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# Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance?

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## Abstract

**Introduction:** The aim of this study was to explore the impact of augmented creatinine clearance and differing minimum inhibitory concentrations (MIC) on piperacillin pharmacokinetic/pharmacodynamic (PK/PD) target attainment (time above MIC ( $fT_{>MIC}$ )) in critically ill patients with sepsis receiving intermittent dosing.

**Methods:** To be eligible for enrolment, critically ill patients with sepsis had to be receiving piperacillin-tazobactam 4.5 g intravenously (IV) by intermittent infusion every 6 hours for presumed or confirmed nosocomial infection without significant renal impairment (defined by a plasma creatinine concentration greater than 171  $\mu\text{mol/L}$  or the need for renal replacement therapy). Over a single dosing interval, blood samples were drawn to determine unbound plasma piperacillin concentrations. Renal function was assessed by measuring creatinine clearance ( $CL_{CR}$ ). A population PK model was constructed, and the probability of target attainment (PTA) for 50% and 100%  $fT_{>MIC}$  was calculated for varying MIC and  $CL_{CR}$  values.

**Results:** In total, 48 patients provided data. Increasing  $CL_{CR}$  values were associated with lower trough plasma piperacillin concentrations ( $P < 0.01$ ), such that with an MIC of 16 mg/L, 100%  $fT_{>MIC}$  would be achieved in only one-third ( $n = 16$ ) of patients. Mean piperacillin clearance was approximately 1.5-fold higher than in healthy volunteers and correlated with  $CL_{CR}$  ( $r = 0.58$ ,  $P < 0.01$ ). A reduced PTA for all MIC values, when targeting either 50% or 100%  $fT_{>MIC}$  was noted with increasing  $CL_{CR}$  measures.

**Conclusions:** Standard intermittent piperacillin-tazobactam dosing is unlikely to achieve optimal piperacillin exposures in a significant proportion of critically ill patients with sepsis, owing to elevated drug clearance. These data suggest that  $CL_{CR}$  can be employed as a useful tool to determine whether piperacillin PK/PD target attainment is likely with a range of MIC values.

## Introduction

Effective antibacterial therapy is crucial for improving outcomes for patients with sepsis [1]. Current international guidelines stress the importance of early administration of broad-spectrum agents [2], with the caveat that significant dose adjustment may be required in patients who are critically ill. This is a reflection of the unique physiology often encountered in these patients [3], which may dramatically distort pharmacokinetics (PK). Changes in antibacterial volume of distribution,

plasma protein binding and drug clearance are well described in the literature [4]. They lead to poorly predictable and often subtherapeutic plasma concentrations [5].

The minimum antibacterial exposure required in clinical practice to maximize bacterial killing and optimize clinical outcomes remains controversial. For  $\beta$ -lactams, preclinical studies support maintaining prolonged free drug concentrations above the minimum inhibitory concentration (MIC) of the likely pathogen [6]. *In vivo* animal data indicate that this period should be at least 40% to 70% of the dosing interval (40% to 70%  $fT_{>MIC}$ ) [7], although various retrospective clinical evaluations have recommended more aggressive targets, such as 100%  $fT_{>MIC}$  [8] and trough concentration to MIC ratios ( $C_{\text{min}}:\text{MIC}$ )  $>5$  [9].

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More recently, in a large multinational point prevalence study of antibacterial concentrations in critical illness, researchers demonstrated that clinical failure is three times more likely when  $\beta$ -lactam exposure is less than 50%  $fT_{>MIC}$  [5] and that increasing exposures are associated with an increased likelihood of clinical cure.

Whereas these data demonstrate why achievement of target drug exposures is important, they do not robustly define which patients are at risk of subtherapeutic dosing. Clinicians commonly consider the likely pathogen, its susceptibility profile and the potential for drug toxicity when selecting an empirical dosing regimen. An assessment of renal function is common, with evidence of acute or chronic renal impairment often triggering dose reduction to avoid drug accumulation. For  $\beta$ -lactams, the converse—dose escalation in the setting of augmented renal function—has been infrequently reported in clinical practice.

Previously published data, however, suggest that patients with augmented renal clearance (ARC), which often manifests as an elevated urinary creatinine clearance ( $CL_{CR}$ ), are at particular risk of subtherapeutic  $\beta$ -lactam concentrations [10,11]. This, therefore, represents an attractive measure to guide dose selection, although few data are available that integrate  $CL_{CR}$ , pathogen susceptibility and drug exposures. As such, the aim of this analysis was to explore the impact of elevated  $CL_{CR}$  and different pathogen susceptibilities, on piperacillin pharmacokinetic/pharmacodynamic (PK/PD) target attainment in critically ill patients receiving intermittent dosing.

## Material and methods

### Setting

This single-centre observational study was undertaken in a tertiary level, university-affiliated intensive care unit (ICU). Ethical approval was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC 2007/188), with written informed consent obtained from either the patient or the patient's nominated substitute decision-maker.

### Study population

Patients were eligible for enrolment if they were between 18 and 80 years of age and were receiving piperacillin-tazobactam for the treatment of sepsis (defined as presumed or confirmed nosocomial infection while manifesting a systemic inflammatory response syndrome [12]). Patients were excluded if they (1) did not have an intraarterial line inserted as part of routine management (to allow repeated plasma sampling without additional venipuncture), (2) had renal impairment (defined by a plasma creatinine concentration (CR) greater than 171  $\mu$ mol/L or the need for renal replacement therapy) or (3) had a history of allergy to piperacillin or iodine. This,

therefore, represents a convenience sample of critically ill septic patients admitted to our institution without significant renal impairment.

### Study protocol

The protocol pertaining to this study has been published in detail elsewhere [13]. In brief, 4.5 g of piperacillin-tazobactam (Tazocin EF; Pfizer Australia Pty Ltd, West Ryde, NSW, Australia) diluted in 50 ml of 0.9% sodium chloride was administered over 20 minutes as part of the patient's prescribed course of therapy. Blood samples to determine plasma piperacillin concentrations were drawn predose and at 20 minutes (end of infusion), 40 minutes, 60 minutes, 210 minutes and 360 minutes. All urine samples were collected via an indwelling urinary catheter over the dosing interval, following which urine volume and urinary CR concentration were determined by laboratory analysis. Plasma CR concentrations on the day of investigation were used to calculate  $CL_{CR}$ . No specific  $CL_{CR}$  value was used to define renal impairment or ARC, as our aim was to use these measures as continuous variables in analysis.

Additional data, including the requirement for mechanical ventilation, vasopressor support, modified Sequential Organ Failure Assessment (SOFA) score (excluding the neurological component) and 24-hour fluid balance, were documented on the day of drug administration. Admission Acute Physiology and Chronic Health Evaluation (APACHE) II score, body mass index (BMI) and ICU and in-hospital mortality were also recorded.

### Sample handling, storage and measurement

Blood samples were immediately placed on ice and centrifuged within 60 minutes at 3,000 rpm for 10 minutes. Plasma samples were then stored at  $-80^{\circ}\text{C}$  until analysis. An ultraviolet high-performance liquid chromatography (HPLC-UV) assay was used to measure piperacillin concentrations in plasma. All bioanalytical techniques were validated and conducted in accordance with the criteria of the US Food and Drug Administration's guidance for industry on bioanalysis [14]. To isolate the unbound fraction for analysis, protein-bound piperacillin was removed from the plasma sample with centrifugal filter devices (Centrifree 30,000 NMWL; Merck Millipore, Tullagreen, Ireland). The lower limit of quantification for unbound piperacillin concentrations was 1 mg/L.

### Plasma concentration data

The final (360 minutes) plasma sample was taken as the trough unbound piperacillin concentration ( $C_{\min}$ ). These samples were then compared to an MIC of 16 mg/L to determine whether 100%  $fT_{>MIC}$  would have been achieved. This represents the highest MIC for susceptible bacteria (for example, the *Pseudomonas aeruginosa* MIC

is 16 mg/L for piperacillin/tazobactam) as per the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [15]. We chose to assess the adequacy of dosing in terms of this ‘worst-case scenario’, as MIC data are often not initially available to the clinician. The 100%  $fT_{>MIC}$  target was utilized in this analysis, as more aggressive drug exposures have been demonstrated to improve both microbiological and clinical outcomes [5,8,9].

#### Population pharmacokinetics modelling

Concentration-time data were analysed using nonlinear mixed-effects modelling (NONMEM version 7.1; GloboMax, Ellicott City, MD, USA). A Digital Fortran compiler was used, and the runs were executed using Wings for NONMEM [16]. The first-order conditional estimation method with interaction was used throughout model building. Unbound plasma piperacillin concentrations were fitted to one-, two- or three-compartment linear models using subroutines from the NONMEM library. Between-subject variability (BSV) was evaluated using an exponential variability model. Various models for residual unexplained variability (RUV) were also tested.

#### Pharmacokinetics model diagnostics

Visual inspection of diagnostic scatter plots and the NONMEM objective function value (OFV) were used to evaluate goodness of fit. Statistical comparison of nested models was undertaken in the NONMEM program using log-likelihood ratios, which are assumed to be  $\chi^2$ -distributed. On the basis of a  $\chi^2$  test of the difference in OFV, a decrease in the OFV of 3.84 units ( $P < 0.05$ ) for 1 degree of freedom was considered statistically significant. Decreases in BSV of one of the parameters of at least 10% were also accepted for inclusion in a more complicated model.

#### Population pharmacokinetics bootstrap

A nonparametric bootstrap method ( $n = 1,000$ ) was used to study the uncertainty of the pharmacokinetic parameter estimates in the final model. From the bootstrap empirical posterior distribution, we were able to obtain the 95% confidence interval (2.5% to 97.5% percentiles) for the parameters, as described previously [17].

#### Probability of target attainment

Monte Carlo simulations performed in NONMEM were employed to determine the probability of target attainment (PTA) with varying MIC (2 to 64 mg/L) and  $CL_{CR}$  (10 to 300 ml/min in 10-ml/min increments) values using a standard 4.5-g piperacillin-tazobactam dose administered every 6 hours as an intermittent 20-minute infusion. The PTAs for achieving 50%  $fT_{>MIC}$  and 100%  $fT_{>MIC}$  with piperacillin were calculated.

#### Cumulative fraction of response

The cumulative fraction of response (CFR) determines the likely success of treatment by comparing the pharmacodynamic exposure (PTA) against the MIC distribution of a specific population of microorganisms [18]. The wild-type MIC distribution for *Pseudomonas aeruginosa* against piperacillin was obtained from the EUCAST database [15]. The CFR was calculated for both 50%  $fT_{>MIC}$  and 100%  $fT_{>MIC}$  by using a range of  $CL_{CR}$  values. Dosing was *a priori* considered successful if the CFR was at least 80%.

#### Statistical analysis

Continuous data are presented as the mean (standard deviation) or median (interquartile range). Categorical data are presented as counts (%). Correlation was assessed by means of a scatter graph and Pearson correlation coefficient ( $r$ ). For comparisons between groups, we used an independent Student's  $t$ -test, Mann–Whitney  $U$  test, or one-way analysis of variance for continuous data, as well as a  $\chi^2$  or Fisher's exact test for categorical data, where analysis assumptions were met. A  $P$ -value  $< 0.05$  was considered statistically significant, and all analyses were performed using SPSS version 21 software (IBM SPSS, Chicago, IL, USA).

## Results

#### Demographic data

Forty-eight patients were included in the analysis. All patients were receiving 4.5 g of piperacillin-tazobactam by intermittent IV infusion over 20 minutes every 6 hours for treatment of presumed or confirmed nosocomial infection. Demographic, admission, anthropometric, illness severity and outcome data are presented in Table 1. Sampling occurred after a median of 9 (4 to 13) doses and, on average, 5.2 (3.7) days postadmission to the ICU. Half of the patients were receiving piperacillin-tazobactam for treatment of nosocomial pneumonia. The cohort was relatively young and overweight with moderate to severe illness severity. The vast majority required invasive mechanical ventilation ( $>90\%$ ), whereas only one-fourth needed vasopressor support. As per the inclusion criteria, plasma CR concentrations were relatively low (79.5 (31.4)  $\mu\text{mol/L}$ ). The mean  $CL_{CR}$  over the study period was 122 (59.2) ml/min, although there was significant variability between patients: 15 patients had a  $CL_{CR} < 90$  ml/min, 22 had a  $CL_{CR} > 130$  ml/min and 16 had a  $CL_{CR} > 150$  ml/min.

#### Plasma concentration data

In 11 patients, the  $C_{\min}$  value was either below the lower limit of detection ( $n = 10$ ) or not available ( $n = 1$ ). Using an MIC of 16 mg/L, piperacillin intermittent infusion would achieve 100%  $fT_{>MIC}$  ( $C_{\min} > 16$  mg/L) in only 16 (34.0%) of 47 patients. Older age ( $P = 0.01$ ), higher

**Table 1 Demographic, anthropometric, illness severity and outcome data<sup>a</sup>**

Variable	N = 48
Age, yr	47.3 (17.9)
Male sex, n (%)	27 (56.3)
Height, m	1.70 (0.11)
Weight, kg	88.4 (24.2)
BMI, kg/m <sup>2</sup>	30.7 (8.78)
BSA, m <sup>2</sup>	1.98 (0.26)
Admission category/system, n (%)	
Medical	n = 13
Cardiac	1 (7.7)
Gastrointestinal	3 (23.1)
Neurological	2 (15.4)
Respiratory	5 (38.5)
Primary bacteraemia	1 (7.7)
Oncology	1 (7.7)
Surgical	n = 13
Gastrointestinal	7 (53.8)
Gynaecological	1 (7.7)
Maxillofacial	2 (15.4)
Neurological	2 (15.4)
Vascular	1 (7.7)
Trauma	n = 22
Burns	6 (27.3)
Facial	1 (4.5)
Abdominal	4 (18.2)
Neurological	5 (22.7)
Orthopaedic	3 (13.6)
Thoracic	3 (13.6)
APACHE II score	19.4 (6.79)
Modified SOFA score, median (IQR)	3.5 (2 to 6)
Mechanical ventilation, n (%)	45 (93.8)
Use of vasopressors, n (%)	12 (25.0)
Presumed/confirmed site of infection, n (%)	
Intraabdominal	14 (29.2)
Skin/soft tissue	5 (10.4)
Respiratory	24 (50.0)
Urinary	1 (2.1)
Primary bacteraemia	1 (2.1)
Unknown	3 (6.3)
24-hr fluid balance, ml	553 (1836)
Plasma CR, μmol/L	79.5 (31.4)
Measured CL <sub>CR</sub> , ml/min	122 (59.2)
ICU length of stay, days	18.2 (11.5)
ICU mortality, n (%)	4 (8.3)
Hospital mortality, n (%)	5 (10.4)

<sup>a</sup>APACHE, Acute Physiology and Chronic Health Evaluation; BMI, Body mass index; BSA, Body surface area; CL<sub>CR</sub>, Creatinine clearance; CR, Creatinine; ICU, Intensive care unit; IQR, Interquartile range; SD, Standard deviation; SOFA, Sequential Organ Failure Assessment. Data presented are mean (SD) unless otherwise stated.

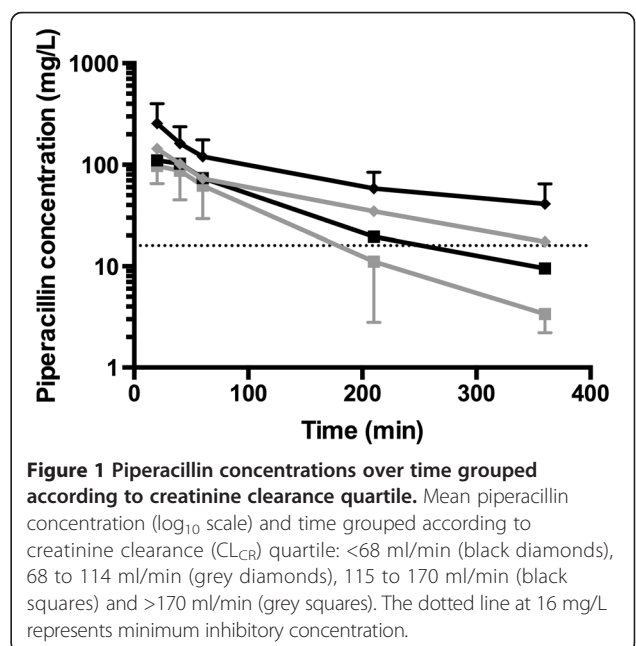
modified SOFA score ( $P < 0.01$ ), lower CL<sub>CR</sub> ( $P < 0.01$ ), greater positive 24-hour fluid balance ( $P = 0.04$ ) and more frequent application of vasopressor therapy ( $P = 0.01$ ) were characteristics of patients likely to have higher C<sub>min</sub> values, and therefore achieve this PK/PD target. No statistically significant differences were noted in BMI, APACHE II scores or the need for mechanical ventilation. Unbound plasma piperacillin concentration time profiles grouped by CL<sub>CR</sub> quartile are presented in Figure 1. Higher CL<sub>CR</sub> was significantly associated with lower unbound trough plasma piperacillin concentration ( $P < 0.01$ ).

**Pharmacokinetic model building**

The time course of unbound plasma piperacillin concentrations was best described by a two-compartment linear model with combined residual error and BSV on the volume of the central (V<sub>c</sub>) and peripheral compartments (V<sub>p</sub>), drug clearance (CL) and an infusion lag descriptor (ALAG; defined as the time taken for the residual drug to get through the IV line after completion of the 20-minute infusion, which was included as zero order input). The only covariate that improved the fit of the model was, for piperacillin CL, CL<sub>CR</sub> normalized to 100 ml/min, which decreased the OFV by 18.62 ( $P < 0.01$ ). In the final model, this was described as follows:

$$TVCL = CL \times CL_{CR}/100,$$

where TVCL is the typical value of piperacillin CL. The mean parameter estimates from the final covariate model, as well as the 95% confidence intervals from all



bootstrap runs, are shown in Table 2. Total volume of distribution ( $V_d$ ) was calculated as the sum of  $V_c$  and  $V_p$ . The goodness-of-fit plots were acceptable with an  $r$ -value of 0.95 for the observed versus individual predicted concentrations.

Those patients who would fail to achieve 100%  $fT_{>MIC}$  (16 mg/L) had higher drug CL ( $P < 0.01$ ) and no statistically significant difference in piperacillin  $V_d$  ( $P = 0.647$ ). As demonstrated in Figure 2, a moderate correlation was noted between  $CL_{CR}$  and piperacillin CL overall ( $r = 0.58$ ,  $P < 0.01$ ). The PTAs for 50%  $fT_{>MIC}$  and 100%  $fT_{>MIC}$  with varying MIC and  $CL_{CR}$  values are presented in Figure 3.

The CFR for piperacillin over a range of  $CL_{CR}$  values using the EUCAST MIC distribution for *Pseudomonas aeruginosa* is presented in Table 3.

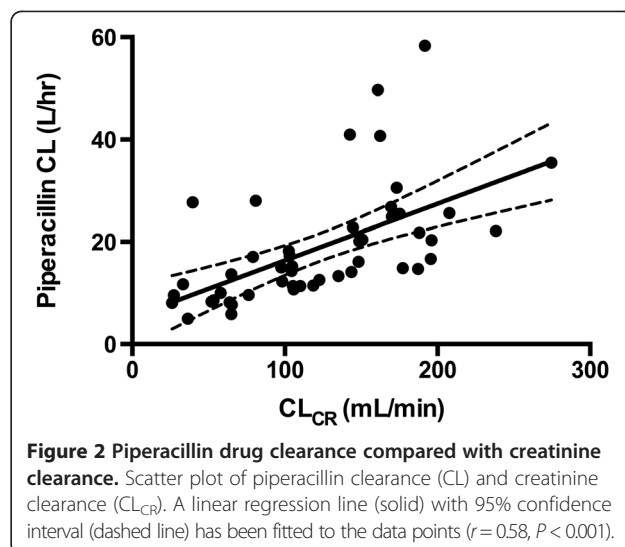
### Discussion

In this clinical analysis, we sought to explore the impact of elevated  $CL_{CR}$  and different susceptibilities of bacteria on piperacillin PK/PD target attainment when administered by intermittent infusion in a large cohort of critically ill patients with sepsis. With a MIC at the upper limit of the susceptible range for piperacillin (16 mg/L), only about one-third of patients would achieve 100%  $fT_{>MIC}$ . The primary mechanism underlying this observation appears to be significantly elevated drug CL in parallel with higher  $CL_{CR}$  in some patients. This phenomenon

**Table 2 Mean parameter estimates and bootstrap mean (95% confidence interval) estimates for the final population pharmacokinetic model<sup>a</sup>**

Parameter	Model	Bootstrap		
		Mean	95% confidence interval	
			Mean	2.5%
Fixed effects				
CL (L/hr)	16.3	16.2	14.0	18.9
$V_c$ (L)	19.9	15.9	0.7	27.8
$V_p$ (L)	18.8	21.3	11.1	32.3
Q (L/h)	37.3	42.9	22.0	73.3
ALAG (hr)	0.8	0.13	0.01	0.31
Random effects BSV (% CV)				
CL (L/hr)	56.0	55.3	45.2	65.4
$V_c$ (L)	29.6	23.5	0.2	45.7
$V_p$ (L)	67.6	69.2	24.6	158.4
ALAG (hr)	0.3	0.4	0.05	0.8
Random error				
RUV (% CV)	1.0	1.3	0.3	3.1
RUV (SD, mg/L)	0.3	0.3	0.2	0.4

<sup>a</sup>ALAG, Infusion lag time; BSV, Between-subject variability; CL, Clearance; CV, Coefficient of variation; Q, Intercompartmental clearance; RUV, Residual unexplained variability; SD, Standard deviation;  $V_c$ , Volume of the central compartment;  $V_p$ , Volume of the peripheral compartment.

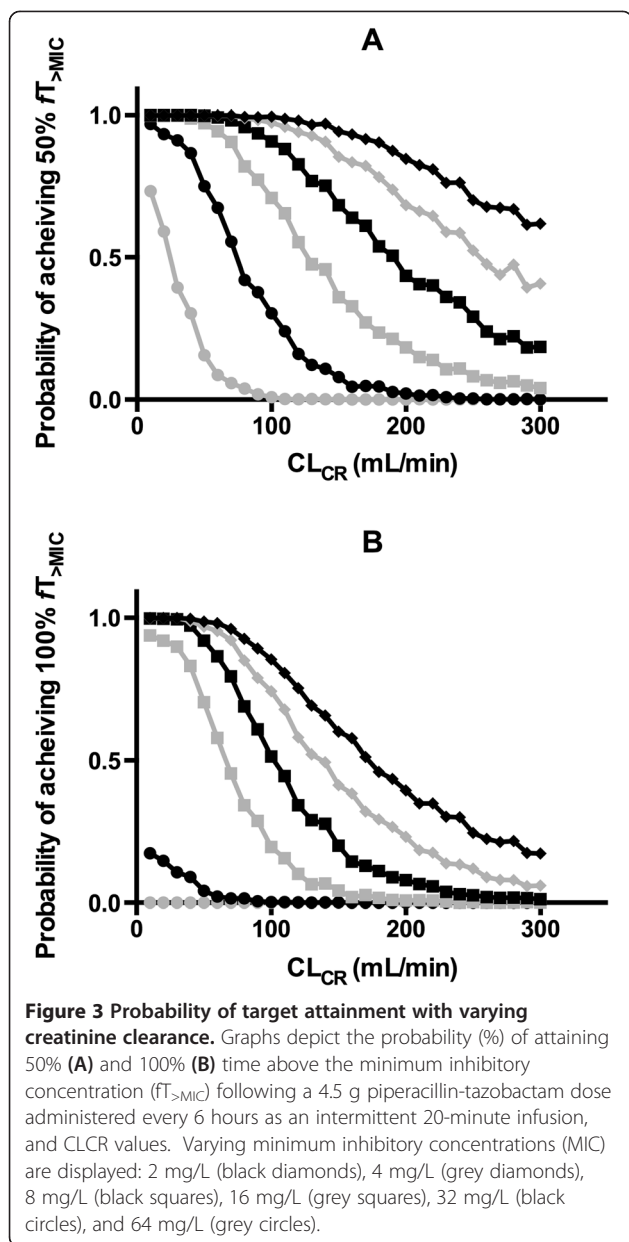


**Figure 2 Piperacillin drug clearance compared with creatinine clearance.** Scatter plot of piperacillin clearance (CL) and creatinine clearance ( $CL_{CR}$ ). A linear regression line (solid) with 95% confidence interval (dashed line) has been fitted to the data points ( $r = 0.58$ ,  $P < 0.001$ ).

of augmented renal clearance [19,20] is being described in critically ill patients with increasing frequency [21,22], which suggests that clinicians should be wary of conventional dosing in this setting. Indeed, the CFR suggests that only with lower  $CL_{CR}$  values (<90 ml/min) will an adequate fraction of *Pseudomonas aeruginosa* isolates be suitably covered with this dosing regimen.

Pharmacokinetic modelling for the study cohort revealed a mean piperacillin CL of approximately 1.5-fold that reported in healthy volunteers [23]. Similar derangement in piperacillin CL has been reported in previous studies of critically ill patients [24,25], highlighting the unique PK observed in this setting [4]. Of note, piperacillin  $V_d$  was also significantly larger overall. Changes in  $V_d$  have been observed with other  $\beta$ -lactams in critical illness [26] and likely reflect the substantial fluid shifts frequently encountered [27]. Use of unbound piperacillin concentrations in the PK model may also have contributed to the higher  $V_d$  observed, although use of free concentrations is essential to describe the pharmacologically active fraction of piperacillin.

The specific mechanisms underlying ARC in critically ill patients remain uncertain. Researchers have recently identified a modest correlation between cardiac index and  $CL_{CR}$  in patients with sepsis [28], suggesting that increased renal perfusion and solute delivery may be a key factor. Younger age and lower illness severity scores have previously been identified as risk factors for ARC [28,29], which is further demonstrated by our study data. Work by Shimamoto *et al.* highlights the role of systemic inflammation, with an increasing number of systemic inflammatory response syndrome criteria being strongly correlated with higher drug clearance and lower plasma concentrations in nonventilated patients receiving vancomycin [30]. Together, these findings imply an important interaction between systemic inflammation



and available organ reserve, factors that are often neglected in antibacterial dosing regimens [31]. As such, the characteristics of patients included in this study (younger age, admission posttrauma and less organ dysfunction) are useful in defining scenarios where a measured CL<sub>CR</sub> or therapeutic drug monitoring should be employed to determine the need for higher than standard piperacillin dosing.

The prevalence of ARC varies significantly, depending upon the definition employed and institutional case mix [32-35]. In a recent multicentre study of CL<sub>CR</sub> in critically ill patients with 'normal' plasma CR concentrations, researchers identified an incidence of ARC (CL<sub>CR</sub> ≥130 ml/min/1.73 m<sup>2</sup>) of approximately 65% in the first 7 days in the ICU [36].

**Table 3** Cumulative fraction of response for piperacillin over a range of creatinine clearance values<sup>a</sup>

CL <sub>CR</sub> (ml/min)	CFR, 50% $fT_{>MIC}$ (%)	CFR, 100% $fT_{>MIC}$ (%)
10	<b>87.2</b>	<b>81.3</b>
30	<b>86.0</b>	<b>80.6</b>
60	<b>83.5</b>	72.6
90	78.6	57.2
120	71.7	40.4
150	62.7	28.5
180	55.5	20.0
210	46.3	13.3
240	40.8	9.9
270	31.0	6.3
300	28.3	4.9

<sup>a</sup>50%  $fT_{>MIC}$ , 50% time above the minimum inhibitory concentration; 100%  $fT_{>MIC}$ , 100% time above the minimum inhibitory concentration; CFR, Cumulative fraction of response; CL<sub>CR</sub>, Creatinine clearance. Data represent the CFR when targeting 50%  $fT_{>MIC}$  and 100%  $fT_{>MIC}$  with a range of CL<sub>CR</sub> values following a 4.5 g piperacillin-tazobactam dose administered every 6 hours as an intermittent 20 minute infusion. The wild-type MIC distribution of *Pseudomonas aeruginosa* has been employed. Boldface represents those CL<sub>CR</sub> values where target exposures would be achieved in at least 80% of isolates.

Importantly, patients who manifested ARC on day 1 were significantly more likely to do so on subsequent measures, indicating that augmented drug CL is unlikely to be short-lived. A lower incidence (about 52%) of ARC was observed in a mixed cohort of critically ill patients receiving antibacterial therapy, although an association with greater therapeutic failure was demonstrated [29].

Other investigators have highlighted the importance of renal function in informing  $\beta$ -lactam dosing. Patel and colleagues examined piperacillin PK data from 105 hospitalized patients to determine optimal intermittent and extended-infusion dosing in those with renal impairment [37]. Of interest, with an estimated CL<sub>CR</sub> of 100 ml/min and a traditional regimen of 4.5 g administered IV every 6 hours, the probability of target attainment (50%  $fT_{>MIC}$ ) decreased sharply (<80%) with MIC values greater than 4 mg/L [34]. With our data, we identified higher CL<sub>CR</sub> thresholds (Figure 3), although this likely reflects differences in case mix and the use of measured rather than estimated CL<sub>CR</sub>. Importantly, previous data reinforce the significant disparity between calculated and measured CL<sub>CR</sub> in patients manifesting ARC [38,39].

More recently, Carrier *et al.* examined meropenem and piperacillin-tazobactam target attainment in a cohort of critically ill patients receiving extended-infusion dosing. In those patients manifesting ARC (CL<sub>CR</sub> ≥130 ml/min), the probability of achieving either 50%  $fT_{>MIC}$  or 100%  $fT_{>MIC}$  was significantly reduced [40]. Regression analysis also identified CL<sub>CR</sub> as the only significant predictor of target attainment, a finding also demonstrated

by Hites *et al.* in their work exploring  $\beta$ -lactam exposure in obese, non-critically ill patients [41]. Our data compare favourably with these studies, although the current analysis involves a wider range of MIC values, highlighting the impact of variable bacterial susceptibility. Pea and colleagues similarly examined meropenem continuous infusion dosing in critically ill patients with severe Gram-negative infection [42]. Dosing nomograms to achieve specific steady-state concentrations were developed with a linear relationship between dose and estimated  $CL_{CR}$  [42].

Changing bacterial susceptibility represents a global challenge in medical practice. Our analyses highlight the importance of the MIC as the denominator in the PK/PD relationship in determining adequate antibacterial dosing. Less susceptible pathogens are more common in the ICU [43], and significant regional variation in resistance patterns also exists [44]. In two large antibacterial susceptibility prevalence studies,  $MIC_{90}$  values for piperacillin-tazobactam against *Pseudomonas aeruginosa* were reported at or above 64 mg/L [45,46]. Our data suggest that achieving 50%  $fT_{>MIC}$  in such a scenario is unlikely with conventional piperacillin intermittent dosing and reinforce the use of a much lower susceptibility breakpoint (16 mg/L) with this dosing strategy. However, even in this circumstance, an elevated  $CL_{CR}$  will significantly reduce the probability of target attainment, as demonstrated in Figure 3. In contrast, where a highly susceptible pathogen is identified and piperacillin is used as directed therapy, standard doses may still be sufficient, even with extremely high  $CL_{CR}$  values. Importantly, this underlines the significance of such microbiological susceptibility data in accurate clinical decision-making.

Our study has several limitations. The data were drawn from a single centre and as such may not be representative of case mix at other institutions. Our inclusion criteria were designed to select a cohort of patients without significant renal impairment, as effective antibacterial dosing in this group is less likely with standard dosing. As such, ARC is likely to have been more common in our study cohort than in a broader ICU population. However, our relatively high plasma CR cutoff allowed us to explore renal function (as determined by  $CL_{CR}$ ) as a covariate in PK modelling. We did not include tazobactam PK, because it is not active against *Pseudomonas aeruginosa*, although, as it is renally eliminated, increased drug CL is also likely in ARC. We examined the likelihood of target attainment using varying susceptibility levels rather than clinical MIC data. This improves generalizability for empiric dosing, although it limits conclusions about the adequacy of drug exposure in any specific patient. Furthermore, given the small sample size, we are unable to make any firm conclusions about the clinical implications of these analyses.

## Conclusions

Our results indicate that an empiric intermittent infusion of 4.5 g of piperacillin-tazobactam is unlikely to achieve optimal piperacillin exposure in a significant proportion of critically ill patients with sepsis, particularly when targeting less susceptible pathogens. This appears to be driven primarily by an increase in drug CL in some patients, and our data reinforce the value of  $CL_{CR}$  in predicting whether optimal exposures are likely. As such, clinicians should be wary of the adequacy of conventional dosing in patients manifesting ARC, and research should now be focused on the use of novel administration strategies in such patients, in addition to correlating changes in antibacterial PK with clinical outcomes.

## Key messages

- Elevated  $CL_{CR}$  in septic critically ill patients is associated with higher piperacillin CL, a concept referred to as *augmented renal clearance*, or ARC.
- When employing intermittent administration, this will result in suboptimal plasma concentrations for significant periods of the dosing interval.
- Increasing  $CL_{CR}$  reduces the probability of target attainment ( $fT_{>MIC}$ ), particularly with more resistant organisms.
- When considering the MIC distribution of *Pseudomonas aeruginosa*, 6-hourly dosing of 4.5 g piperacillin-tazobactam is unlikely to provide sufficient piperacillin exposure when the  $CL_{CR}$  is  $\geq 90$  ml/min.

## Abbreviations

ALAG: Infusion lag descriptor; APACHE: Acute Physiology And Chronic Health Evaluation; ARC: Augmented renal clearance; BMI: Body mass index; BSV: Between-subject variability; CFR: Cumulative fraction of response; CL: Drug clearance;  $CL_{CR}$ : Creatinine clearance;  $C_{min}$ : Trough concentration; CR: Creatinine; CV: Coefficient of variation; EUCAST: European Committee on Antimicrobial Susceptibility Testing;  $fT_{>MIC}$ : Fraction of the dosing interval for which the concentration remains above the minimum inhibitory concentration; HPLC-UV: High-performance liquid chromatography-ultraviolet; ICU: Intensive care unit; IDC: Indwelling urinary catheter; IQR: Interquartile range; LOS: Length of stay; MIC: Minimum inhibitory concentration; NONMEM: Nonlinear mixed-effects modelling; OFV: Objective function value; PD: Pharmacodynamic; PK: Pharmacokinetic; PTA: Probability of target attainment; Q: Intercompartmental clearance; RUV: Residual unexplained variability; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; TVCL: Typical value of piperacillin clearance;  $V_c$ : Volume of the central compartment;  $V_d$ : Volume of distribution;  $V_p$ : Volume of the peripheral compartment.

## Competing interests

JL has received an honorarium from AstraZeneca. MSR has previously consulted for Janssen-Cilag, AstraZeneca, Pfizer and Gilead; has been involved in advisory boards for Janssen-Cilag and AstraZeneca; and has received unrestricted grants from Janssen-Cilag, AstraZeneca and Novartis. AAU has received an honorarium and travel support from Pfizer. DLP has received a research grant from AstraZeneca and acted as a consultant for Merck, Acureon, Johnson & Johnson, Sanofi-Aventis and Three Rivers Pharmaceuticals. AstraZeneca and Edwards Lifesciences provide an annual unrestricted donation to the Burns, Trauma and Critical Care Research Centre (BTCCRC), The University

of Queensland. All of the remaining authors declare that they have no competing interests in relation to this article.

#### Authors' contributions

JL, MSR, DLP, PSK and JAR conceived of the study. AAU, PJ, JAR, PSK and JL were involved in protocol development, ethical approval and implementation. AAU, PJ and JAR collected the data. SCW completed the laboratory analysis and quality assurance. CMJK, KP, JAR and KK performed the statistical and pharmacokinetic analyses. AAU wrote the initial manuscript draft, and all of the remaining authors contributed to subsequent revisions. AAU takes responsibility for archiving the data and guarantees the integrity of the paper from inception to publication. All of the authors have read and approved the article for publication.

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