



Subtherapeutic piperacillin concentrations in neurocritical patients

Caroline Damen^{a,b,*}, Sofie Dhaese^a, Alain G. Verstraete^{c,d}, Veronique Stove^{c,d}, Jan J. De Waele^a

^a Department of Critical Care Medicine, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Gent, Belgium

^b Department of Internal Medicine, Elisabeth Tweesteden Hospital, Doctor Deelenlaan 5, 5042 AD Tilburg, the Netherlands

^c Department of Laboratory Medicine, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Gent, Belgium

^d Department of Diagnostic Sciences, Ghent University, Corneel Heymanslaan 10, 9000 Gent, Belgium

ARTICLE INFO

Keywords:

Subtherapeutic antibiotic concentrations
Beta-lactam antibiotics
Piperacillin/tazobactam
Critically ill
Neurocritical care

ABSTRACT

Purpose: Increased renal elimination is the leading cause for subtherapeutic concentrations of renally cleared antibiotics and it has been hypothesized that brain damaged patients in the intensive care unit (ICU) are particularly at risk. The objective of this study is to determine the prevalence of subtherapeutic piperacillin concentrations in neurocritical patients and to investigate if having a neurocritical diagnosis is a risk factor for this.

Materials and methods: Single center retrospective analysis of a prospective cohort study of adult ICU patients receiving continuous infusion piperacillin/tazobactam. Patients were categorized as either having a neurocritical diagnosis or not. An unbound piperacillin concentration > 4× the epidemiologic cut-off value (ECOFF) of *Pseudomonas aeruginosa* was selected as the PKPD target of choice. Multivariable logistic regression was performed to identify risk factors for subtherapeutic piperacillin concentrations.

Results: 356 patients had a measured creatinine clearance (mCrCl) and matched piperacillin concentration, 52 of which had a neurocritical diagnosis. Subtherapeutic piperacillin concentrations were reported significantly more frequent in neurocritical patients. In multivariate analysis, the only risk factor identified for subtherapeutic piperacillin concentration was an increasing mCrCl.

Conclusion: Subtherapeutic piperacillin concentrations are common in neurocritical patients yet having a neurocritical admission diagnosis was not identified as an independent risk factor.

© 2019 Elsevier Inc. All rights reserved.

1. Introduction

Infection and sepsis are common in critically ill patients and are a major cause of morbidity and mortality [1–3]. Early antibiotic treatment, source control and supportive therapy are the backbone of sepsis management [4–7]. Appropriate dosing of antibiotics is vital as it is likely to improve clinical cure and survival rates and may aid in limiting the spread of resistance [4,8]. Because of their broad antimicrobial spectrum and their low toxicity, beta-lactam antibiotics are frequently used as first line therapy in sepsis and septic shock [5].

Abbreviations: ICU, Intensive Care Unit; PK, Pharmacokinetics; ARC, Augmented Renal Clearance; SOFA, Sequential Organ Failure Assessment; TBI, Traumatic Brain Injury; SAH, Subarachnoid Hemorrhage; SICU, Surgical Intensive Care Unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; ECMO, Extracorporeal Membrane Oxygenation; RRT, Renal Replacement Therapy; mCrCl, Measured Creatinine Clearance; PDMS, Patient Data Management System; ICB, Intracranial Bleeding; iCVA, Ischemic Cerebrovascular Accident; ECOFF, Epidemiologic Cut-off Value; MIC, Minimum Inhibitory Concentration.

* Corresponding author at: Department of Critical Care Medicine, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Gent, Belgium.

E-mail address: cmf.damen@etiz.nl (C. Damen).

Subtherapeutic beta-lactam antibiotic concentrations are a common finding in critically ill patients [9]. Both pathogen and patient related challenges prevent achieving therapeutic concentrations with beta-lactam antibiotics [10]. Bacteria isolated in intensive care unit (ICU) patients in general are less susceptible to most antibiotics when compared with bacteria identified in samples from non-ICU patients [10]. Moreover, a large variability in the pharmacokinetics (PK) of beta-lactam antibiotics in ICU patients has been described [5,10]. Augmented renal clearance (ARC) is assumed to be the leading cause for under dosage of renally cleared drugs such as beta-lactam antibiotics, vancomycin or aminoglycosides [10–12]. Other risk factors for subtherapeutic antibiotic concentrations are higher total body weight, lower albumin levels, younger age, lower Sequential Organ Failure Assessment (SOFA) score and male sex [5,9].

It has been claimed that brain-damaged patients are particularly at risk of ARC [13]. Some studies suggest an unknown cytokine influences both, brain autoregulation and kidney autoregulation [6,14]. In patients with traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) a prevalence of ARC of >80% has been described [6,15]. In addition, a recent study showed that vancomycin clearance is higher in neurosurgical patients than in the general population and neurosurgery was the only

identified risk factor for this higher clearance even when corrected for risk factors for ARC [3].

The purpose of this study was to determine the prevalence of subtherapeutic piperacillin concentrations in patients where neurological disease or neurotrauma was the primary reason for ICU admission. The second aim was to explore if having a neurocritical diagnosis is an additional risk factor for low piperacillin concentrations, independently to the high risk of ARC in neurocritical patients.

2. Materials and methods

2.1. Study design and data collection

This was a single center retrospective analysis of a prospective collected database at the department of Critical Care Medicine of Ghent University Hospital. For this analysis, data were used from a prospective database of patients admitted to the surgical ICU (SICU) and receiving piperacillin/tazobactam in continuous infusion. All patients admitted to the SICU between March 2016 and April 2018 were screened for inclusion. Inclusion criteria were: admission to the SICU, administration of piperacillin/tazobactam in continuous infusion, a minimum age of 18 years old and the presence of an arterial line for sample collection. The need for written consent was waived by the ethics committee and blood samples were collected under opt-out sampling. This database did not contain patients receiving extracorporeal membrane oxygenation (ECMO) or renal replacement therapy (RRT) during antibiotic therapy. For the purpose of this specific study, patients without a measured creatinine clearance (mCrCl) were excluded from further analysis.

All patients received a loading dose of 4/0.5 g piperacillin/tazobactam over 30 min, the standard dosing regimen was 16/2 g piperacillin/tazobactam over 24 h and dose adaptations were made by the treating physician and based on mCrCl: <15 mL/min, 8/1 g/24 h; 15–29 mL/min, 12/1.5 g/24 h; >30 mL/min, 16/2 g/24 h. Data collected included demographic data (age, sex, race), biometric data (weight, height) and disease severity scores such as the “Acute Physiology and Chronic Health Evaluation II” (APACHE II) score upon admission and the SOFA-score on the day of sampling. ICU mortality and hospital mortality were registered.

Ethical approval was obtained from Ghent University Hospital Ethics Committee (Registration No. 2016/0264).

2.2. Defining neurocritical diagnosis

The diagnoses at admission were registered in the patient data management system (PDMS) by the treating physician. Patients were divided into two groups for analysis: a group of patients with neurocritical diagnosis and a control group of patients without neurocritical diagnosis. All patients with brain damage e.g. patients with TBI, SAH, intracranial bleeding (ICB), ischemic cerebrovascular accident (iCVA), status epilepticus, subdural hematoma, meningitis/encephalitis, brain edema, hydrocephalus and skull fractures were categorized as neurocritical patients.

2.3. Defining augmented renal clearance

ARC is defined as a clearance of >130 mL/min [10,16] and severe ARC as a clearance of >200 mL/min. An 8-hourly urinary collection using an indwelling urinary catheter was used to calculate the measured creatinine clearance. In critically ill patients, the mCrCl in the same patients may vary significantly over time [6,17]. If multiple samples were available for one patient, the sample with the highest mCrCl was selected for analysis as well as the antibiotic concentration and SOFA-score on the same day. The highest mCrCl was chosen to avoid missing subtherapeutic concentrations as increased renal clearance is the major risk factor for subtherapeutic beta-lactam concentrations [10–12].

2.4. Antibiotic target concentrations

Blood samples were collected during the daily morning routine to build the prospective database used for this study. A residual sample of the 3-mL blood gas syringes (RAPIDLyte; Siemens Healthcare Diagnostics Deerfield, IL, USA) was sent to the laboratory where they were stored at 4 °C until further processing [18]. Within 24 h, samples were transferred to a 1.5-mL Eppendorf tube, and centrifuged at 16162 xg for 8 min (Beckman Coulter, Brea, CA, USA) [18]. Immediately after centrifugation, plasma was collected and stored at –80 °C until analysis, which was performed within 3 months [18]. The plasma concentration of piperacillin was determined by ultrahigh performance liquid chromatography coupled with tandem mass spectrometry [19]. The lower limit of quantification for piperacillin was 1.5 mg/L [19].

An unbound antibiotic concentration of >4 x the epidemiologic cut-off value (ECOFF) was selected as the target of choice because this concentration is associated with maximal bacterial killing and a positive clinical outcome [5,20]. For piperacillin, the ECOFF and clinical breakpoint for *Pseudomonas aeruginosa* is 16 mg/L [21]. Because unbound piperacillin concentrations were not measured and an estimated 20% of piperacillin is bound to albumin, a measured total piperacillin concentrations <80 mg/L was considered as subtherapeutic [22].

2.5. Statistical analysis

Results were expressed as median and interquartile range for continuous variables unless otherwise stated, and as numbers and percentages for categorical variables. Comparison between continuous variables was done with the unpaired *t*-test or Mann-Whitney *U* test as appropriate and comparison between categorical variables was done with the Chi-square test. Multivariable logistic regression was performed to assess the influence of the variable risk factors on piperacillin plasma concentrations. For the regression, the following variables were included as predictor of low piperacillin concentrations: mCrCl, body weight, plasma albumin, sex, age and SOFA-score [4,5,9,23]. No collinearity was found between these risk factors as assessed by the variance inflation factor (VIF). All tests were two-tailed and a *p*-value <.05 was considered statistically significant. Statistical analysis was performed using the R language and software environment for statistical computation, version 3.5.0. [R Development Core Team (2018), Vienna, Austria. URL: <http://www.R-project.org>], the software package R studio, version 1.1.456 [RStudio Team (2016). Boston, USA. URL: <http://www.rstudio.com>] and the software packages car [<https://CRAN.R-project.org/package=car>] and generalhoslem [<https://CRAN.R-project.org/package=generalhoslem>].

3. Results

3.1. Demographic data

In total, 395 patients received piperacillin in continuous infusion and for 356 unique patients, a mCrCl and matched piperacillin concentration were available. Seventy five samples were collected the first day of therapy (between 0 and 24 h after starting piperacillin), 125 samples were collected the second day of therapy (between 24 and 48 h). One hundred fifty-six samples were collected after 48 h of therapy. Fifty-two patients had a neurocritical diagnosis of which 25 were admitted with (poly)neurotrauma, 11 with SAH, 10 ICB, 2 with iCVA, 1 with subdural hematoma, 1 with hydrocephalus, 1 with metabolic encephalopathy due to hyponatremia and 1 status epilepticus. The other 304 patients had various diagnoses but not a single neurocritical one: 177 patients were admitted with a surgical diagnosis, 120 with a medical diagnosis and 7 were trauma patients without traumatic brain injury.

Baseline demographic data are presented in Table 1. In univariate analysis, patients with a neurocritical diagnosis were significantly younger, had a significantly higher APACHE II score and had a significantly

Table 1
Demographic data of patients with a neurocritical diagnosis and patients with a non-neurocritical diagnosis.

TOTAL	Neurocritical	Other diagnosis	p-Value
N = 356	N = 52	N = 304	
Age (years)	54.5 (41.50 – 63.25)	66.0 (55.0 – 74.0)	<0.001
Male sex	30 (57.7%)	207 (68.1%)	0.14
Weight (kg)	74.6 (13.0)*	75.7 (18.3)*	0.62
Height (cm)	172 (10.4)*	171 (9.5)*	0.52
BMI (kg/m ²)	25.0 (3.9)*	25.6 (5.9)*	0.38
APACHE II	23.0 (20.8 – 26.0)	19.0 (15.0 – 26.0)	0.024
SOFA-score	6.0 (2.5 – 9.0)	5.0 (3.0 – 8.0)	0.45
Plasma creatinine (mg/dL)	0.62 (0.54 – 0.71)	0.77 (0.52 – 1.24)	<0.001
mCrCl (ml/min)	173 (121 – 208)	99 (56 – 153)	<0.001
Patients with ARC	36 (69.2%)	113 (37.2%)	<0.001
Patients with severe ARC	17 (32.7%)	32 (10.5%)	<0.001
Albumin (g/dL)	27.5 (3.8)*	23.6 (4.4)*	<0.001
Hospital mortality	12 (23.1%)	64 (21.1%)	0.74

Bold indicates statistically significant results.

* Mean (standard deviation).

higher albumin when compared with patients with a non-neurocritical diagnosis. Also, mCrCl was significantly higher in neurocritical patients and significantly more ARC and severe ARC was observed in the neurocritical group. Sex, weight, height, APACHE II, SOFA-score on the day of sampling and mortality were similar in both groups.

3.2. Subtherapeutic piperacillin concentrations

The prevalence of subtherapeutic piperacillin concentration was 51.4% (183/304); the median piperacillin concentration was 78.1 mg/L (IQR 52.2–126.1 mg/L). In univariable analysis, subtherapeutic piperacillin concentrations were more frequent in the group consisting of patients with a neurocritical diagnosis compared to patients with a non-neurocritical diagnosis (83% (43/52) vs. 46% (140/304), $p < .001$). In neurocritical patients, the median piperacillin concentration was 41.8 mg/L (IQR 31.1–70.7 mg/L) whereas in non-neurocritical patients it was 85.7 mg/L (IQR 58.0–134.5 mg/L, $p < .001$).

3.3. Risk factors for subtherapeutic piperacillin concentration in critically ill patients

Multivariate logistic regression analysis showed that having a neurocritical admission diagnosis was not associated with subtherapeutic piperacillin concentrations. The only risk factor identified for subtherapeutic piperacillin concentrations was mCrCl ($p < .001$). Body weight, sex, age, SOFA-score and albumin were not identified as risk factors for subtherapeutic piperacillin concentrations (Table 2). The goodness-of-fit-test was done with Hosmer-Lemeshow and the p-value was 0.66.

4. Discussion

This study demonstrated a high prevalence of subtherapeutic piperacillin concentrations in patients with a neurocritical diagnosis, admitted to the SICU. Nevertheless, having a neurocritical admission

Table 2
Risk factors for subtherapeutic piperacillin concentrations in the critically ill using multivariable logistic regression.

Characteristic	OR	95%-CI	p-Value
Neurocritical diagnosis	2.28	0.89–6.27	0.095
mCrCl	1.03	1.02–1.03	<0.001
Body Weight	1.02	1.00–1.04	0.067
Male Sex	1.40	0.73–2.72	0.31
Age	0.98	0.97–1.00	0.13
SOFA-score	0.96	0.89–1.03	0.21
Albumin	1.03	0.97–1.10	0.32

diagnosis was not found as an independent risk factor for subtherapeutic piperacillin concentrations. The only risk factor for subtherapeutic piperacillin concentrations identified in multivariable logistic regression was a higher mCrCl.

Recognizing patients at risk of subtherapeutic antibiotic concentrations is important as it may lead to antibiotic failure and a worse clinical outcome [4,24]. Having a neurocritical diagnosis has been linked to ARC and inadequate antibiotic concentrations in the past [13]. However, in this study we found that neurocritical diagnosis was not associated with subtherapeutic piperacillin concentrations. The presence of sepsis in a younger ICU patient should trigger the treating physician to obtain a mCrCl and consider the probability of subtherapeutic piperacillin concentrations, independently of the admission diagnosis.

The prevalence of subtherapeutic piperacillin concentrations is reported inconsistently in the literature, mainly due to the different designs of these studies (i.e. different antibiotic targets and modes of administration). For example, Aardema et al. [22] found that in the maintenance phase 57.6% of samples were below the target concentration of 80 mg/L. This is little higher than the prevalence of subtherapeutic piperacillin concentrations we found, but they used a standard dosing regimen of 12/1.5 g piperacillin tazobactam in continuous infusion after a loading dose of 4/0.5 g piperacillin tazobactam, which is lower than the dosing regimen we used [22]. Carrié et al. [26] used 16/2 g piperacillin tazobactam in continuous infusion as standard dosing regimen. They found that 19% of critically ill patients had subtherapeutic piperacillin concentrations, but the target concentration in this study was lower (16 mg/L) [26].

Another more recent study concluded that the vancomycin clearance is higher in neurosurgical patients compared with others even when corrected for risk factors for ARC [3]. This finding is potentially in line with our findings, because the study corrected only for risk factors for ARC and not for mCrCl. In this study mCrCl was used as a continuous variable because dichotomizing confounding variables (i.e. ARC yes or no) may result in an inflation of the type-I error rate [25].

The prevalence of ARC found in this study was lower than the prevalence described in previous studies of neurocritical subgroups [1,6,14,15]. A possible reason why we found a lower prevalence of ARC than previous studies is because instead of studying specific subgroups (such as patients with SAH or TBI), a mixed neurocritical population was studied.

This study has a number of limitations. First, no information about the organisms and MICs were available for analysis and it is therefore possible that the number of patients with subtherapeutic piperacillin concentrations were overestimated as the ECOFF (16 mg/L) of *Pseudomonas aeruginosa* was used to calculate target attainment. Also, only the unbound fraction of a drug at the site of infection is able to exert its antimicrobial effect [10]. As tissue perfusion in ICU patients may be highly variable, therapeutic plasma concentrations may not necessarily lead to therapeutic infections site concentrations [10].

Predicting antibiotic target attainment in critically ill patients is challenging as a lot of patient specific factors influence antibiotic concentrations. It is important to keep investigating which patient factors influence antibiotic target non-attainment and to explore the underlying pathophysiological mechanisms. By doing so, dosing regimens that are more tailored to patient-specific factors may be used in the future.

5. Conclusion

Subtherapeutic piperacillin concentrations in patients admitted to the SICU with a neurocritical diagnosis are common. Nevertheless, we were unable to demonstrate that having a neurocritical admission diagnosis is an independent risk factor for subtherapeutic piperacillin concentrations. The only risk factor tied to subtherapeutic piperacillin concentrations was a higher measured creatinine clearance.

Declaration of Competing Interest

None.

Acknowledgements

The authors wish to thank the nurses of the Department of Critical Care Medicine for their assistance in collecting the samples and the laboratory technicians from Ghent University Toxicology Laboratory for analyzing the plasma samples.

Funding

Sofie Dhaese is funded by a Centre of Research Excellence grant (APP1099452) from the National Health and Medical Research Council awarded to Jason A. Roberts. Jan De Waele is senior clinical investigator funded by the Research Foundation Flanders (FWO, Ref. 1881015N).

References

- [1] Udy AA, Jarrett P, Lassig-Smith M, Stuart J, Starr T, Dunlop R, et al. Augmented renal clearance in traumatic brain injury: a single-center observational study of atrial natriuretic peptide, cardiac output, and creatinine clearance. *J Neurotrauma* 2017;34(1):137–44.
- [2] Lord AS, Nicholson J, Lewis A. Infection prevention in the neurointensive care unit: a systematic review. *Neurocrit Care* 2018;31(1):196–210.
- [3] Kim AJ, Lee JY, Choi SA, Shin WG. Comparison of the pharmacokinetics of vancomycin in neurosurgical and non-neurosurgical patients. *Int J Antimicrob Agents* 2016;48(4):381–7.
- [4] Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. *Curr Opin Crit Care* 2015;21(5):412–20.
- [5] Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β -lactams. *Crit Care* 2011;15(5):R206.
- [6] Udy A, Boots R, Senthuran S, Stuart J, Deans R, Lassig-Smith M, et al. Augmented creatinine clearance in traumatic brain injury. *Anesth Analg* 2010;111(6):1505–10.
- [7] Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Crit Care Med* 2018;46(6):997–1000.
- [8] Timsit JF, Bassetti M, Cremer O, Daikos G, de Waele J, Kallil A, et al. Rationalizing antimicrobial therapy in the ICU: a narrative review. *Intensive Care Med* 2019;45(2):172–89.
- [9] Imani S, Buscher H, Day R, Gentili S, Jones GRD, Marriott D, et al. An evaluation of risk factors to predict target concentration non-attainment in critically ill patients prior to empiric β -lactam therapy. *Eur J Clin Microbiol Infect Dis* 2018;37(11):2171–5.
- [10] Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis* 2014;14(6):498–509.
- [11] Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís M. Augmented renal clearance in critically ill patients: a systematic review. *Clin Pharmacokinet* 2018;57(9):1107–21.
- [12] Barletta JF, Mangram AJ, Byrne M, Hollingworth AK, Sucher JF, Ali-Osman FR, et al. The importance of empiric antibiotic dosing in critically ill trauma patients: are we under-dosing based on augmented renal clearance and inaccurate renal clearance estimates? *J Trauma Acute Care Surg* 2016;81(6):1115–21.
- [13] Carrie C, Bentejac M, Cottenceau V, Masson F, Petit L, Cochard JF, et al. Association between augmented renal clearance and clinical failure of antibiotic treatment in brain-injured patients with ventilator-acquired pneumonia: a preliminary study. *Anaesth Crit Care Pain Med* 2018;37(1):35–41.
- [14] Dias C, Gaio AR, Monteiro E, Barbosa S, Cerejo A, Donnelly J, et al. Kidney-brain link in traumatic brain injury patients? A preliminary report. *Neurocrit Care* 2015;22(2):192–201.
- [15] May CC, Arora S, Parli SE, Fraser JF, Bastin MT, Cook AM. Augmented renal clearance in patients with subarachnoid hemorrhage. *Neurocrit Care* 2015;23(3):374–9.
- [16] Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of augmented renal clearance on drug dosing in critically ill patients: a focus on antibiotics. *Pharmacotherapy* 2015;35(11):1063–75.
- [17] De Waele JJ, Dumoulin A, Janssen A, Hoste EA. Epidemiology of augmented renal clearance in mixed ICU patients. *Minerva Anestesiol* 2015;81(10):1079–85.
- [18] Dhaese SAM, Roberts JA, Carlier M, Verstraete AG, Stove V, De Waele JJ. Population pharmacokinetics of continuous infusion of piperacillin in critically ill patients. *Int J Antimicrob Agents* 2018;51(4):594–600.
- [19] Carlier M, Stove V, De Waele JJ, Verstraete AG. Ultrafast quantification of β -lactam antibiotics in human plasma using UPLC-MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci* 2015;978–979:89–94.
- [20] 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(7):677–88.
- [21] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.1. <http://www.eucast.org>; 2018.
- [22] Aardema H, Nannan Panday P, Wessels M, van Hateren K, Dieperink W, Kosterink JGW, et al. Target attainment with continuous dosing of piperacillin/tazobactam in critical illness: a prospective observational study. *Int J Antimicrob Agents* 2017;50(1):68–73.
- [23] Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive Care Med* 2013;39(12):2070–82.
- [24] Claus BO, Hoste EA, Colpaert K, Robays H, Decruyenaere J, De Waele JJ. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. *J Crit Care* 2013;28(5):695–700.
- [25] Barnwell-Ménard JL, Li Q, Cohen AA. Effects of categorization method, regression type, and variable distribution on the inflation of type-I error rate when categorizing a confounding variable. *Stat Med* 2015;34(6):936–49.
- [26] Carrié C, Legeron R, Petit L, Ollivier J, Cottenceau V, d'Houdain N, 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.