OFV), parameter precision (relative standard errors), shrinkage of IIV, and goodness-of-fit plots. A decrease in the OFV ( $\Delta$ OFV), greater than 3.84 for 1 degree of freedom (df) or 5.99 for 2 dfs, between two nested models was considered statistically significant at  $P < 0.05$  ( $\chi^2$  test) for model

improvement. Diagnostic goodness-of-fit plots included: conditional weighted residuals (CWRES) versus time, CWRES versus model-predicted population concentration (PRED), observation versus PRED, and observation versus model-predicted individual concentration (IPRED).

Perl-speaks-NONMEM software (version 5.2.6, <https://uopharma.cometrics.github.io/PsN/>) was used to search covariates, implement non-parametric bootstrap to obtain 95% CI, and evaluate a model with a visual predictive check (VPC). Stepwise forward selection and backward elimination processes were conducted for significant covariates for structural PK parameters. Statistical significance was set at  $P < 0.01$  ( $\Delta\text{OFV} < -6.635$  by  $\chi^2$  test,  $df = 1$ ) for selection and  $P < 0.001$  ( $\Delta\text{OFV} > 10.83$  by  $\chi^2$  test,  $df = 1$ ) for elimination. Significant covariates have potential clinical relevance and statistical significance. First, we explored the effect of the presence of ECMO on PK parameters. Afterwards, we tested ECMO type [veno-arterial (VA) or veno-venous (VV)], rpm, and flow rate, in addition to other covariates, for parameters found to be affected by ECMO. The tested covariates for total clearance (CL) were sex, age, height, body surface area (BSA), serum protein level, serum albumin level, serum creatinine level, serum cystatin C level, primary diagnosis, comorbidity, and renal function. The renal function was estimated by applying the Cockcroft-Gault equation, MDRD, modified MDRD, CKD-EPI, and modified CKD-EPI equations

to determine the CL. The modified MDRD and CKD-EPI values were adjusted using individual BSA values calculated using the Du Bois formula. The filtration markers for CKD-EPI were creatinine, cystatin C, or both.<sup>24</sup> The tested covariates for other PK parameters were sex, age, height, BSA, serum protein level, serum albumin level, primary diagnosis, and comorbidity. VPC with prediction- and variability-correction (VPC<sub>PVC</sub>) was performed by comparing observed concentrations with 80% prediction intervals from 1000 simulated datasets. A non-parametric bootstrap helped evaluate the stability of the final model. The median and 95% CI for model parameters of bootstrap samples ( $n = 2000$ ) were generated to evaluate the final parameter estimates. R software (version 4.1.0, [www.r-project.org](http://www.r-project.org)) was used to process modelling output and visualization.

### PD target attainment

The first Monte Carlo simulation evaluated the adequacy of the currently recommended dosage regimen [for a creatinine clearance (CL<sub>CR</sub>) >40 mL/min, 4.5 g q6h; for a CL<sub>CR</sub> of 20–40 mL/min, 3.375 g q6h; for a CL<sub>CR</sub> <20 mL/min, 2.25 g q6h], when empirically treating adult patients for nosocomial pneumonia with piperacillin/tazobactam. Moreover, 50 000 PK parameters of virtual patients were generated by applying a

**Table 1.** Patient characteristics<sup>a</sup>

Parameter	All	ECMO	Non-ECMO	P value
ECMO type		VA = 18/VV = 1		
CRRT, yes/no	y = 8/n = 30	y = 8/n = 11	y = 0/n = 19	
Sex, male/female	m = 25/f = 13	m = 15/f = 4	m = 10/f = 9	
Age (years)	66.5 (53.3–78.8)	58 (46.5–64.5)	79 (67.5–83)	<0.0001 <sup>c</sup>
Height (cm)	165 (130–172)	168 (163–174)	160 (154–170)	0.0248 <sup>c</sup>
Weight (kg)	60 (50–70)	70 (55–72.4)	54 (46–61)	0.0019 <sup>c</sup>
Body surface area (m <sup>2</sup> )	1.65 (1.53–1.81)	1.76 (1.61–1.89)	1.56 (1.43–1.66)	0.0019 <sup>c</sup>
ICU duration (days)	3.0 (1.0–4.0)	1.0 (1.0–3.5)	3.0 (3.0–5.0)	0.0051 <sup>d</sup>
APACHE II	20 (16.3–23.8)	24.0 (19.5–26.0)	17.0 (13.5–20.0)	0.0028 <sup>c</sup>
SOFA	7.0 (5.0–11)	9.0 (7.5–12)	5.0 (3.5–6.5)	0.0003 <sup>c</sup>
BUN (mg/dL)	25.0 (16.5–31.6)	25.1 (16.9–31.9)	21.3 (15.2–30.1)	0.6509 <sup>d</sup>
Serum creatinine (mg/dL)	1.11 (0.70–1.61)	1.55 (0.86–1.87)	0.77 (0.56–1.50)	0.0174 <sup>c</sup>
Cystatin C (mg/dL)	1.36 (0.96–1.67)	1.07 (0.95–1.52)	1.46 (1.00–1.74)	0.2738 <sup>c</sup>
Albumin (g/dL)	2.75 (2.43–3.10)	2.80 (2.50–3.20)	2.60 (2.45–2.95)	0.6812 <sup>c</sup>
Protein (g/dL)	4.95 (4.43–5.38)	4.70 (4.30–5.35)	5.00 (4.55–5.35)	0.1342 <sup>c</sup>
CL <sub>CR</sub> , Cockcroft-Gault (mL/min)	55.0 (40.7–77.7)	56.9 (39.9–79.2)	53.1 (40.9–76.3)	0.7111 <sup>c</sup>
GFR				
MDRD (mL/min/1.73 m <sup>2</sup> )	64.7 (43.2–101)	44.3 (37.0–86.9)	79.0 (47.4–121)	0.0877 <sup>d</sup>
Modified MDRD (mL/min) <sup>b</sup>	62.3 (43.0–95.7)	46.4 (37.2–94.8)	79.7 (49.0–94.9)	0.3138 <sup>d</sup>
CKD-EPI (mL/min/1.73 m <sup>2</sup> )	59.2 (42.8–97.5)	45.2 (39.3–89.1)	74.3 (45.2–110)	0.1484 <sup>d</sup>
Modified CKD-EPI (mL/min) <sup>b</sup>	60.4 (42.9–87.7)	49.1 (39.8–92.7)	67.3 (46.8–85.5)	0.6300 <sup>d</sup>
CKD-EPI <sub>CYS</sub> (mL/min/1.73 m <sup>2</sup> )	52.8 (38.7–81.0)	72.5 (43.4–81.7)	46.8 (34.1–73.2)	0.1327 <sup>d</sup>
Modified CKD-EPI <sub>CYS</sub> (mL/min) <sup>b</sup>	53.7 (36.9–73.7)	70.8 (45.9–86.3)	44.0 (30.9–65.7)	0.0288 <sup>c</sup>
CKD-EPI <sub>CR_CYS</sub> (mL/min/1.73 m <sup>2</sup> )	59.3 (43.1–93.4)	47.7 (43.1–93.8)	62.9 (45.3–90.3)	0.9884 <sup>d</sup>
Modified CKD-EPI <sub>CR_CYS</sub> (mL/min) <sup>b</sup>	57.4 (42.3–84.2)	56 (40.2–91.7)	58.8 (42.8–77.4)	0.4566 <sup>d</sup>

Unless indicated otherwise, results shown are the median (IQR).

<sup>a</sup>Abbreviations: ECMO, extracorporeal membrane oxygenation; VA, veno-arterial; VV, veno-venous; BSA, body surface area; BUN, serum blood urea nitrogen level; CL<sub>CR</sub>, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, equation of Chronic Kidney Disease Epidemiology Collaboration based on creatinine level; CKD-EPI<sub>CYS</sub>, equation of CKD-EPI based on cystatin C level; CKD-EPI<sub>CR\_CYS</sub>, equation of CKD-EPI with creatinine and cystatin C levels; CRRT, continuous renal replacement therapy.

<sup>b</sup>The modified MDRD and CKD-EPI equations adjusted to individual BSA are  $\text{GFR (mL/min)} = \text{GFR (MDRD or CKD-EPI)} \times (\text{BSA}/1.73 \text{ m}^2)$ .

<sup>c</sup>Independent t-test.

<sup>d</sup>Wilcoxon rank sum test.

**Table 2.** Population pharmacokinetic parameter estimates for piperacillin

Parameter	Estimates	RSE (%)	Bootstrap median (95% CI)
<b>Structural model</b>			
$CL = \theta_1 \times e^{(\theta_2 \times (CECYS - 52.77))}$			
$\theta_1$ (L/h)	5.05	6.67	5.04 (4.36–5.7)
$\theta_2$	0.00932	13.5	0.00933 (0.00679–0.0129)
$V_{C\_ECMO}$ (L)	7.38	15.0	7.38 (5.25–9.51)
$V_{C\_nonECMO}$ (L)	16.5	18.0	16.3 (11.4–22.8)
Q (L/h)	6.28	23.9	6.28 (3.94–9.30)
$V_p$ (L)	6.27	16.2	6.28 (4.7–8.51)
<b>Interindividual variability</b>			
CL (%)	33.7	11.8	32.6 (24.6–40.0)
$V_{C\_ECMO}$ (%)	45.9	17.4	44.8 (28.1–63.3)
$V_{C\_nonECMO}$ (%)	65.3	31.5	72.5 (53.8–94.9)
<b>Residual variability</b>			
Proportional error (%)	26.9	11.3	26.5 (20.3–32.8)

Abbreviations: RSE, relative standard error; CECYS, glomerular filtration rate calculated by CKD-EPI cystatin C equation; CL, total clearance;  $V_C$ , central volume of distribution;  $V_p$ , peripheral volume of distribution; Q, intercompartmental clearance between  $V_C$  and  $V_p$ .

log-normal distribution for each PK parameter or each covariate with NONMEM. Then, 50000 MICs from 0.25 to 128 mg/L were generated and randomly assigned to them using R software. The MIC distribution of piperacillin/tazobactam against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, collected globally by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), was used to generate the MICs. Fifty thousand concentration–time (in minutes) profiles at steady-state were generated to explore the PTA with the PK parameters of virtual patients. The treatment target index for piperacillin is the percentage of a dosing interval during which the free (*f*) drug concentration remains above the MIC at steady-state conditions ( $\%fT_{>MIC}$ ). The tested targets were  $50\%fT_{>MIC}$ ,  $100\%fT_{>MIC}$ , and  $100\%fT_{>4 \times MIC}$ . A dosage regimen was considered optimal if the PTA was  $\geq 90\%$ . The *f* was fixed at 0.91.<sup>25</sup>

The second simulation dataset was generated to search the optimal dosage regimen for the PK/PD targets. One thousand virtual patients were generated by applying a log-normal distribution for each PK parameter, while renal function, a significant covariate on CL, was generated using a uniform distribution within the range 0–170 mL/min/1.73 m<sup>2</sup>. The virtual patients were assigned to six renal function groups (0–20, 20–40, 40–60, 60–90, 90–130, or 130–170 mL/min/1.73 m<sup>2</sup>). PTAs for the target of  $50\%fT_{>MIC}$  were explored with the second dataset and combinations of three doses (2, 3, or 4 g), two dosing intervals (6 or 8 h), three infusion times (0.5, 2, or 4 h), and MICs (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, and 128 mg/L). PTAs for the target of  $100\%fT_{>MIC}$  and  $100\%fT_{>4 \times MIC}$  were explored with daily dose combinations (8, 12, or 16 g/day), infusion methods (standard 0.5 h infusion, prolonged 4 h infusion, or continuous infusion), and the aforementioned MICs, while the interval was fixed to 6 h.

## Results

### Patient characteristics

The demographics of the 38 patients are described in Table 1. Nineteen adult patients received ECMO (VA ECMO, *n* = 18; VV ECMO, *n* = 1). Eight of the 19 patients in the ECMO group and 1 of the 19 patients in the non-ECMO group received continuous renal replacement therapy (CRRT). Patients on ECMO support were

**Table 3.** Population pharmacokinetic parameter estimates for tazobactam

Parameter	Estimates	RSE (%)	Bootstrap median (95% CI)
<b>Structural model</b>			
$CL = \theta_1 \times e^{(\theta_2 \times (CECYS - 52.77))}$			
$\theta_1$ (L/h)	6.33	8.13	6.31 (5.39–7.31)
$\theta_2$	0.0113	13.9	0.0114 (0.00893–0.0159)
$V_{C\_ECMO}$ (L)	13.3	11.3	13.2 (10.4–16.2)
$V_{C\_non-ECMO}$ (L)	20.2	19.1	20.0 (14.7–29.5)
Q (L/h)	10.5	24.3	10.4 (6.42–16.2)
$V_p$ (L)	8.96	11.6	8.98 (7.15–11.3)
<b>Interindividual variability</b>			
CL (%)	37.9	13.3	36.8 (26.7–46.9)
$V_{C\_ECMO}$ (%)	38.6	13.9	37.2 (23.9–48.8)
$V_{C\_non-ECMO}$ (%)	64.8	33.9	64.8 (48.2–86.6)
<b>Residual variability</b>			
Proportional error (%)	22.9	13.9	22.6 (16.3–28.8)

Abbreviations: RSE, relative standard error; CECYS, glomerular filtration rate calculated by CKD-EPI cystatin C equation; CL, total clearance;  $V_C$ , central volume of distribution;  $V_p$ , peripheral volume of distribution; Q, intercompartmental clearance between  $V_C$  and  $V_p$ .

younger [median age (IQR); 58.0 (46.5–64.5) versus 79.0 (67.5–83.0) years; *P* < 0.0001]. The severity scores, including APACHE II [median (IQR); 24.0 (19.5–26.0) versus 17.0 (13.5–20.0); *P* = 0.0028] and SOFA scores [median (IQR); 9.0 (7.5–12) versus 5.00 (3.50–6.50); *P* = 0.0003], were significantly higher in the ECMO group.

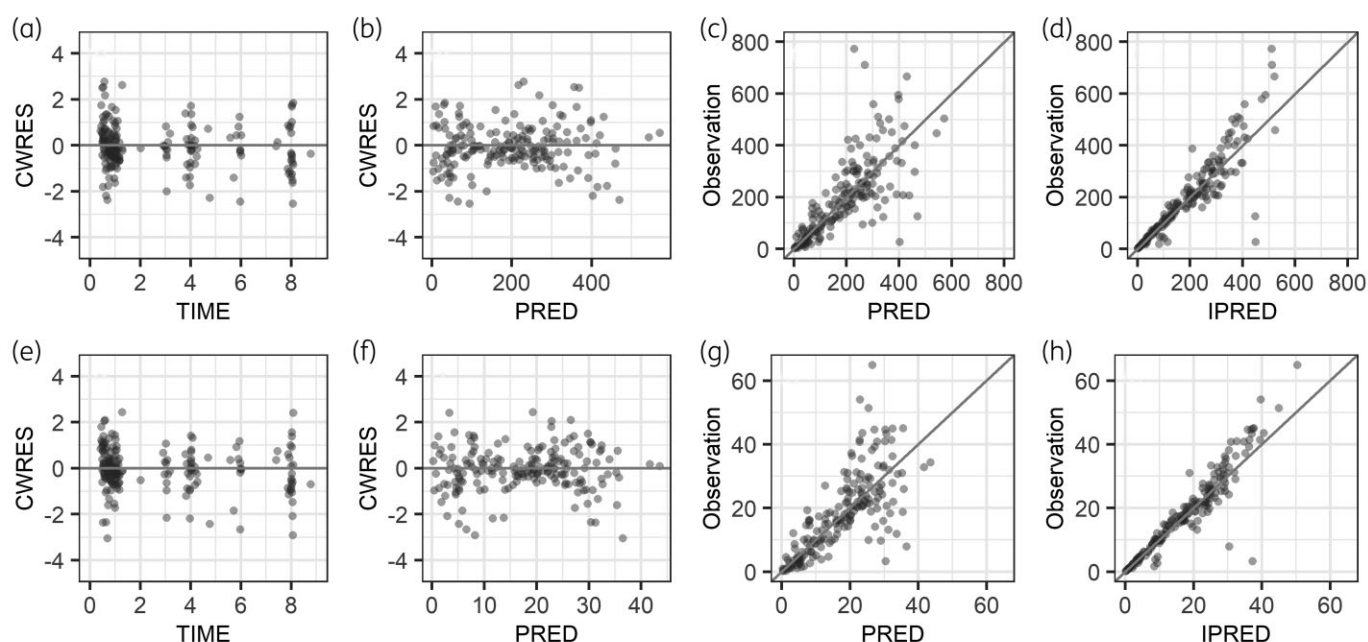
### Population PK analysis

A total of 226 plasma samples were used for the population PK model for piperacillin/tazobactam. One tazobactam concentration below the LLOQ was excluded from the analysis. Both the time courses of piperacillin/tazobactam concentrations were best described by two-compartment models. The structural PK parameters for the two-compartment model were total CL,  $V_d$  for the central compartment ( $V_C$ ),  $V_d$  for the peripheral compartment ( $V_p$ ), and intercompartmental CL between  $V_C$  and  $V_p$  (Q), as indicated in Tables 2 and 3. Allometric scaling was applied to CL,  $V_C$ , Q, and  $V_p$ . The expression for the scaling was:

$$\theta_i = \theta_m \times \left( \frac{WT}{70} \right)^k$$

where  $\theta_i$  is the PK parameter value for a subject with a body weight of WT kg,  $\theta_m$  is the median parameter value for a subject with 70 kg, and *k* is the allometric coefficient, with a value of 0.75 for clearance terms and 1 for volume terms.

The between-subject variances (BSVs) were estimated for CL and  $V_C$  for piperacillin and tazobactam. The time course for individual observed, individual predicted, and population predicted concentrations are shown in Figure S1 for piperacillin and Figure S2 for tazobactam (available as Supplementary data at JAC Online). Estimated glomerular filtration rate (eGFR), calculated using the CKD-EPI equations based on cystatin C level,



**Figure 1.** Goodness-of-fit plots for piperacillin (top) and tazobactam (bottom): (a) and (e) conditional weighted residuals versus time, (b) and (f) conditional weighted residuals versus population predicted concentration, (c) and (g) observed concentration versus population predicted concentration, and (d) and (h) observed concentration versus individual predicted concentration.

was identified as a significant covariate for CL in the final PK model of piperacillin and tazobactam (Table 2 and Table 3, respectively). The presence of ECMO significantly decreased the  $V_C$  of both piperacillin and tazobactam.

Figure 1 represents diagnostic goodness-of-fit plots for the final PK model. Most CWRES and the concentrations were evenly distributed around the line of identity, indicating appropriate structural models for piperacillin and tazobactam and no bias in PK parameters. Figures S3 to S6 illustrate VPC<sub>PVC</sub> plots for piperacillin and tazobactam. The observed 90th, 50th, and 10th percentiles fell within the 95% CIs of the simulated 90th, 50th, and 10th percentiles, respectively, indicating that the final PK models appropriately describe the observed concentrations and have good predictive performance.

### PD target attainment

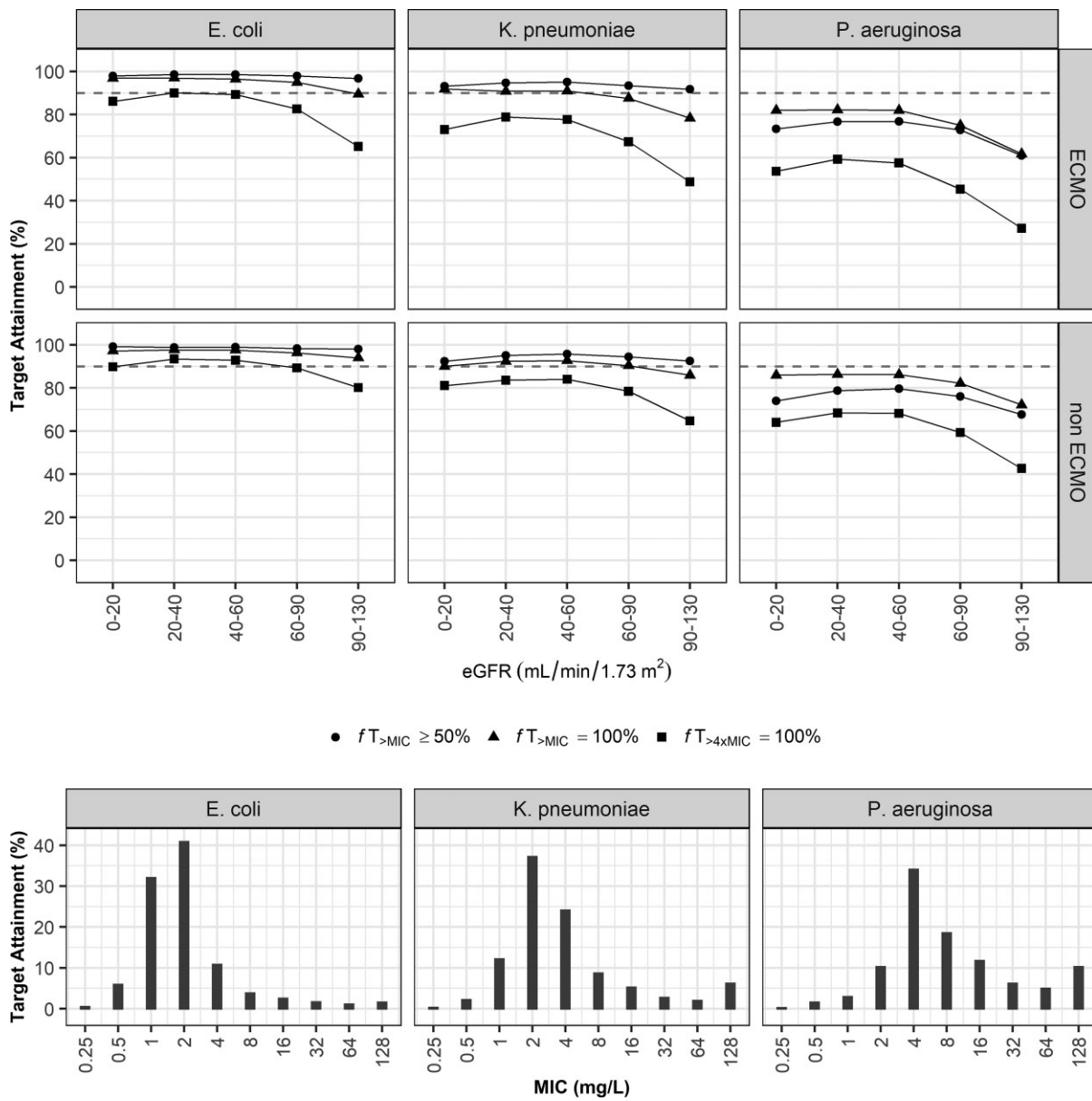
There was a trend toward lower PTA in patients using ECMO when antibiotics were used empirically. (Figure 2). Patients infected with *E. coli* attained a PTA  $\geq 90\%$  with the currently recommended dosage regimen, when the target was  $50\%fT_{>MIC}$ . Patients infected by *K. pneumoniae* also attained a PTA  $\geq 90\%$  with the recommended regimen, when the target was  $50\%fT_{>MIC}$ , whereas patients did not reach a PTA  $\geq 90\%$  when the target was  $100\%fT_{>4 \times MIC}$ . Patients infected by *P. aeruginosa* did not achieve a PTA  $\geq 90\%$  via the recommended regimen for all targets.

The PTAs for the target of  $50\%fT_{>MIC}$  with various combinations of renal functions, doses, two dosing intervals, three infusion times, and MICs are illustrated in Figure 3. For ECMO patients with an eGFR of 20–40 mL/min/1.73 m<sup>2</sup>, the

recommended dosage regimen of 3 g q6h by IV infusion over 0.5 h was optimal (PTA  $\geq 90\%$ ) when MIC was  $\leq 32$  mg/L. For non-ECMO patients with an eGFR of 90–130 mL/min/1.73 m<sup>2</sup>, the recommended dosage regimen of 4 g q6h by IV infusion over 0.5 h was optimal (PTA  $\geq 90\%$ ), when MIC was  $\leq 16$  mg/L. Figure 4 indicates PTAs for the target of  $100\%fT_{>MIC}$ . For ECMO patients with an eGFR of 90–130 mL/min/1.73 m<sup>2</sup>, the recommended dose of 4 g q6h by IV infusion over 0.5 h did not achieve a PTA  $\geq 90\%$  when MIC was  $\geq 4$  mg/L; however, the same daily dose, with prolonged infusion of 4 h, attained a PTA  $\geq 90\%$  when MIC was  $\leq 8$  mg/L, and the same daily dose, with continuous infusion, achieved a PTA  $\geq 90\%$  when MIC was  $\leq 32$  mg/L. For non-ECMO patients with an eGFR of 130–170 mL/min/1.73 m<sup>2</sup>, prolonged infusion for 4 h attained a PTA over 90% when MIC was  $\leq 4$  mg/L, and the same daily dose with continuous infusion achieved a PTA  $\geq 90\%$  when MIC was  $\leq 32$  mg/L. The PTAs for the target of  $100\%fT_{>4 \times MIC}$  are shown in Figure 5. For ECMO patients with an eGFR of 40–60 mL/min/1.73 m<sup>2</sup>, the recommended dose of 4 g q6h by IV infusion over 0.5 h did not achieve a PTA  $\geq 90\%$  when MIC was  $\geq 2$  mg/L. If continuous infusion was applied, the treatment target was achieved with the same daily dose when MIC was  $\leq 16$  mg/L. For non-ECMO patients, with an eGFR of 130–170 mL/min/1.73 m<sup>2</sup>, a dosage regimen of 4 g q6h by IV infusion over 0.5 h achieved a PTA  $\geq 90\%$  when MIC was  $\leq 0.25$  mg/L, while daily dose administration via continuous infusion attained the target when MIC was  $\leq 8$  mg/L.

### Discussion

ECMO can increase the  $V_d$  of hydrophilic drugs, and the  $V_d$  and CL of lipophilic drugs.<sup>26</sup> Fluid shift or systemic inflammation

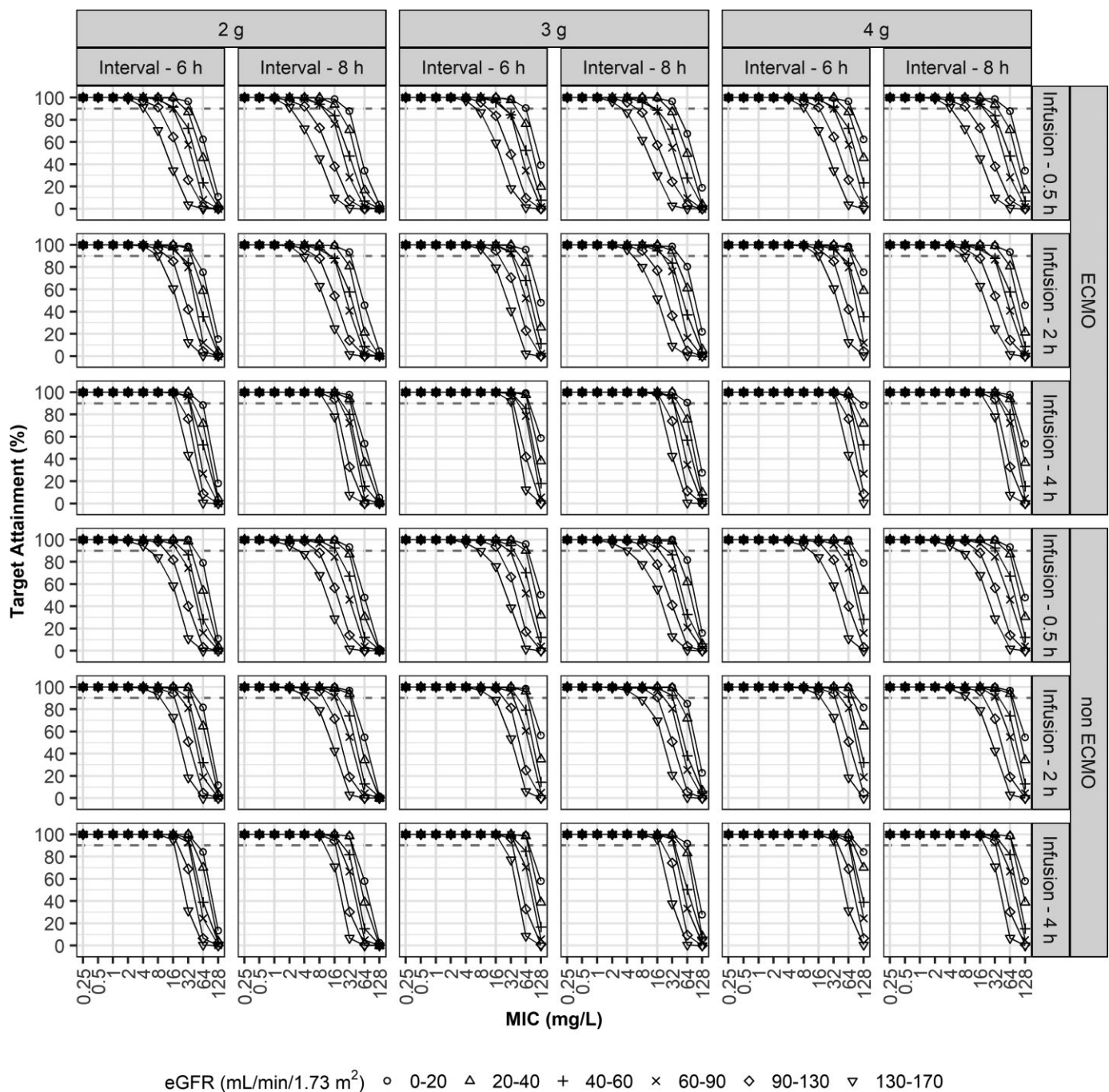


**Figure 2.** Probabilities of target attainment of empirical therapy by recommended dosing regimen for patients with creatinine clearance of 0–130 mL/min/1.73 m<sup>2</sup>. Bars indicate the MIC distribution for *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

response caused by critical illness and haemodilution or drug sequestration in the ECMO circuit can increase the V<sub>d</sub> of hydrophilic drugs such as piperacillin and tazobactam,<sup>27</sup> leading to decreased concentrations, and consequently, treatment failure.<sup>26,28</sup> Although a retrospective study found no difference in piperacillin PK between ECMO and non-ECMO cohorts, it was inadequate for supporting such a conclusion because it included only 14 patients.<sup>18</sup> In a recent prospective case–control study, ECMO use did not affect piperacillin/tazobactam PK. Despite being the largest study (including 21 patients on ECMO), it did not include any significant covariates such as renal function or ECMO use.<sup>20</sup> Contrary to the results reported thus far, our

population PK analysis, involving 19 ECMO and 19 non-ECMO patients, showed a decrease of the V<sub>c</sub> in patients on ECMO.

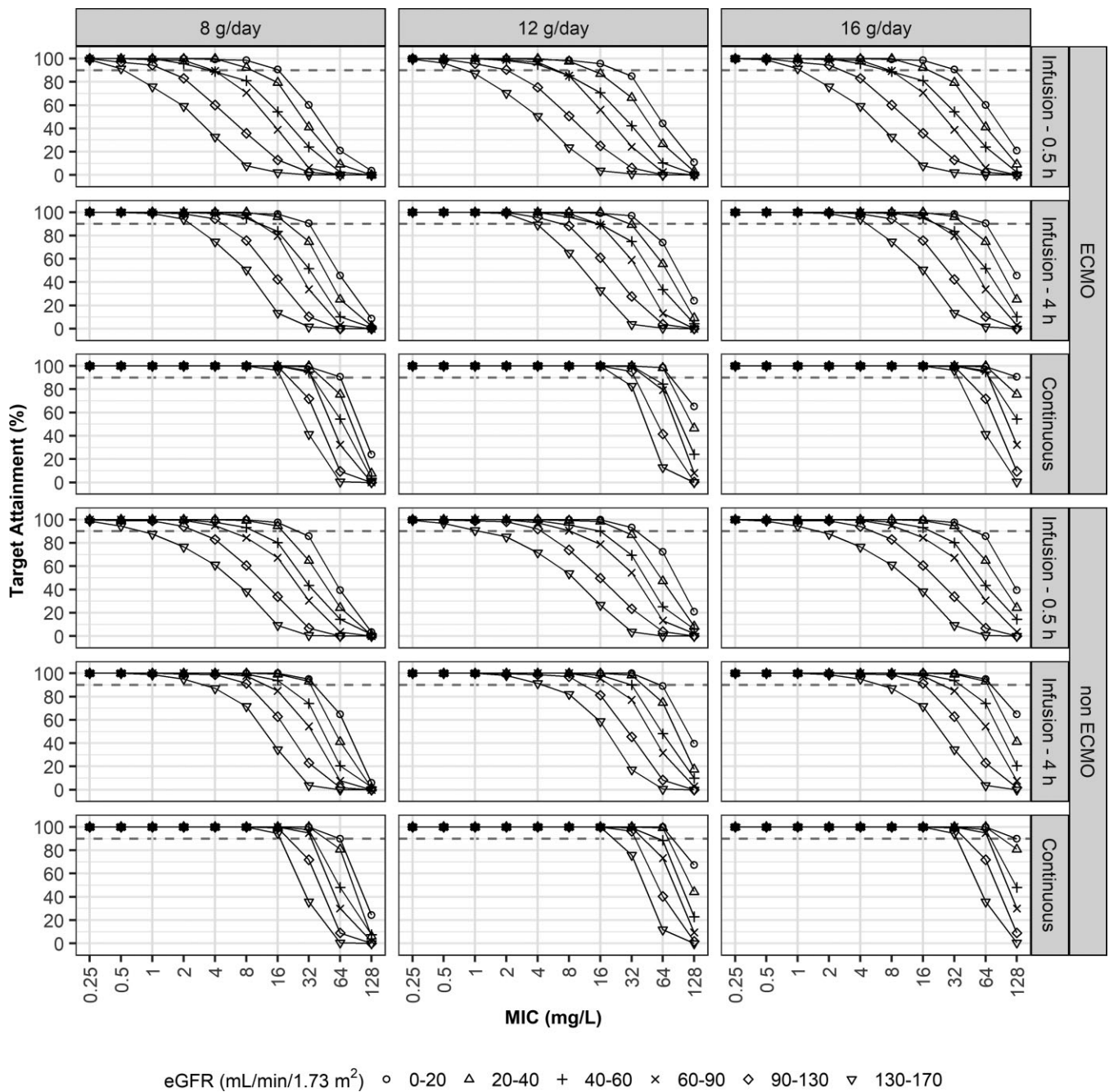
The PK of piperacillin/tazobactam were best described via a two-compartment model, with first-order elimination as in previous studies (Table 4). In our study, typical values of weight-normalised CL and V<sub>SS</sub> (V<sub>c</sub> + V<sub>p</sub>) of piperacillin for ECMO patients were 0.0867 L/h/kg and 0.195 L/kg, respectively. Those for non-ECMO patients were 0.0940 L/h/kg and 0.422 L/kg, respectively. These estimates are comparable to results of nine previous studies, wherein the median (range) of CL and V<sub>SS</sub> for adults were 0.108 (0.0418–0.231) L/h/kg and 0.271 (0.209–0.571) L/kg, respectively. A notable difference was that an ECMO-related V<sub>c</sub>



**Figure 3.** Probabilities of target attainment (50%  $fT_{>MIC}$ ). Simulation results in critically ill and patients with three doses (2, 3, or 4 g) and two dosing intervals (6 or 8 h), three infusion times (0.5, 2, or 4 h), various renal functions, and various MICs.

decrease was observed in our study. Although there have been many studies on the effect of ECMO on the PK of antimicrobials, there have been few studies on the effect of ECMO on the PK of piperacillin. We expected that the  $V_d$  of piperacillin would increase because piperacillin is a hydrophilic drug; however, the results of our population PK analysis showed the opposite. Since ECMO and non-ECMO patients were not matched cohorts, there were many statistically significant different factors when

comparing demographic factors, but ECMO use was identified as the only factor affecting the  $V_c$  in the stepwise covariate search of our population PK approach. The cause of the reduced  $V_d$  by the ECMO use seems to be the ECMO type. In our study, VA ECMO was applied to 18 of 19 patients, and it seems that these results were derived because non-pulsatile blood flow during VA ECMO reduced capillary blood circulation and tissue perfusion.<sup>37-39</sup> A recent population PK study of vancomycin in ECMO



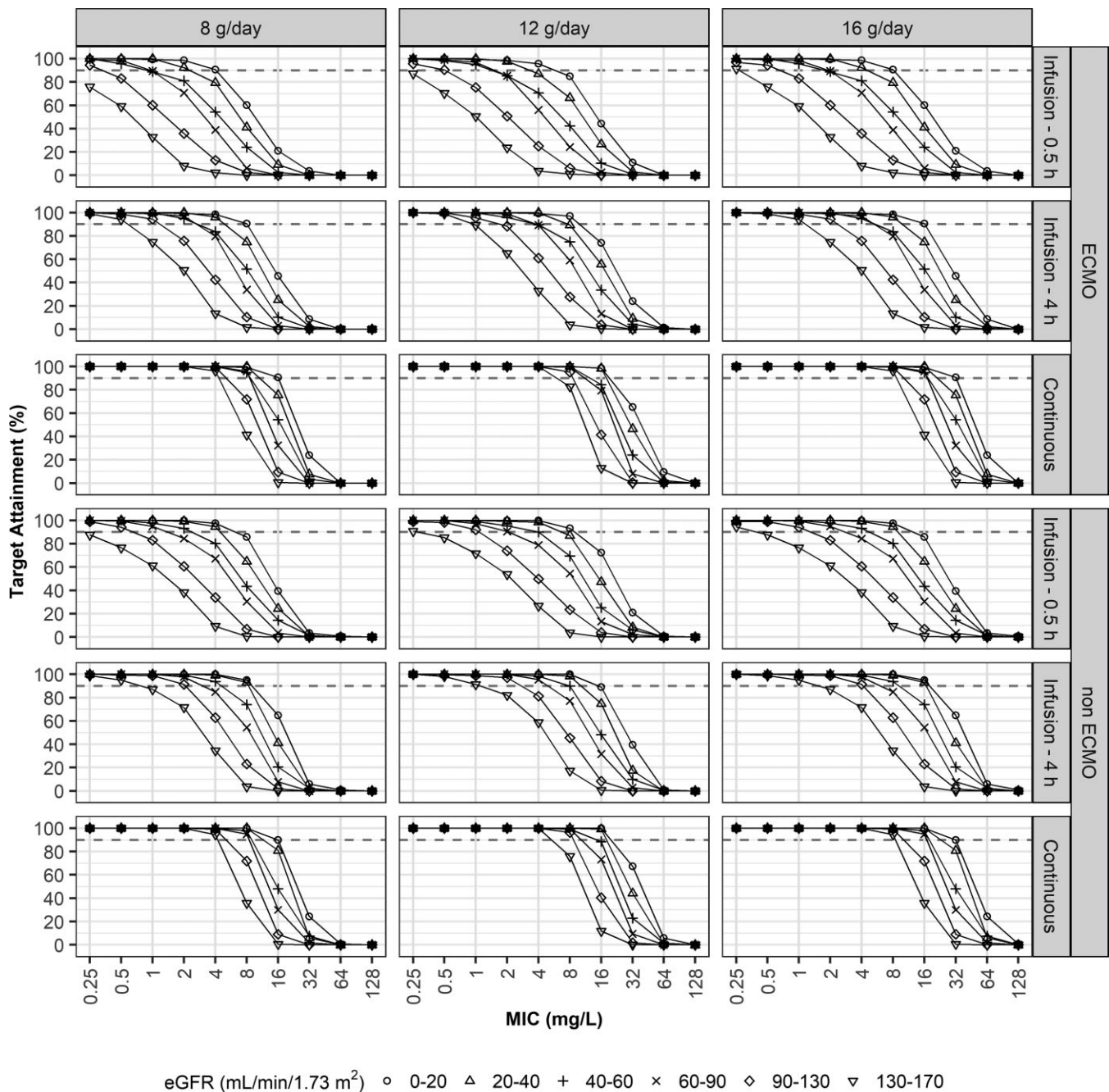
**Figure 4.** Probabilities of target attainment (100%  $fT_{>MIC}$ ). Simulation results in critically ill patients with three infusion methods (standard 30 min, prolonged 4 h, or continuous), various renal functions, and various MICs. The dosing interval was fixed to 6 h for intermittent infusion.

patients showed that VA ECMO reduced intercompartmental blood flow.<sup>40</sup> Since there have been only a few studies on the effect of ECMO type on PK, it is necessary to consider the ECMO type in future studies.

The results of the present study do not agree with those of previous studies on patients receiving ECMO support,<sup>15,18,20,41</sup> as in the present study, piperacillin/tazobactam PK was affected by ECMO. The strength of the present study derives from population PK modelling with a comparatively large number of patients

receiving ECMO ( $n=19$ ), rather than a sparse sample without population PK modelling.<sup>15,18,41</sup> Furthermore, the dosage regimen suggested by model-based simulations in our study has an important clinical implication. In contrast, the previous largest population PK study had no specific dose recommendations despite the insufficient achievement of target concentrations of piperacillin/tazobactam observed in ECMO patients.<sup>20</sup> The results of population PK model-based simulations to achieve  $\geq 90\%$  PTA at  $50\%fT_{>MIC}$  suggested that the current dosage regimen of





**Figure 5.** Probabilities of target attainment ( $100\% fT_{>4 \times MIC}$ ). Simulation results in critically ill patients with three infusion methods (standard 30 min, prolonged 4 h, or continuous), various renal functions, and various MICs. The dosing interval was fixed to 6 h for intermittent infusion.

piperacillin/tazobactam IV infusion over 30 min is not sufficient to treat *P. aeruginosa* infections, but is sufficient to treat *E. coli* or *K. pneumoniae* infections. To achieve  $\geq 90\%$  PTA at  $100\% fT_{>MIC}$  or  $100\% fT_{>4 \times MIC}$ , prolonged infusion over 4 h or continuous infusion over 24 h of 16 g/day should be considered, particularly when the MIC is above 8 mg/L or eGFR in patients is between 130–170 mL/min/1.73 m<sup>2</sup>. Our proposed dosage regimen is prolonged infusion over 4 h in patients without augmented renal clearance (ARC) and continuous infusion over 24 h in patients

with ARC, to achieve  $100\% fT_{>MIC}$  when MIC >8 mg/L (Figure 4). This dosage regimen should be validated in future clinical trials that include patients receiving ECMO. Additionally, whether infusion duration or a high dose regimen to achieve  $100\% fT_{>4 \times MIC}$  affects neurotoxicity associated with elevated piperacillin levels should be evaluated.<sup>42–44</sup> Studies have indicated a positive effect of prolonged or continuous infusion of piperacillin/tazobactam on clinical outcomes in critically ill patients.<sup>13,14</sup> Additionally, therapeutic drug monitoring

**Table 4.** Comparison of typical values of population pharmacokinetic parameter estimates for two compartment models of piperacillin<sup>a</sup>

Study	Age (years)	WT (kg)	CL <sub>CR</sub> (mL/min)	CL <sup>b,c</sup> (L/h/kg)	V <sub>C</sub> <sup>†</sup> (L/kg)	Q <sup>c</sup> (L/h/kg)	V <sub>P</sub> <sup>†</sup> (L/kg)	V <sub>SS</sub> <sup>†</sup> (L/kg)	Half-life (h)
Patel et al. <sup>29</sup>	53.2	71.3	91.6	0.184	0.187	0.377	0.0844	0.271	0.705
Asin-Prieto et al. <sup>30</sup>	57.0	74.0	43.0	0.108	0.282	0.277	0.289	0.571	1.82
Kim et al. <sup>31</sup>	69.0	58.2	47.0	0.119	0.335	0.0394	0.0646	0.400	1.95
Sime et al. <sup>32</sup>	61.0	78.0	94.0	0.231	0.183	0.257	0.0514	0.235	0.550
Andersen et al. <sup>33</sup>	57.0	76.0	83.9	0.113	0.163	0.0466	0.0458	0.209	1.00
Sukarnjanaset et al. <sup>34</sup>	60.0	56.6	54.9	0.0949	0.165	0.376	0.137	0.302	1.21
Ishihara et al. <sup>35</sup>	86.5	45.5	38.0	0.101	0.118	0.441	0.153	0.271	0.816
Bue et al. <sup>36</sup>	70.5	79.0	–	0.0418	0.0857	0.195	0.127	0.212	1.42
Fillatre et al. (ECMO) <sup>20</sup>	59.5	75.5	46.8	0.0664	0.233	0.0928	0.138	0.371	2.44
This study (ECMO)	58.0	70.0	72.5	0.0867	0.105	0.0897	0.090	0.195	0.840
This study (non-ECMO)	79.0	54.0	53.1	0.0940	0.306	0.116	0.116	0.422	2.26

<sup>a</sup>Abbreviations: Age, mean or median age; WT, mean or median weight; CL<sub>CR</sub>, mean or median creatinine clearance; CL, total clearance; V<sub>C</sub>, central volume of distribution; V<sub>P</sub>, peripheral volume of distribution; Q, intercompartmental clearance between V<sub>C</sub> and V<sub>P</sub>; V<sub>SS</sub>, steady-state volume of distribution.

<sup>b</sup>Piperacillin total clearance for a patient with the mean or median renal function of each study.

<sup>c</sup>If weight-normalized values were not reported, these values are pharmacokinetic parameter estimates divided by the mean or median of the reported weights.

(TDM)-guided use of piperacillin/tazobactam and dosing software to optimize piperacillin/tazobactam therapy have recently been studied.<sup>45–48</sup> Despite heterogeneity about prolonged or continuous piperacillin/tazobactam use, to achieve 100%  $fT_{>MIC}$  or 100%  $fT_{>4 \times MIC}$ , its TDM can be integrated into antimicrobial stewardship programmes as standard care for critically ill patients.<sup>49,50</sup>

Our study has some limitations. First, our study was not a matched cohort study. We simply collected drug concentrations from patients who received or did not receive ECMO. Nevertheless, no other covariates were selected and the ECMO use was found to be an important factor affecting V<sub>C</sub>. Second, we did not include fat-free mass in the covariate test, since we overlooked that the fat-free mass is an important indicator of alteration in body composition. We will consider the fat-free mass in future antibiotic PK studies. Third, we did not collect urine samples and could not quantitatively determine the renal clearance and non-renal clearance of piperacillin. Fourth, we did not build an integrated model of piperacillin and tazobactam that could provide more information about the PK profile of both the drugs. Because we did not administer only one drug (either piperacillin or tazobactam) to the patients, we could not build a more informative integral model for explaining the effect of the presence of one drug on the PK of the other. Fifth, our final PK model does not directly elucidate clinical outcomes.

This study describes the piperacillin/tazobactam PK profiles in critically ill adult patients with a two-compartment model, wherein the eGFR (calculated using the CKD-EPI equation based on cystatin C level) was a significant covariate for CL of both piperacillin and tazobactam. Moreover, the presence of ECMO decreased the V<sub>C</sub> of both piperacillin and tazobactam. Our simulation results suggest that the current dosage regimen of piperacillin/tazobactam may be suboptimal, considering the treatment target of 100%  $fT_{>MIC}$  or 100%  $fT_{>4 \times MIC}$ , particularly when the MIC is above 8 mg/L or when patients have an eGFR of 130–170 mL/min/1.73 m<sup>2</sup>. Since some patients did not achieve the treatment targets in previous studies,<sup>15,18,20,41</sup> we advocate

TDM using a PK model to realize individualized dosing and precision medicine.

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## Transparency declarations

None to declare.

## Supplementary data

NONMEM code and Figures S1 to S6 are available as Supplementary data at JAC Online.

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