# Covariate determinants of effective dosing regimens for time-dependent beta-lactam antibiotics for critically ill patients

Milan Kaska<sup>a,b</sup>, Eduard Havel<sup>a,b</sup>, Iva Selke-Krulichova<sup>b</sup>, Petr Safranek<sup>a</sup>, Jan Bezouska<sup>b</sup>, Jirina Martinkova<sup>a</sup>

**Aims.** Critically ill patients undergoing aggressive fluid resuscitation and treated empirically with hydrosoluble time-dependent beta-lactam antibiotics are at risk for sub-therapeutic plasma concentrations. The aim of this study was to assess the impact of two covariates – creatinine clearance (Cl<sub>cr</sub>) and cumulative fluid balance (CFB) on pharmacokinetics/pharmacodynamics (PK/PD) target attainment within a week of treatment with meropenem (ME) or piperacillin/tazobactam (PIP/TZB).

**Methods.** In this prospective observational pharmacokinetic (PK) study, 18 critically ill patients admitted to a surgical Intensive Care Unit (ICU) were enrolled. The primary PK/PD target was free antibiotic concentrations above MIC at 100% of the dosing interval (100% fT > MIC) to obtain maximum bactericidal activity. Drug concentration was measured using liquid chromatography-tandem mass spectrometry.

**Results.** The treatment of both 8 septic patients with IV extended ME dosing 2 g/3 h q8 h and 10 polytraumatized patients with IV intermittent PIP/TZB dosing 4.0/0.5 g q8 h was monitored. 8/18 patients (44%) manifested augmented renal clearence (ARC) where  $Cl_{cr} \ge 130 \text{ mL/min/1.73 m}^2$ .

Maximum changes were reported on days 2–3: the median positive CFB followed by the large median volume of distribution:  $Vd_{me}$ =70.3 L (41.9–101.5),  $Vd_{pip}$  = 46.8 L (39.7–60.0). 100%  $fT_{me}$ >MIC was achieved in all patients on ME (aged ≥60 years), and only in two patients (non-ARC, aged ≥65 years) out of 10 on PIP/TZB. A mixed model analysis revealed positive relationship of CFB<sub>pip</sub> with Vd<sub>pip</sub> (P=0.021).

**Conclusion.** Assuming that the positive correlation between CFB and Vd exists for piperacillin in the setting of the pathological state, then CFB should predict Vd<sub>Dip</sub> across subjects at each and every time point.

**Key words:** beta-lactam antibiotics, meropenem, piperacillin, pharmacokinetics/pharmacodynamics target, critically ill patient

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<sup>a</sup>Department of Surgery, University Hospital Hradec Kralove, Sokolska 581, 50005 Hradec Kralove, Czech Republic

<sup>b</sup>Academic Department of Surgery, Faculty of Medicine in Hradec Kralove, Charles University and Department of Surgery, University Hospital, Sokolska 581, 50005 Hradec Kralove, Czech Republic

Corresponding author: Milan Kaska, e-mail: kaskam@lfhk.cuni.cz

#### **INTRODUCTION**

Critically ill patients undergoing aggressive fluid resuscitation and treated empirically with hydro-soluble  $\beta$ -lactams piperacillin/tazobactam (PIP/TZB) and meropenem (ME) may be at risk for sub-therapeutic plasma concentrations as a result of non-attainment of PK/PD targets considered crucial for appropriate bactericidal action. The bactericidal effect of these antibiotics is time-dependent, expressed as % of time in the dosing interval (T) when the plasma concentration of the free drug (f) is elevated above the minimum inhibitory concentration (MIC) for the suspected pathogen – (%fT > MIC). Ideally, this should be 100% of the dosing interval with maximal bacterial killing achieved at concentrations > one MIC or bacterial eradication achieved at four to five times the MIC (ref.¹).

Nevertheless, PK/PD target attainment (the desired %fT>MIC) is dependent on pathophysiological factors (covariates) generated by changes in organ function during the course of the disease in critically ill patients. Extravascular volume expansion with fluid loading and increased capillary permeability may alter the volume

of distribution<sup>2</sup>, while changes in renal function can significantly influence drug renal clearance. This covariate might significantly influence hydrophilic drug Vd and could be a key factor for PK/PD target non-attainment. Therefore, its value could allow prediction of an individual loading dose compensating for extravascular fluid shift during the first days of therapy.

Another important value is the development of augmented renal clearance (ARC) – a phenomenon in which renal excretion of hydro-soluble beta-lactams is increased. ARC is defined by a creatinine clearance (Cl<sub>cr</sub>) more than or equal to 130 mL/min while plasma creatinine concentrations remain normal³. For the assessment of ARC, a cut-off of Cl<sub>cr</sub>  $\geq$ 130 mL/min normalized by the body surface area (BSA) calculated as weight (kg)<sup>0.425</sup> × height (cm)<sup>0.725</sup> × 71.84/10000 (ref.⁴) and was used based on previous data demonstrating an association with subtherapeutic ß-lactam concentrations, while using standard dosing¹.5,6. The ARC incidence in critically ill patients is high and varies between 30% and 85% (ref.⁵-9) depending on the population studied and the cut-off values used for its definition8,10.

Extravascular volume expansion assessed as positive cumulative fluid balance (CFB) was reported in ICU patients undergoing aggressive fluid resuscitation for prevention against hypotension and prolonged vasopressor use<sup>11,12</sup>. This covariate might significantly influence hydrophilic drug Vd and could be a key factor for PK/PD target non-attainment. Therefore, its value could allow prediction of an individual loading dose compensating for extravascular fluid shift during the first days of therapy.

The primary aim of this study was to verify the impact of covariates, mainly CFB and Cl<sub>cr</sub> on the PK/PD target attainment (%/T>MIC). 7-day monitoring was considered to be long enough to describe the two phases of IV fluid therapy namely Resuscitation and Optimisation aimed at correction of shock and maintenance of tissue perfusion, which are the most important for monitoring, as both intensity and treatment strategy should be individualized<sup>11</sup>.

#### MATERIALS AND METHODS

#### **Ethical consideration**

The study protocol was in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki, and was approved by the Ethics Committee of the University Hospital Hradec Králové, Czech Republic in June 27, 2012. All patients or their relatives signed the informed consent before inclusion in the study.

## **Study patients**

Enrolled in this prospective observational pharmacokinetic study were 18 critically ill patients admitted to the Surgical ICU of the University Hospital in Hradec Králové, Czech Republic. The inclusion criteria were a diagnosis of severe sepsis or septic shock or a systemic inflammatory response (SIRS), together with treatment with a broad-spectrum beta-lactam antibiotic meropenem (ME) respectively piperacillin-tazobactam (PIP/TAZ), provided that the patients signed the informed consent. Patients meeting any of the following criteria were excluded: age less than 18 years or more than 85 years, an expected ICU stay <24 h, allergy to any of the investigated antibiotics, any evidence of chronic kidney disease or renal replacement therapy, chronic liver disease (cirrhosis or ongoing liver dysfunction with hepatitis) (ref. 13,14). Participants were not allowed to receive any histamine-2-receptor antagonist due to interaction with tubular creatinine secretion<sup>15</sup>.

Patients were admitted to ICU on day 0. Administration of antibiotics was started on day 0 and plasma concentration monitoring was initiated on day 2 (after the fourth to fifth dose), except for patients who underwent some additional treatment (re-operation). In such a case, the start of monitoring was postponed to day 3-4.

The duration of antibiotic monitoring was related to ICU stay and was usually terminated on day 6-7 regardless of the duration of antibiotic treatment.

# Dose adjustement

Antibiotic dosing was administered according to local guidelines for empiric antibiotic therapy. ME was used in

the case of suspected colonization by extended spectrum beta-lactamase positive Gram-negative bacteria. Eight patients with peritonitis received an extended infusion dose of 2 g ME every 8 h given by 3 hours IV infusion using a syringe pump via a central venous catheter. Ten polytraumatized patients received empiric intermittent treatment with 4.0/0.5 g PIP/TAZ given by 1-h IV infusion every 8 h via the same way.

All patients were given IV fluid therapy with balanced crystalloids as early goal-directed therapy<sup>12</sup>. 24 hours (daily) fluid balance (DFB) was recorded as the difference between daily fluid intake and output and the CFB was calculated as the total volume of fluid accumulated over a set period of time<sup>11</sup>.

In all study patients, demographic, pre-existing chronic disease, admission diagnosis and biological data were collected in institutional databases. The severity of illness of each patient was characterized using the Acute Physiology and Chronic Health Evaluation (APACHE II) or the Injury Severity Score (ISS) (ref. 16) and sequential organ failure assessment (SOFA) (ref. 17). Treatment of patients with catecholamines and mechanical ventilation was recorded, as was duration of ICU and hospital stay. Hemodynamic data were collected as baseline, and 8 and 24 h after the start of the protocol.

#### Laboratory analysis

Serial blood samples were collected over days 2 to 7 as follows: pre-dose, and at 1, 2.5, 4.5 and 6.5 h post-dose for PIP/TAZ (PIP); pre-dose and at 1, 2.5, and 4.5 h postdose for ME. Specimens were centrifuged at 3.000 rpm for 10 min within 30 min of sampling, and then frozen at -80 °C until analysis. Via an indwelling urinary catheter, urine samples were taken at 0-T (over the postdose interval, i.e. between the end of infusion to the next dose administration), and as 24-hour urine collection. The samples were analysed at the Central Laboratory of Clinical Chemistry Department, University Hospital in Hradec Králové using the previously validated method based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) (ref. 18). The limits of detection of PIP and ME were 0.003 mg/L in plasma and urine. The calibration curves for both beta-lactam antibacterials were linear over the concentration range of 0.84-201 mg/L with correlation coefficient  $(r^2) = 0.999$ . The limit for quantification was 0.047 mg/L (for PIP) and 0.048 mg/L (for ME). Total plasma concentrations were measured. Correction for PIP protein binding (22%) was based on the published data<sup>19</sup>. Total plasma concentration of ME was not corrected as plasma protein binding is only 2% and considered not significant.

#### Pharmacokinetic analysis

Plasma and urine drug concentrations were used to estimate PK variables using the non-compartmental analysis as follows: the elimination rate constant ( $k_e$ ) was calculated by least-squares linear regression of the log-linear portion of the plasma concentration-time curves, and elimination half-life ( $t_{1/2}$ ) was calculated as  $0.693/k_e$ . The area under the plasma concentration-time curve

 $(AUC_{0:T})$  was obtained using the linear trapezoidal rule. Total (plasma, systemic) clearance  $(Cl_{tot})$  was estimated as dose/AUC<sub>0:T</sub> and renal clearance  $(Cl_{ren})$  as  $Au_{0:T}$ /AUC<sub>0:T</sub>, where  $Au_{0:T}$  is the amount of the antibiotic excreted in urine over the postdose interval. Volume of distribution  $(Vd) = Cl_{tot}/k_e$  (ref.  $^{20}$ ).

The 24-hour creatinine clearance (Cl<sub>cr</sub>) was measured every study day<sup>5</sup>. Cl<sub>cr</sub> =  $U_v \times U_{cr} / (1.440 \times S_{cr}) \times 1.73 \text{m}^2 / \text{BSA}$ , where  $U_v$  is urinary volume,  $U_{cr}$  the urinary creatinine concentration (µmol/L),  $S_{cr}$  is the serum creatinine concentration in the middle of a sampling period (µmol/L) (ref.<sup>5</sup>), and BSA is body surface area.

#### Pharmacodynamic analysis

The PK/PD target was free drug concentration maintained above the MIC of the suspected pathogen for 100 % of the dosing interval (100%/T > MIC target), where MIC is a hypothetical target (minimum inhibitory concentration) for the susceptibility breakpoint of the least susceptible microorganisms (wild-type *Pseudomonas* spp.) for which these antibiotics were used (according to EUCAST) (ref.<sup>21</sup>) in accordance with previous studies<sup>5,9</sup>.

#### PK/PD target attainment

The percentage time of the free fraction above the MIC (%fT>MIC) was evaluated by a graphical method<sup>22</sup> or calculated using a mathematical expression<sup>23</sup>.

This was defined as  $\%f\rm T_{pip}$  >MIC (16 mg/L) for PIP and  $\%f\rm T_{me}$  > MIC (2 mg/L) for ME.

#### Clinical response testing during the clinical study

- a) Definition of treatment outcome: a/ Positive treatment outcome was completion of the treatment course without change or addition of antibiotic therapy or commencement or additional antibiotics within 48 h of discontinuation of the antibiotic therapy.
- b) The disappearance of all signs related to aseptic or septic SIRS, or improvement in the form of marked or moderate reduction in their severity and number of signs. Clinical parameters of SIRS were evaluated according to SOFA main symptoms: respiratory parameters (FiO<sub>2</sub>, PaO<sub>2</sub>, and ventilation style), blood parameters (platelets),

liver function (bilirubin), central nervous system condition (GCS), cardiovascular parameters (MAP), vasopressors administration, kidney functions (serum and urine creatinine, urine output) – all at the start and on the end of the study.

c) Hemodynamic monitoring and testing the organ functions and return to the normal tissue perfusion: physical examination and review of observations such as peripheral perfusion, oedema, oxygen saturation, and ECG. A daily fluid balance that could be in equilibrium or even negative by the study end (day 7). Fluid balance was considered the essential biomarker of critical illness.

#### Statistical analysis

Continuous data are presented as the median (interquartile range). Statistical software package – Sigma Plot 13 SPSS, Inc. Chicago, IL, USA was used for comparison of data between groups and intra-patient data by means of non-paired and paired t-test.

#### **Identification of covariates**

Statistical analysis was performed using the NCSS 9 software - Hintze, J. (2013) NCSS 9. NCSS, LLC. Kaysville, Utah, USA, www.ncss.com (ref.<sup>24</sup>). To evaluate changes in both %fT and Vd during antibiotic treatment and the impact of CFB and Cl<sub>cr</sub>, we used mixed effect models - a general procedure, which allows for repeated measurements. For MER, the day of treatment was entered as a categorical fixed effect, with CFB and Cl<sub>cr</sub> as covariates. The variable patient was entered as a random effect.

For PIP, the variable day of treatment was entered as a possible covariate together with CFB. The distribution of  $\text{Cl}_{cr}$  values enabled us to divide them into two categories: below 130 mL/min/1.73m² and above this value – and enter  $\text{Cl}_{cr}$  as a factor. The patient x time interaction represented the random model. The significance of the fixed components was tested with an F-test adjusted by Kenward – Roger correction. The significance level was  $P \ge 0.05$ . If appropriate, Bonferroni adjustment for multiple tests was used.

**Table 1.** Baseline demographic characteristics and prognostics scoring systems and systemic therapies.

Variable	Polytrauma	Peritonitis
	(n=8)	(n=10)
Age (years) <sup>+</sup>	53.7 (±16.5)	69.0 (±10.8)
M/F(n)	6/4	8/0
Body weight (kg) <sup>+</sup>	80.5 (±10.4)	84.1 (±15.2)
$BMI^+$	27.1 (±3.1)	27.1 (±3.5)
ISS (points)*	29.5 (25.0-75.0)	-
APACHE II (points)*	-	24 (18.0-27.0)
SOFA (points) *	7.5 (3-14)	8.0 (3-16)
Vasopressor – noradrenaline IV (μg/kg/h) *	13.2 (0-62.5)	19.6 (0-51.3)
Artificial ventilation time (h)*	110 (15-744)	62 (0-341)

M-male, F-female, \*data given as mean (±SD), \*data given as median (range)

## **RESULTS**

18 patients were enrolled after admission to the Surgical ICU of the University Hospital in Hradec Králové, Czech Republic. The reason for admission was abdominal sepsis (n=8) or polytrauma manifesting SIRS (n=10) (Table 1). Patients suffering from abdominal sepsis were treated with ME and polytraumatized patients were given PIP. Prospective data collection was conducted on study days (over 2-7) dependent on therapeutic procedures (re-operation, special examination). Finally, the study days were stratified into 3 groups including day 2-3, 4-5, and 6-7, respectively.

Blood samples were taken as follows: one predose and

three postdose blood samples (for ME detection) were taken during 3 study days from 8 ICU patients. One predose and four postdose samples (for PIP detection) were taken during 3 study days in 5 ICU patients, and during 2 study days in 5 patients. In total 221 samples were analysed. Urine samples: single concentrations were obtained for each patient from urine collected over the postdose interval and a 24h – urine collection per study day. In total 104 urine samples were obtained and analysed.

Eight/18 patients (44%) manifested ARC ( $\rm Cl_{cr}$ >130 mL/min/1.73m²) – seven polytrauma subjects, one with sepsis. Three/8 patients manifested ARC on one occasion during the 7-study days, 5/8 patients on more than one occasion of  $\rm Cl_{cr}$  measurements.

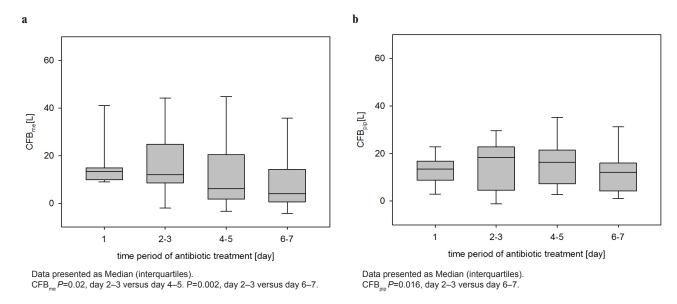
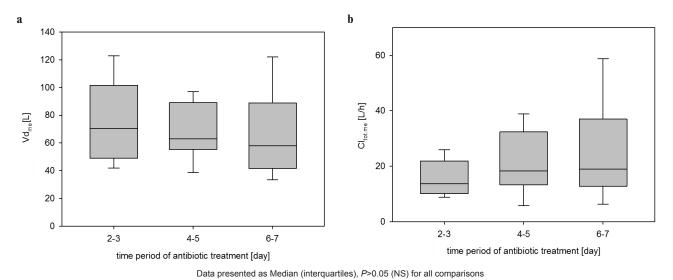
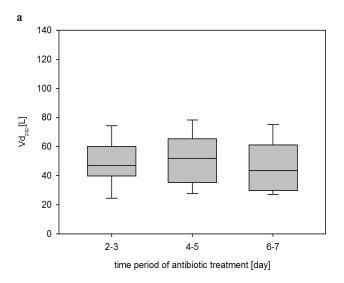


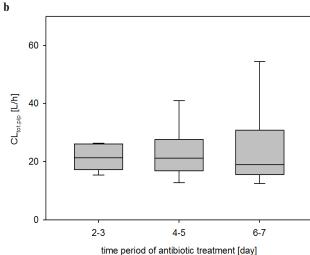
Fig. 1. Cumulative fluid balance (CFB) in a/ septic patients treated with meropenem (CFB<sub>me</sub>) and b/ polytraumatized patients treated with piperacillin/tazobactam (CFB<sub>pip</sub>) during 7 days.

CFB [L] measured as the difference between fluid input and loss results from increased vascular permeability and fluid loading. The extreme values in  $CFB_{me}$  were noticed in the patient with the initial  $Cl_{cr} = 9$  mL/min. The median  $CFB_{me}$  and  $CFB_{pip}$  reached a maximum on day 2-3 and slowly declined afterwards if fluid therapy was stopped and enhanced vascular permeability returned to a normal state.



**Fig. 2.** Meropenem a/ volume of distribution (Vd<sub>me</sub>) and b/ total clearance (Cl<sub>tot.me</sub>) estimated in septic patients treated with meropenem at extended infusion dosing 2 g over 3 h every 8 h for 7 days.





Data presented as Median (interquartiles), P>0.05 (NS) for all comparisons

Fig. 3. Piperacillin a/ volume of distribution ( $Vd_{pip}$ ) and b/ total clearance ( $Cl_{tot,pip}$ ) estimated in polytraumatized patients treated with piperacillin/tazobactam at intermittent dosing 4.0/0.5 g every 8 h for 7 days.

No polytrauma patient experienced reduced renal function (Cl<sub>cr</sub><50 mL/min).

Among septic patients, 2/8 patients (25%) experienced normal renal function (50 mL/min> Cl<sub>cr</sub><120 mL/min), and 5/8 patients (63%) had abnormal renal function (Cl<sub>cr</sub><50 mL/min). One ARC subject was identified.

The median CFB<sub>me</sub> and CFB<sub>pip</sub> reached a maximum on day 2–3 and slowly declined afterwards when fluid loading was stopped and the high vascular permeability returned to a normal value (Fig. 1a, b). The large median Vd<sub>me</sub> was registered on day 2–3: 70.3 L (41.9–101.5) (Fig. 2a), i. e. 0.79 (0.63–1.0)L/kg. The median Cl<sub>tot,me</sub> was 15.0 L/h (12.0–20.8) on day 2–3 (Fig. 2b), while the median Cl<sub>ren,me</sub> reached only 44.5 % (28.0–54.5) of Cl<sub>tot,me</sub>. The median half-life of elimination (T<sub>1/2,me</sub>) reached 3.5 h on day 2–3, and subsequently 2.5 h on day 6–7 (P=0.029). The predefined target 100%/T > 2 mg/L was attained in all patients including 1/8 of patients who attained 4 MIC>100%/T<8 MIC, and 2/8 who experienced 100%/T>8 MIC. The median %/T was declining towards the termination of antibiotic monitoring (day 7).

The median CFB  $_{\rm pip}$  reached a maximum 18.2 L (4.6–22.8) on day 2–3 of treatment and slowly declined (Fig. 1b). Simultaneously the median Vd  $_{\rm pip}$  attained 46.8 (39.7–60.0) L, i.e. 0.63 (0.56–0.78)L/kg and slowly declined during next days of treatment (Fig. 3a). The median Cl  $_{\rm tot,pip}$  was 21.3 (18.4–24.3)L/h, and that of Cl  $_{\rm ren,pip}$  attained 17.6 (14.3–17.1) L/h – reached 72 (63–81)% of the former. No significant decrease in drug clearance occurred over a 7-day treatment. T  $_{\rm 1/2,pip}$  was reduced from 1.7 hour (on day 2–3) to 1.4 hour (on day 6–7) (P=0.043).

The predefined target 100%fT>16 mg/L was attained only in two non-ARC patients (aged 65 and 67 years). 50%fT and 30%fT were attained in 5/10 subjects and 3/10 subjects, respectively. Seven patients with sub-therapeutic plasma concentration were ARC subjects.

# The impact of two covariates - Cl<sub>cr</sub> and CFB on %fT and antibiotic Vd

The mixed model analysis of PIP data revealed a statistically significant difference in %fT $_{\rm pip}$  for two categories of Cl $_{\rm cr}$  (Cl $_{\rm cr}$ >130 mL/min and Cl $_{\rm cr}$ <130 mL/min) (P= 0.0018) (Table 2). Also, the analysis of ME data showed a significant inverse relationship between %fT $_{\rm me}$  and Cl $_{\rm cr}$ : %fT $_{\rm me}$  declined with elevated value of Cl $_{\rm cr}$  (P=0.012) (Table 3). There was non-significant relationship between CFB $_{\rm me}$  and Vd $_{\rm me}$  (P=0.10) (Table 3), while Vd $_{\rm pip}$  became much larger with a higher value of CFB (P=0.021) (Table 2).

#### **Clinical response to treatment**

- a. During patients ICU stay (terminated by day 7-10), there was no modification of antibiotic therapy.
- b. The initial clinical or laboratory data describing the patient states are given in Table 1. By the end of 7-day monitoring the score value of SOFA median (range) in patients suffering from polytrauma dropped as follows 7.5 (3–14) to 2 (2–9), *P*<0.001 and in abdominal peritonitis 8 (3–16) to 2.5 (0–8), *P*<0.001.

No patient died within the stay in the ICU so as later.

# **DISCUSSION**

This study demonstrates significant higher values of the Vd of both betalactam antibiotics given to the ICU patients if compared with data reported for healthy volunteers or less seriously ill patients  $^{25-28}$ . The impact of age and decreasing  $\text{Cl}_{\text{cr}}(\text{ref}.^{29})$  was noticed in renal clearance estimation. Values of the median  $\text{Cl}_{\text{tot,me}}$  and that of  $\text{Cl}_{\text{tot,pip}}$  were higher than that estimated in healthy volunteers  $^{30}$ , and compatible with patients 'data  $^{31}$  in the septic patients > 60 year old,  $\text{Cl}_{\text{ren,me}}$  reached only 44.5% of  $\text{Cl}_{\text{tot,me}}$  and indicated the augmented extrarenal clearance in critically

**Table 2.** Piperacillin. Description of fixed effects in models for  $\%fT_{pip}$  and  $Vd_{pip}$ .

Effect Name	Effect Estimate (Beta)	Effect Standard Error	P	95% CI	
				Lower Limit	Upper Limit
Fixed effects for $%fT_{pip}$					
Intercept	28.52	8.96	0.005	9.81	47.23
Day of treatment	0.41	1.44	0.777	-2.61	3.43
CFB	1.26	0.34	0.001	0.55	1.97
$Cl_{cr} \le 130 \text{ mL/min}$	20.70	5.71	0.002	8.75	32.65
$Cl_{cr} > 130 \text{ mL/min}$	0	0			
Fixed effects for Vd <sub>pip</sub>					
Intercept	0.47	0.17	0.012	0.11	0.83
$Cl_{cr} \le 130 \text{ mL/min}$	-0.03	0.12	0.832	-0.27	0.22
$Cl_{cr}^{cr} > 130 \text{ mL/min}$	0	0			
Day of treatment	-0.01	0.03	0.708	-0.07	0.05
CFB	0.02	0.01	0.021	0.00	0.03

**Table 3.** Meropenem. Description of fixed effects in models for  $\%fT_{me}$  and  $Vd_{me}$ .

Effect Name	Effect Estimate	Effect Standard Error	P	95% CI	
	(Beta)			Lower Limit	Upper Limit
Fixed effects for %fT <sub>me</sub>					
Intercept	514.38	112.82	0.003	247.31	781.46
day of treatment = 2	-64.16	71.43	0.384	-217.17	88.85
day of treatment = 4	63.89	67.12	0.359	-81.08	208.85
day of treatment = 6	0	0			
Cl <sub>cr</sub>	-4.51	1.30	0.012	-7.63	-1.39
CFB	6.49	2.87	0.071	-0.78	13.76
Fixed effects for Vd <sub>me</sub>					
Intercept	25.82	23.86	0.319	-31.81	83.45
day of treatment = 2	2.06	13.97	0.884	-27.64	31.77
day of treatment = 4	-6.22	12.38	0.624	-32.96	20.53
day of treatment = 6	0	0			
$\operatorname{Cl}_{\operatorname{cr}}$	0.44	0.26	0.150	-0.22	1.10
CFB	1.24	0.61	0.105	-0.38	2.85

ill older patients also reported by others<sup>25</sup>. This outcome is considered a consequence of increased exposure to dehydropeptidase 1, causing nonspecific hydrolysis in tissue to an inactive metabolite<sup>27</sup>.

The primary PK/PD target were free antibiotic concentrations above the MIC at 100% of the dosing interval (100%/T > MIC). As demonstrated above, 7-study day monitoring revealed that intermittent dosing 4.0/0.5 g q8h of PIP, and extended infusion dosing 2.0 g/3 h q8h of ME was sufficient for obtaining this predefined exposure in non-ARC patients aged  $\geq$  60 year, approximately, but was not achieved in younger ARC patients in accordance with previous reports  $^{5,27}$ . If fourfold the MIC is the target of intervention, then  $\%/T_{\rm me}$  ranges 40–100 % with low values within 40–70% attributed to 3 patients with normal or augmented renal clearance. Accordingly,  $\%/T_{\rm pip}$  is within 8–26%.

This failure after conventional dosing is considered a result of sub-therapeutic plasma concentration-time profiles and changes in PK parameters (Vd and Cl), affected by two main covariates: Cl<sub>cr</sub> and positive CFB. Positive CFB (reflecting extravascular volume expansion) results from increased capillary permeability and IV fluid loading

which is widely regarded as the first step in the resuscitation of critically ill and injured patients who have evidence of impaired organ perfusion. The present study shows a rapid increase in *CFB* during days 0-1 culminating on days 2-3, that is followed by a large value of Vd of ME and PIP. A normal value of Vd reflecting both the dose and extracellular distribution usually ranges 0.2-0.4 L/kg. In a pathological setting this value can exceed the real extracellular fluid volume as a result of higher penetration into intraabdominal and pulmonary tissues, skin or peritoneal fluids, or may reflect higher tissue binding<sup>25,32</sup>. Thus positive CFB underlines the importance of individual dosing that would compensate an intravascular drug deficit due to extravascular volume expansion.

This study also denotes the impact of two pathological models – polytrauma and sepsis – on kinetic variables mediated via the covariates. CFB correlated with  $Vd_{pip}$  (in polytraumatized patients) while not with  $Vd_{me}$  (in sepsis). This difference can be attributable to the patient (age, renal function), to the properties of a drug and especially to the pathological setting. It seems that positive correlation between CFB and Vd does not develop in the pathological state suppressing renal functions as shown via  $Cl_{cr}$ 

Therefore, we cannot exclude a significant relationship between  $CFB_{me}$  and  $Vd_{me}$  that could be registered in a study conducted with numerous patients who experience normal or augmented renal clearance.

The influence of Cl<sub>cr</sub> may be bidirectional: high Cl<sub>cr</sub> predicts non-achievement of the predefined %fT (ref.<sup>5,22</sup>) and failure of antibiotic therapy as shown in patients treated with conventional dosing of piperacillin. Reduced Cl<sub>cr</sub> and consequent low antibiotic Cl<sub>ren</sub> can result in drug accumulation<sup>22,30</sup> and elevated %fT. Unfortunately, Cl<sub>cr</sub> was shown to be a covariate not predictive of variations in drug PK/PD target attainment in such setting<sup>33</sup>. Is CFB next covariate that should be taken into consideration as the predictor of the first (loading) doses and that presented by Cl<sub>cr</sub> as the predictor of next dosing adaptation?

#### Limitation

This study has a number of limitations. First, only a small number of patients were eligible, even if these subjects were monitored 2–3times a 7-day treatment. Secondly, %fT was based on 1-week empirical treatment with broad spectrum beta-lactams and MIC obtained from EUCAST, but de-escalation does not seem to resolve the problem of under-dosing. The probability that therapeutic exposure of critically ill patients would be achieved was shown even lower for narrower-spectrum antibiotics with conventional dosing than that for the broad-spectrum drugs<sup>34</sup>. Thirdly, the target attainment defined as 100%fT >MIC and/or 100%fT >4 MIC should be analysed since the first 24 h of treatment.

This aside, we believe that a more detailed analysis of the relationship between Vd a CFB and its practical use is worth studying next. Fluid balance as a predictor of drug Vd available at the bedside would help critically ill ICU patients, who require adequate dosing within 24 h after the start of treatment and /or next dose adaptation<sup>35</sup>.

# **CONCLUSION**

Assuming that the positive correlation between CFB and Vd exists for piperacillin in the pathological setting, then CFB should predict Vd across subjects at each and every time point. The authors recommend to use two times higher starting dose of piperacilin/tazobactam and 100% T > 4 MIC for PK/PD target attainment in critically ill patient undergoing aggressive fluid resuscitation than in standard type of patient.

#### **ABBREVIATIONS**

%/T, the percentage time during the dosing interval (T) where the free (unbound) drug concentration (f) remained above the MIC of the suspected pathogen; APACHE II, Acute physiology and chronic health evaluation II; ARC, Augmented renal clearance; AUC, Area under the curve; BSA, Body surface area; Cl<sub>ren</sub>, Renal clearance; Cl<sub>cr</sub>, Creatinine clearance; Cl<sub>tot</sub>, Total (plasma) body clearance; CFB, Cumulative fluid balance; DFB,

Daily fluid balance; EUCAST, European committee for antibiotic testing; GSS, Glasgow coma scale; ICU, Intensive care unit; k<sub>e</sub>, Elimination rate constant; ISS, Injury severity score; LC-MS/MS, Liquid chromatography coupled to tandem mass spektrometry; MAP, Medial arterial pressure; ME, Meropenem; MIC, Minimal inhibitory concentration; PIP, Piperacilin/tazobactam; PD, Pharmacodynamics; PK, Pharmacokinetics; S<sub>cr</sub>, Serum creatinine concentration; SIRS, Systemic inflammatory response syndrome; SOFA, Sequential organ failure assessment; Vd, Volume of distribution.

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Author contributions: As the principal investigator, MK had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis in tight cooperation with JM. Study concept and design were performed by EH, PS, and JM. Drafting of the manuscript was executed by MK and JM. ISK was focused on statistical analysis of results. JB cooperated in graphic tasks and IT processes. Critical revision of the manuscript was done by MK and JM. All authors checked and approved the final manuscript.

Availability of data and materials: All data, that is included in the analysis and from which the conclusions are drawn, are available in the Department of Surgery, Teaching Hospital, Sokolská 581, 50005 Hradec Králové, Czech Republic.

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