Early target attainment of continuous infusion piperacillin/tazobactam and meropenem in critically ill patients: A prospective observational study

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ABSTRACT

Purpose: To evaluate target attainment of empirically dosed continuous infusion piperacillin/tazobactam (TZP) and meropenem (MER) in critically ill patients.

Patients and methods: Patients were sampled on a daily basis. TZP or MER concentrations were evaluated during the first two days antibiotic therapy. The lower limit of the target range was defined as unbound concentrations equaling 4 times the epidemiological cutoff value of *P. aeruginosa*. The upper limit of the target range was based on the risk of toxicity, i.e. unbound concentrations >160 mg/L for TZP and > 45 mg/L for MER. Multivariable logistic regression was used to evaluate factors associated with target attainment.

Results: Data from 253 patients were analyzed. Overall, 76/205 (37.1%) and 36/48 (75%) of the patients receiving TZP or MER respectively, attained target concentrations. In multivariable analysis, estimated creatinine clearance was identified as a risk factor for target non-attainment (OR 0.988, 95%CI [0.982;0.994]). Patients receiving MER were more likely to attain target concentrations compared with patients receiving TZP (OR 6.02, 95%CI [2.12;18.4]).

Conclusion: Target attainment of empiric antibiotic therapy in critically ill patients was low (37%) for TZP and moderate (75%) for MER, despite the use of a loading dose and despite optimization of the mode of infusion.

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1. Introduction

Effective antibiotic therapy for the treatment of infectious diseases in critically ill patients is paramount to achieve a favorable clinical outcome. Failure of antibiotic therapy may occur for many reasons, for instance, infection with micro-organisms not susceptible to empirical therapy, lack of source control, patient-specific factors such as immunosuppression and subtherapeutic antibiotic concentrations [1-3].

From a clinical point of view, empirical antimicrobial drug dosing regimens should ideally achieve drug concentrations that are high enough to kill and prevent regrowth of all micro-organisms deemed susceptible to the drug, immediately after the first dose and at least until microbiology reports of the pathogen are available [4]. Once the microbiology report of the pathogen is available, changes to the type of antibiotic and/or, changes to antibiotic dosing can be considered.

Piperacillin/tazobactam (TZP), a penicillin derivative, and meropenem (MER), a carbapenem, are beta-lactam antibiotics commonly prescribed to treat serious infections in the ICU. As other beta-lactam antibiotics, TZP and MER are characterized by a time-dependent mode of action, i.e. their killing-properties depend on the time (T) free (f) concentrations remain above the minimal inhibitory concentration (MIC), i.e. $\%fT_{>MIC}$. Currently, experts are advocating for target concentrations of $100\%\,fT_{\geq 4 \times MIC}$, i.e. the PK/PD target [5].

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Obtaining target antibiotic concentrations with empirical dosing regimens in ICU patients is challenging as the PK of antimicrobial drugs may be profoundly altered during critical illness. A common occurrence in critically ill patients is the finding of increased renal clearance due to an increased cardiac output and an increased volume of distribution because of third spacing and hypoalbuminemia. For beta-lactam antibiotics specifically, both findings may substantially lower antibiotic concentrations [6]. Therefore, empirical dosing in critically ill patients is likely to be suboptimal when the altered PK of antimicrobial drugs is not taken into account. Low antibiotic concentrations have previously been linked to clinical failure and the emergence of antimicrobial resistance [7,8] while high concentrations have been linked to toxicity, which is mainly neurotoxicity in the case of beta-lactam antibiotics [9].

In this prospective observational study, it was our aim to evaluate the achievement of target concentrations in the context of empiric continuous infusion TZP and MER therapy in critically ill patients.

2. Patients and methods

2.1. Patients

This prospective observational study was conducted in the Department of Intensive Care Medicine of Ghent University Hospital (Ghent, Belgium). Ethical approval was obtained from the Ghent University Hospital Ethics Committee (registration number 2016/0264). The need for informed consent was waived by the Ethics Committee. Patients were eligible for inclusion if they were admitted to the surgical ICU and received either TZP or MER in continuous infusion. Patients younger than 18 years and patients receiving extracorporeal membrane oxygenation (ECMO) or renal replacement therapy (RRT) during antibiotic therapy were excluded from analysis. Only one antibiotic episode per patient (either TZP or MER) was recorded. TZP dosing was as follows: measured creatinine clearance (CL_{CR}) <15 mL/min: 8/1 g /24 h, CL_{CR} 15–29 mL/min: 12/1.5 g /24 h and for a CL_{CR} ≥ 30 mL/min 16/2 g/24 h was prescribed. MER dosing was as follows: CL_{CR} < 15 mL/min: 1 g /24 h, CL_{CR} 15–29 mL/min: 2 g /24 h and for a CL_{CR} ≥ 30 mL/min, a dosing regimen of 3 g /24 h was used. All patients received a loading dose, 4/0.5 g /30 min for TZP and 1 g /30 min for MER, immediately prior to the initiation of the continuous infusion regimen. CL_{CR} was determined by measuring urinary creatinine clearance concentrations in an 8-h urinary collection using an indwelling urinary catheter. Additional data such as additional biochemistry, demographic data, the modified Sequential Organ Failure Assessment score (SOFA), the Acute Physiology and Chronic Health Evaluation (APACHE II) score on admission ICU and hospital survival were prospectively recorded.

2.2. Bioanalysis of TZP and MER plasma concentrations

A residual sample of 3 mL blood gas tubes (lithium heparin blood gas tubes, Siemens, Tarrytown, USA) was sent to the core laboratory of the Dept. of Laboratory Medicine at Ghent University Hospital where they were first stored in a refrigerator at 4 °C until they were collected by the toxicology laboratory technicians. Storage at 4 °C was never longer than 24 h. After transferring to an Eppendorf tube, plasma samples were centrifuged at 16162 ×g for 8 min (Microfuge 16, Beckman Coulter, Brea, California). Immediately afterwards, the plasma samples were stored at −80 °C until analysis. All samples were analyzed within 3 months. The total (bound+unbound) plasma concentration of piperacillin (PIP) and MER was determined by ultra-performance liquid chromatography tandem mass spectrometry (UPLC – MS/MS). Tazobactam concentrations were not analyzed in this study. The lower limit of quantification (LLOQ) for PIP and MER was 1.5 mg/L and 1.1 mg/L respectively [10].

2.3. Definition of target attainment

The lower limit of the target window was defined based on the epidemiological cutoff value (ECOFF). The ECOFF of *P. aeruginosa*, one of the most common gram-negative bacteria isolated in ICU patients, was used for both TZP (ECOFF of 16 mg/L) and MER (ECOFF of 2 mg/L) [11,12]. These cutoff values represent a worst-case scenario for empirical dosing and are equal to the clinical breakpoints for *P. aeruginosa* as published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [11]. As the MIC value of an individual strain often poorly represents true antimicrobial susceptibility, Mouton, et al [13] have recommended to consider MICs from a distribution point of view for target attainment calculation in individual patients. An MIC result within a range of values with the epidemiological cut-off as upper limit, indicates that it is within the wild-type distribution. It is therefore reasonable to use the ECOFF as value to calculate target attainment for empirical dosing regimens. Therefore, a minimum unbound concentration of 100% $fT_{≥4xECOFF}$, i.e. 64 mg/L for TZP and 8 mg/L for MER, was adopted as lower limit of the target range as recommended by experts [5]. The percentage of target attainment with 100% $fT_{≥1xECOFF}$ and 100% $fT_{≥2xECOFF}$ as lower limit was also reported.

Despite the fact that beta-lactam antibiotics are usually considered to be safe, high concentrations may cause toxicity [9]. Quinton, et al [14] defined a threshold for neurotoxicity of 157 mg/L for TZP when infused continuously in ICU patients. To our knowledge, there is no data on toxicity of continuously infused MER. Imani, et al [9] evaluated intermittent infusion MER and correlated neurotoxicity to through concentrations (C_{min}) of 64.2 mg/L and nephrotoxicity to C_{min} levels of 44.45 mg/L for MER. Based on this data, an unbound TZP concentration of 160 mg/L and an unbound MER concentration of 45 mg/L was adopted as upper limit of the therapeutic window for both TZP and MER continuous infusion concentrations.

The achievement of target concentrations, i.e. unbound concentrations within the predefined target window, of empirically dosed TZP and MER was evaluated during the first 2 days (i.e. 48 h) of therapy, assuming that usually no or few microbiology results are available within this timeframe.

As we measured only total concentrations of both PIP and MER, analyses were performed with calculated free or unbound concentrations. We assumed a level of protein binding of 30% for PIP and 2% for MER, which was previously deemed appropriate [15,16].

2.4. Statistical analysis

All statistical analyses were performed using R (version 3.4.2; Institute for Statistics and Mathematics[http://www.r-project.org/])) and RStudio (version 1.1.383; RStudio, Inc. Boston, MA, USA). Continuous variables are presented as mean and standard deviation (SD) for normally distributed data and as median and interquartile range (IQR) for non-normally distributed data. Categorical variables are presented as percentages (%). The Students' *t*-test was used to compare normally distributed continuous variables, while the Mann-Whitney *U* test was used to compare non-normally distributed continuous variables. Differences between categorical variables were evaluated by the Pearson Chi-square test or Fischer's exact test as appropriate. The within-patient coefficient of variation (CV) was calculated by computing the standard deviation (SD)/mean ratio of all antibiotic concentrations per patient. Multivariable logistic regression was used to predict target attainment of empirical dosing TZP and MER within the first 2 days of therapy. Predefined predictors of target attainment were derived from TZP and MER PK/PD literature and included estimated creatinine clearance (Cockroft-Gault), total body weight, albumin concentration and APACHE II score [17-24]. Type of antibiotic (either TZP or MER) was also included as predictor. A *p*-value <0.05 was considered significant. Bootstrapping ($n = 1E5$) of the confidence intervals was undertaken

for internal model validation using the 'boot' package in R (https://cran.r-project.org/web/packages/boot/index.html).

3. Results

3.1. Patient characteristics

In total, 253 patients, 164 (64.8%) of which were male, were included for analysis. The mean (SD) age of the patients was 62.2 (15) years and the mean (SD) APACHE II score upon admission was 23.5 (8.4). Median (IQR) SOFA score was 5 (0–9). Median (IQR) CL_{CR} was 74.7 (31.1–128.9) mL/min. The majority of patients were admitted for surgical emergencies (50.6%), while 43.1%, 5.5% and 0.4% percent were admitted for medical emergencies, trauma or burns respectively. Of these 253 patients, 205 (81%) received TZP and 48 (19%) received MER. Out of all patients, 217 (85.6%) survived their ICU stay and 189 (74.7%) patients were alive at the end of their hospital stay. Free concentrations of continuous infusion PIP ranged from 11 mg/L to 422.8 mg/L, while free concentrations of continuous infusion MER ranged from 2.03 mg/L to 57.7 mg/L. Table 1 represents a univariable analysis of admission, demographic, laboratory and disease severity data for patients receiving TZP versus patients receiving MER. Patients receiving TZP weighed less, had a lower APACHEII score upon admission, a lower SOFA score at time of sampling, a lower estimated creatinine clearance, a shorter duration of therapy, a shorter length of ICU stay and a higher ICU and hospital survival when compared to patients receiving MER.

3.2. Target concentrations of empirical dosed TZP and MER during the first 2 days of therapy

Overall, 141 (55.8%) had one (or two) plasma samples with an antibiotic free concentration that did not fall within the predefined target window with 100% $fT_{\geq 4xECOFF}$ as lower limit, i.e. 64–160 mg/L and 8–45 mg/L for PIP and MER respectively. More specifically, 129 (62.9%) of the 205 patients receiving TZP and 12 (25%) of the 48 patients receiving MER had free concentrations outside the target range. These proportions (62.9% for TZP and 25% for MER) were significantly different ($\chi^2 = 21.16$, df = 1, p-value ≤0.001).

Most of the patients not achieving predefined target free concentrations had free concentrations below the lower limit of the target range, i.e. 120 out of 253 (47.4%) patients. More specifically, of the 129 TZP and 12 MER patients with free concentrations outside the predefined window, 110 (85.3%) TZP patients and 10 (83.3%) MER patients had one or more free concentrations below 64 mg/L for TZP and below 8 mg/L for MER.

According to univariable analysis, patients not achieving target free concentrations were younger, more likely to be trauma patients and more likely to survive their hospital stay. These patients also had a slightly lower APACHE II score upon admission, a lower SOFA score on the day of sampling, a lower serum creatinine, a larger positive fluid balance, a higher CL_{CR} and a higher estimated creatinine clearance (using the Cockroft-Gault formula) (Table 2).

When the lower limit of the target range was set to 100% $fT_{\geq 2xECOFF}$, the percentage of patients with free concentrations not within the target window was 18.2% (20.9% of the patients receiving TZP and 6.3% of the patients receiving MER). When 100% $fT_{\geq 1xECOFF}$ was defined as the lower limit, the percentage of the total number of patients that did not achieve target free concentrations within the predefined target range further dropped to 16.2%, with 19.5% for TZP patients and 2.1% for MER patients.

Multivariable logistic regression identified estimated creatinine clearance (Cockroft-Gault) as significant predictor of target attainment. Increasing creatinine clearance decreases the chances of achieving target free concentrations. Multivariable analysis also demonstrated that patients receiving MER were more likely to achieve target free concentrations when compared to patients receiving PIP. Other predefined variables (weight, APACHE II score and albumin) were no significant predictors of target attainment (Table 3).

4. Discussion

Achievement of target concentrations (unbound PIP concentrations between 64 and 160 mg/L and unbound MER concentrations between 8 and 45 mg/L) during the first two days of continuous infusion TZP (16/2 g /24 h) or MER (3 g /24 h) therapy was <40% for TZP and

Table 1
Univariable analysis of patients receiving piperacillin/tazobactam versus patients receiving meropenem.

Variable	TZP ($n = 205$)	MER ($n = 48$)	p-value
Age (yr), mean, SD	62.4 (15.5)	63 (12.7)	0.781
Gender, male (%)	129 (62.9%)	35 (72.9%)	0.192
Weight (kg), mean, SD	74.6 (16.1)	82.8 (18.7)	0.006
Height (cm), mean, SD	170.3 (15.1)	173 (9.8)	0.125
APACHE II, mean, SD	22.9 (8.1)	26 (9.3)	0.036
SOFA, median, IQR	4 (0–8)	7 (3–11)	0.005
Serum creatinine (mg/dL), median, IQR	0.8 (0.6–1.2)	0.8 (0.5–1.1)	0.371
CL_{CR} (mL/min), mean, SD	102.1 (63.3)	89.3 (82.4)	0.347
Estimated creatinine clearance (mL/min), mean, SD	95.4 (58.3)	117.8 (68.2)	0.034
Vasopressive therapy, yes (%)	0%	2.1%	0.093
Fluid balance (mL), mean, SD	1303.9 (1751.1)	1549.5 (1882.9)	0.413
Duration of therapy (days), median, IQR	3 (2–5)	5 (2–8)	0.013
ICU length of stay (days),	6 (3–12)	9 (4–19)	0.049
ICU survival (%)	181 (88.3%)	36 (75%)	0.017
Hospital survival (%)	164 (80%)	25 (52.1%)	<0.001
Admission category (%)			
Medical	82	27	0.059
Surgical	110	19	0.111
Trauma	13	1	0.48
Burns	0	1	0.190

CL_{CR} = measured creatinine clearance (mL/min). Estimated creatinine clearance was calculated using the Cockroft-Gault formula.

Table 2
Univariable analysis for patients (not) achieving target concentrations within the first 2 days of therapy.

Variable	Non-TA ($n = 141$)	TA ($n = 112$)	p-value
Age (yr), mean, SD	59 (16.2)	67 (11.9)	<0.001
Gender, male (%)	91 (64.5%)	73 (65.2%)	0.916
Weight (kg), mean, SD	76.3 (16.2)	76.1 (17.7)	0.912
Height (cm), mean, SD	172 (9.92)	169 (18.3)	0.096
APACHE II, mean, SD	22.2 (8.13)	25.1 (8.49)	0.007
SOFA, median, IQR	3 (0–7)	6 (0–11)	<0.001
Serum creatinine (mg/dL), median, IQR	0.69 (0.51–0.92)	0.89 (0.664–1.37)	<0.001
CL_{CR}, mean, SD (mL/min)	124.4 (74)	68.6 (40.5)	<0.001
Vasopressive therapy, yes (%)	0%	0.9%	1
Fluid balance (mL), mean, SD	978.3 (1591.5)	1819.1 (1888.3)	<0.001
Estimated CL_{CR}, mean, SD (mL/min)	112.8 (63.2)	83.1 (53.5)	<0.001
Duration of therapy (days), median, IQR	3 (2–5)	3 (2–6)	0.480
ICU length of stay (days), median, IQR	6 (3–14)	6 (3–13)	0.313
ICU survival (%)	126 (89.4%)	91 (81.3%)	0.067
Hospital survival (%)	116 (82.3%)	73 (65.2%)	0.002
Admission category (%)			
Medical	64 (45.4%)	45 (40.2%)	0.482
Surgical	64 (45.4%)	64 (57.1%)	0.084
Trauma	12 (8.51%)	2 (1.79%)	0.025
Burns	0 (0%)	1 (0.892%)	0.443

CL_{CR} = measured creatinine clearance (mL/min). Estimated creatinine clearance was calculated using the Cockroft-Gault formula. Non-TA = non-target attainment, TA = target attainment.

Table 3
Multivariable logistic regression for target attainment of empirically dosed piperacillin/tazobactam and meropenem.

Predictors	Coefficients (SE)	Odds ratio	Bootstrapped 95% CI for odds ratio	p-value
Estimated creatinine clearance (mL/min)	−0.012 (0.0029)	0.988	0.982;0.994	<0.001
Weight (kg)	−0.0067 (0.0009)	0.993	0973;1.01	0.436
Albumin (mg/dL)	−0.028 (0.023)	0.971	0.926;1.02	0.198
APACHE II score	0.0256 (0.018)	1.026	0.989;1.06	0.141
AB type	1.79 (0.501)	6.016	2.12;18.4	<0.001

SE = standard error, CI = confidence interval, Estimated creatinine clearance was calculated using the Cockcroft-Gault formula, AB type = type of antibiotic (TZP was coded 1 and MER was coded 2).
$R^2 = 0.16$ (Hosmer-Lemeshow), 0.2 (Cox-Snell), 0.261 (Nagelkerke). Model $\chi^2 = 54.6$, $p \leq 0.0001$.

approximately 75% for MER in a heterogeneous population of critically ill patients. Estimated creatinine clearance was identified as a risk factor for target non-attainment, which is in accordance with earlier findings [7,24].

Reaching therapeutic antibiotic concentrations in a timely manner is crucial when treating ICU patients with severe infections as inappropriate antibiotic dosing has been linked to adverse infection outcomes [4,5]. Critically ill patients, because of the profound PK alterations documented in these patients, are at risk for low target attainment when beta-lactam antibiotics are infused intermittently (i.e. bolus to 30 min i.v. infusion) [5,25]. Prolonging the duration of beta-lactam antibiotic infusion has shown the potential to achieve higher target attainment rates compared to intermittent bolus dosing [16].

The results of this study demonstrate that, even with continuous infusion, a significant number of ICU patients does not achieve target therapeutic free concentrations with standard doses of TZP. Likewise, colleagues Carrié, et al [26] documented that 19% of their patients receiving continuous infusion TZP (16 g/24 h) did not achieve free concentrations of 100% $fT_{>MIC}$. To the best of our knowledge, there is no data describing target attainment in ICU patients receiving continuous infusion meropenem during the first two days of therapy. In this study, patients receiving MER were more likely to achieve target unbound concentrations when compared with patients receiving TZP. Nevertheless, patients receiving MER did not have a significantly lower renal clearance when compared to patients receiving TZP (Table 1). While there is no consensus in literature, some authors have suggested that piperacillin has non-linear (as opposed to linear) kinetics and both active tubular secretion and glomerular filtration are considered to contribute to the renal elimination of this drug [27]. Colleagues Vinks, et al [27] documented a significantly higher piperacillin clearance during continuous infusion when compared with clearance during intermittent infusion in a cross-over PK study with eight cystic fibrosis patients. Following this hypothesis, extrapolating piperacillin drug clearance values from intermittent infusion dosing regimens may lead to over prediction of piperacillin concentrations when infused continuously. Active tubular secretion has also been documented for meropenem [28]. However, there are no PK studies at hand demonstrating saturable elimination of meropenem, indicating that saturation of meropenem elimination might not happen at clinically relevant concentrations.

To optimize target attainment rates of empirical beta-lactam dosing regimens during the initial phase of antibiotic therapy, several solutions are available. For example, software guided PK/PD dose-optimization uses population pharmacokinetic modeling combined with Bayesian forecasting to predict antibiotic concentrations [6,23]. This approach is able to estimate the effect of different patient covariates (e.g. creatinine clearance) on target attainment. When no previous antibiotic concentrations are available (e.g. when initiating therapy), this approach may allow us to use a more patient-tailored approach for empirical dosing. In recent studies, this approach has been improved by involving therapeutic drug monitoring (TDM) in the process [29]. PK/PD dosing software combined with TDM and adaptive feedback is probably even more suited to achieve and maintain target concentrations.

This strategy is especially useful for fine-tuning a dosing when therapy is initiated and as soon as antibiotic concentrations are available. It is important to note however that, at this time, there is no evidence of improved clinical outcomes when TDM of beta-lactam antibiotics is used.

This study has several limitations. First, the effect of inappropriate antibiotic concentrations in the early phase of sepsis or septic shock on clinical outcome was not assessed in this study, nor in the study by Carrié et al [26]. While delay of appropriate antibiotic therapy is expected to lead to adverse infection outcomes, a firm link between low beta-lactam antibiotic concentrations and inferior clinical outcome has not yet been demonstrated. In this study, the aim was to describe clinical target attainment of empirically dosed, continuously infused TZP and MER in ICU patients. Empirical dosing regimens are designed to achieve antibiotic concentrations high enough to kill all bacteria deemed susceptible to the drug and assuming a worst-case scenario when no MIC data is available is therefore a pragmatic approach [4].

For the purpose of this study, plasma concentrations were measured as a substitute for tissue concentrations. Infection usually occurs in the interstitial fluid of tissues and it is the concentration of TZP or MER that reaches the site of infection that is of importance. This is a significant limitation as in critically ill patients, tissue penetration may be variable and therefore therapeutic plasma concentrations do not necessarily predict therapeutic tissue concentrations [30].

Third, no unbound TZP or MER concentrations were measured. Only the unbound fraction of the antimicrobial drug is able to exert its antibacterial effect. Therefore, a level of 30% and 2% protein binding was assumed for TZP and MER respectively, which was previously deemed appropriate [15,16]. Also, there is little consensus on the preferred PK/PD target for beta-lactam antibiotics [5]. Carrié, et al [26] adopted a PD target of 100% $fT_{\geq MIC}$. However, the PD target of 100% $fT_{\geq MIC}$ should probably be regarded as a minimum target for continuous infusion as concentrations will be either above or below the MIC for the entire dosing interval when a PD target of 100% $fT_{\geq MIC}$ is applied. Last, because some blood gas tubes were thrown away by accident before they were sent to the laboratory of toxicology, especially when initiating the study, not all patients had samples available for analysis on all days of TZP or MER therapy.

In conclusion, achieving target therapeutic concentrations in critically ill patients with standard, empiric dosing of MER (3 g /24 h), and especially TZP (16/2 g /24 h), remains highly challenging, despite optimization of the mode of infusion.

Conflicts of interest

Jeffrey Lipman has been a consultant for MSD and Pfizer.

Jason A. Roberts has been a consultant for Accelerate Diagnostics, Astellas, Bayer, bioMerieux and MSD as well as having received investigator-initiated grants from MSD, The Medicines Company and Cardeas Pharma.

Jan J. De Waele has been consultant for Accelerate Diagnostics, Bayer Healthcare, MSD and Pfizer.

References

[1] Davey PG, Marwick C. Appropriate vs. inappropriate antimicrobial therapy. Clin Microbiol Infect 2008(14 Suppl 3):15–21.

[2] De Waele JJ, Lipman J, Carlier M, Roberts JA. Subtleties in practical application of prolonged infusion of β-lactam antibiotics. Int J Antimicrob Agents 2015;45:461–3.

[3] Micek ST, Welch EC, Khan J, Pervez M, Doherty JA, Reichley RM, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. Antimicrob Agents Chemother 2010;54:1742–8.

[4] De Waele JJ, Lipman J, Akova M, Bassetti M, Dimopoulos G, Kaukonen M, et al. Risk factors for target non-attainment during empirical treatment with β-lactam antibiotics in critically ill patients. Intensive Care Med 2014;40:1340–51.

[5] Delattre IK, Taccone FS, Jacobs F, Hites M, Dugernier T, Spapen H, et al. Optimizing β-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective? Expert Rev Anti Infect Ther 2017;15:677–88.

[6] Roberts J, Abdul-Aziz M, Lipman J, Mouton J, Vinks A, Felton T, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 2014;14:498–509.

[7] Sime FB, Udy AA, Roberts JA. Augmented renal clearance in critically ill patients: etiology, definition and implications for beta-lactam dose optimization. Curr Opin Pharmacol 2015;24:1–6.

[8] Claus B, Hoste E, Colpaert K, Robays H, Decruyenaere J, Waele J. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 2013;28:695–700.

[9] Imani S, Buscher H, Marriott D, Gentili S, Sandaradura I. Too much of a good thing: a retrospective study of β-lactam concentration-toxicity relationships. J Antimicrob Chemother 2017;72:2891–7.

[10] Carlier M, Stove V, Waele J, Verstraete A. Ultrafast quantification of β-lactam antibiotics in human plasma using UPLC-MS/MS. J Chromatogr B 2015;978–979:89–94.

[11] European Committee on Antimicrobial Susceptibility Testing (EUCAST). Version 8.0. Available from www.eucast.org; 2018.

[12] Bassetti M, Poulakou G, Ruppe E, Bouza E, Van Hal SJ, Brink A. Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach. Intensive Care Med 2017;43:1464–75.

[13] Mouton JW, Muller AE, Canton R, Giske CG, Kahlmeter G, Turnidge J. MIC-based dose adjustment: facts and fables. J Antimicrob Chemother 2017;73:564–8.

[14] Quinton M-CC, Bodeau S, Kontar L, Zerbib Y, Maizel J, Slama M, et al. Neurotoxic concentration of piperacillin during continuous infusion in critically ill patients. Antimicrob Agents Chemother 2017;61.

[15] Mouton JW, van den Anker JN. Meropenem clinical pharmacokinetics. Clin Pharmacokinet 1995;28:275–86.

[16] Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Piperacillin penetration into tissue of critically ill patients with sepsis–bolus versus continuous administration? Crit Care Med 2009;37:926–33.

[17] Alobaid AS, Wallis SC, Jarrett P, Starr T, Stuart J, Lassig-Smith M, et al. Population pharmacokinetics of piperacillin in nonobese, obese, and morbidly obese critically ill patients. Antimicrob Agents Chemother 2017;61.

[18] Crandon JL, Ariano RE, Zelenitsky SA, Nicasio AM, Kuti JL, Nicolau DP. Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Med 2011;37:632–8.

[19] Tsai D, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, et al. Optimising meropenem dosing in critically ill Australian indigenous patients with severe sepsis. Int J Antimicrob Agents 2016;48:542–6.

[20] Tsai D, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, et al. Pharmacokinetics of piperacillin in critically ill Australian indigenous patients with severe Sepsis. Antimicrob Agents Chemother 2016;60:7402–6.

[21] Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 2009;64:142–50.

[22] Öbrink-Hansen K, Juul RV, Storgaard M, Thomsen MK, Hardlei TF, Brock B, et al. Population pharmacokinetics of piperacillin in the early phase of septic shock: does standard dosing result in therapeutic plasma concentrations? Antimicrob Agents Chemother 2015;59:7018–26.

[23] Felton TW, Roberts JA, Lodise TP, Van Guilder M, Boselli E, Neely MN, et al. Individualization of piperacillin dosing for critically ill patients: dosing software to optimize antimicrobial therapy. Antimicrob Agents Chemother 2014;58:4094–102.

[24] Udy AA, Lipman J, Jarrett P, Klein K, Wallis SC, Patel K, et al. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? Crit Care 2015;19:28.

[25] Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014;58:1072–83.

[26] Carrié C, Legeron R, Petit L, Ollivier J, Cottenceau V, Houdain N d', et al.. Higher than standard dosing regimen are needed to achieve optimal antibiotic exposure in critically ill patients with augmented renal clearance receiving piperacillin-tazobactam administered by continuous infusion. J Crit Care 2018;48:66–71.

[27] Vinks AA, Den Hollander JG, Overbeek SE, Jelliffe RW, Mouton JW. Population pharmacokinetic analysis of nonlinear behavior of piperacillin during intermittent or continuous infusion in patients with cystic fibrosis. Antimicrob Agents Chemother 2003;47:541–7.

[28] Moon YS, Chung KC, Gill MA. Pharmacokinetics of meropenem in animals, healthy volunteers, and patients. Clin Infect Dis 1997;24(Suppl. 2):S249–55.

[29] Parker S, Sime F, Roberts J. Optimizing dosing of antibiotics in critically ill patients. Curr Opin Infect Dis 2015;28:497.

[30] Felton TW, Hope WW, Roberts JA. How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it? Diagn Microbiol Infect Dis 2014;79:441–7.