Intensive Care Med (2014) 40:1340–1351
DOI 10.1007/s00134-014-3403-8

ORIGINAL

Risk factors for target non-attainment during empirical treatment with β-lactam antibiotics in critically ill patients

Jan J. De Waele
J. Lipman
M. Akova
M. Bassetti
G. Dimopoulos
M. Kaukonen
D. Koulenti
C. Martin
P. Montravers
J. Rello
A. Rhodes
A. A. Udy
T. Starr
S. C. Wallis
J. A. Roberts

Received: 5 May 2014
Accepted: 10 July 2014
Published online: 23 July 2014

On behalf of the DALI study authors (Appendix).

Take home message: PK/PD target attainment during therapy with β-lactam antibiotics is overall inadequate with intermittent infusion and increased creatinine clearance as independent risk factors for target non-attainment.

J. J. De Waele (✉)
Department of Critical Care Medicine, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
e-mail: jan.dewaele@ugent.be
Tel.: +32 93 32 62 19

J. Lipman · D. Koulenti · A. A. Udy · T. Starr · S. C. Wallis · J. A. Roberts
Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia

J. Lipman · J. A. Roberts
Royal Brisbane and Women's Hospital, Brisbane, Australia

M. Akova
Hacettepe University Hospital, Ankara, Turkey

M. Bassetti
Azienda Ospedaliera Universitaria Santa Maria della Misericordia, Udine, Italy

G. Dimopoulos
Attikon University Hospital, University of Athens Medical School, Athens, Greece

M. Kaukonen
Helsinki University Hospital, Helsinki, Finland

M. Kaukonen
Department of Epidemiology and Preventive Medicine, Monash University, Australian and New Zealand Intensive Care Research Centre (ANZIC RC), Melbourne, Australia

C. Martin
Hospital Nord, Marseille, France

P. Montravers
Centre Hospitalier Universitaire Bichat-Claude Bernard, Paris, France

J. Rello
CIBERES, Vall d'Hebron Institut of Research, Barcelona, Spain

A. Rhodes
St George's Healthcare NHS Trust and St George's University of London, London, UK

A. A. Udy
Department of Intensive Care and Hyperbaric Medicine, The Alfred Hospital, Melbourne, VIC, Australia

Abstract *Purpose:* Risk factors for β-lactam antibiotic underdosing in critically ill patients have not been described in large-scale studies. The objective of this study was to describe pharmacokinetic/pharmacodynamic (PK/PD) target non-attainment envisioning empirical dosing in critically ill patients and considering a worst-case scenario as well as to identify patient characteristics that are associated with target non-attainment. *Methods:* This analysis uses data from the DALI study, a prospective, multi-centre pharmacokinetic point-prevalence study. For this analysis, we assumed that these were the concentrations that would be reached during empirical dosing, and calculated target attainment using a hypothetical target minimum inhibitory concentration (MIC), namely the susceptibility breakpoint of the least susceptible organism for which that antibiotic is commonly used. PK/PD targets were free drug concentration maintained above the MIC of the suspected pathogen for at least 50 % and 100 % of the dosing interval respectively (50 % and 100 % $fT_{>MIC}$). Multivariable analysis was performed to identify factors associated with inadequate antibiotic exposure. *Results:* A total of 343 critically ill patients receiving eight different β-lactam antibiotics were included. The median (interquartile

range) age was 60 (47–73) years, APACHE II score was 18 (13–24). In the hypothetical situation of empirical dosing, antibiotic concentrations remained below the MIC during 50 % and 100 % of the dosing interval in 66 (19.2 %) and 142 (41.4 %) patients respectively. The use of intermittent infusion was significantly associated with increased risk of non-attainment for both targets; creatinine clearance was independently associated with not reaching the 100 % $fT_{>MIC}$ target. *Conclusions:* This study found that—in empirical dosing and considering a worst-case scenario—19 % and 41 % of the patients would not achieve antibiotic concentrations above the MIC during 50 % and 100 % of the dosing interval. The use of intermittent infusion (compared to extended and continuous infusion) was the main determinant of non-attainment for both targets; increasing creatinine clearance was also associated with not attaining concentrations above the MIC for the whole dosing interval. In the light of this study from 68 ICUs across ten countries, we believe current empiric dosing recommendations for ICU patients are inadequate to effectively cover a broad range of susceptible organisms and need to be reconsidered.

Keywords β-Lactam antibiotics · Pharmacokinetics · Pharmacodynamics · Critical care

Introduction

β-Lactam antibiotics (penicillins, cephalosporins and carbapenems) are frequently used to treat severe infection, as they have demonstrated efficacy against most pathogens causing community-acquired and nosocomial disease. These antibiotics display time-dependent activity, with maintenance of unbound (or free) concentrations above the minimum inhibitory concentration (MIC)—or $fT_{>MIC}$—associated with improved efficacy. In vivo experiments have shown that depending on the β-lactam class the minimum time during which concentration should be above the MIC should be 40–70 % of the dosing interval, although clinical data suggests that higher and more prolonged exposures may be necessary to treat severe infection [1–3].

Empirical antibiotic choice and dosing should take into account not only the suspected microorganisms but also bacterial susceptibility to the antibiotic administered [4]. Just as the spectrum of empiric antibiotics is often broad, antibiotics should reach sufficient concentrations to inhibit all microorganisms that are presumed susceptible to the drug. The MIC of a microorganism is an important parameter in this respect but is usually not known when antibiotic therapy is initiated. Therefore it is logical to use susceptibility breakpoints for specific antibiotic/microorganism combinations as a target during the first days of therapy until other data to guide concentration targets becomes available. This implies that higher concentrations should be aimed for in this stage where data regarding susceptibility of the pathogen are lacking.

In recent years, many single-centre studies in specific critically ill patient populations have highlighted the variability of β-lactam antibiotic concentrations [5–9]. Changes in volume of distribution and protein binding as well as clearance of the antibiotic are frequent, predisposing to subtherapeutic or toxic concentrations when standard doses are applied [10].

Although individual factors contributing to antibiotic underexposure have been studied in some detail [7, 11, 12], it remains unclear which patients are at risk of underdosing, especially in the crucial phase of the first 48 h. Furthermore, the clinical factors associated with insufficient β-lactam concentrations have not been studied on a large scale. Utilising the Defining Antibiotic Levels in Intensive care unit patients (DALI) study database [13], the goals of this analysis were (a) to describe the frequency of β-lactam PK/PD target non-attainment in an empirical setting aiming for adequate coverage of likely pathogens and therefore a broad range of MICs and (b) to identify patient characteristics associated with target non-attainment in this hypothetical situation and therefore suboptimal β-lactam exposure for empiric therapy.

Methods

The DALI study was a prospective, multi-centre pharmacokinetic point-prevalence study. The detailed protocol has been published previously [14]. Patients without protocol violations were included in this analysis if they received one of the following antibiotics: amoxicillin (co-administered with clavulanate), ampicillin, cefazolin, cefepime, ceftriaxone, doripenem, meropenem and piperacillin (co-administered with tazobactam) and if data on the method of administration were available (intermittent, extended or continuous infusion). Antibiotic dosing was decided by the clinician in charge of treating the patient. Each patient had two blood samples drawn for each β-lactam antibiotic (mid-dose and trough concentration; for details regarding sampling and bioanalysis we refer to previous publications [13, 14]).

The goal of the current analysis was to calculate target non-attainment, not for the actual infection and pathogens the patients were treated for, but envisioning an empirical situation where the least susceptible organism potentially

causing the infection is targeted. For this analysis, we assumed that the concentrations obtained in the DALI study were also the concentrations that would be reached during empirical dosing, and calculated target non-attainment using a hypothetical target MIC, namely the susceptibility breakpoint of the least susceptible organism for which that antibiotic is commonly used based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC_{90} data (http://www.eucast.org/clinical_breakpoints) (e.g. *Pseudomonas aeruginosa* MIC is 16 mg/L for piperacillin/tazobactam). Again, the breakpoints were chosen for a 'worst-case' scenario in terms of bacterial susceptibility, which reflects the context of empiric therapy.

A comparison between patients, on the basis of attaining these targets, was then undertaken and we tried to identify factors independently associated with target non-attainment. We sought to further explore these relationships for specific scenarios with the richest data. For antibiotics that were administered to more than 50 patients, individual analyses were performed in order to identify factors associated with target non-attainment. Also for the major infection sites a separate analysis was performed.

Data collection

Data collection was performed by trained staff at each participating centre and entered onto a case report form (CRF). Various demographic and clinical data were collected including age, gender, height, weight, fluid balance and measures of organ function and levels of patient sickness severity, as described by the admission acute physiology and chronic health evaluation (APACHE II) score [15], and sepsis organ failure assessment (SOFA) score [16] on the day of sampling. Mortality at 30 days was also collected.

Creatinine clearance (CL_{CR}) was calculated using the Cockroft-Gault formula for all patients except those receiving renal replacement therapy (RRT). Antibiotic dosing data including the dose and frequency of administration, the time of dosing and sampling and the day of antibiotic therapy were collected.

In order to assess the effect of dosing, we calculated the ratio between the dose administered and dosages commonly used in ICU patients, daily dose in ICU (DD_{ICU}: amoxicillin, 4 g; ampicillin, 6 g; piperacillin, 2 g; cefepime, 4 g; cefazolin, 3 g; ceftriaxone, 2 g; meropenem, 3 g and doripenem, 1.5 g).

PK/PD targets

PK/PD targets associated with maximal β-lactam activity in preclinical and some clinical studies were selected as surrogate markers of the appropriateness of dosing. For this analysis, the following PK/PD targets were evaluated:

- 50 % $f\ T_{>MIC}$: free drug concentration maintained above the MIC of the suspected pathogen for at least 50 % of the dosing interval. This was considered as the most conservative PK/PD target.
- 100 % $f\ T_{>MIC}$: free drug concentration maintained above the MIC of the suspected pathogen throughout the entire dosing interval.

Ethical approval

Ethical approval to participate in this study was obtained at all participating centres and informed consent obtained from each patient or their legally authorised representative. The lead site was The University of Queensland, Australia with ethical approval granted by the Medical Research Ethics Committee (no. 2011000283, May 2011).

Statistical analysis

Data are expressed as median values with interquartile ranges (IQR) for continuous variables, numbers and percentages for categorical variables. Univariate comparisons employed a Mann–Whitney *U* test, Chi square test or Fisher's exact test, where analysis assumptions were met. In order to identify important covariates associated with target non-attainment for the two targets mentioned above, a multivariate logistic regression model (single step, forced entry) was constructed using variables for which the *p* value was less than 0.2 in univariate analysis. Goodness of fit was assessed by the Hosmer–Lemeshow statistic. All statistical analyses were performed using the statistical software package IBM-SPSS statistics 20.0 (IBM Corp, New York USA). A two-sided *p* value less than 0.05 was considered statistically significant.

Results

Patients in the DALI study

In 68 ICUs across ten countries, 384 patients receiving β-lactam antibiotics were identified. Forty-one patients were excluded because of protocol violations, or incomplete data sets, leaving 343 evaluable critically ill patients for this analysis [13].

The median patient age was 60 (47–73) years and APACHE II score 18 (13–24) (Table 2). Twenty-three per cent of patients underwent surgery in the 24 h preceding antibiotic sampling and about one tenth of all patients were treated concomitantly with RRT.

The distribution of antibiotic use is summarized in Table 1. In the majority of the patients (75.5 %), antibiotics were used for treatment of infection. In patients treated for infection, the lung was the most frequent source (36.2 %), followed by the abdomen (15.7 %). Other sources of infection included the bloodstream (7.6 %), urinary tract (5.2 %), central nervous system (3.3 %), and skin and soft tissues (2 %). In 29.4 % of the patients, no source of infection was identified on the day of sampling.

Extended or continuous infusion was used in 25 % of patients. Additional patient characteristics are displayed in Table 2.

Target non-attainment: all patients

Considering the MIC of the least susceptible microorganism as the target MIC, PK/PD targets of 50 % $fT_{>MIC}$ and 100 % $fT_{>MIC}$ were not reached by 66 (19.2 %) and 142 (41.4 %) patients respectively. The characteristics of these patients are presented in Table 2.

A multivariate analysis was undertaken to examine for factors associated with PK/PD target non-attainment. The use of intermittent infusion (compared to extended or continuous infusion) significantly increased the probability of target non-attainment for both 50 % $fT_{>MIC}$ and 100 % $fT_{>MIC}$; furthermore, increasing CL_{CR} was associated with not attaining the 100 % $fT_{>MIC}$ target (Table 3). It should be noted that patients receiving RRT ($n = 33$) were excluded from the latter analysis, as no accurate CL_{CR} values were available.

Target non-attainment: intermittent infusion patients only

As the infusion duration was identified as such an important variable for both 50 % and 100 % $fT_{>MIC}$, and as the majority of the patients were treated with intermittent infusion, a separate multivariate analysis was conducted in patients who received intermittent dosing only. In this instance, for 50 % $fT_{>MIC}$, only the indication for drug administration was identified as a significant covariate; patients who received antibiotics as prophylaxis were 2.19 times more likely not to achieve that target (Fig. 1a). In respect to 100 % $fT_{>MIC}$, increasing CL_{CR}, recent surgery, and sampling within the first few days of therapy were significant predictors of target non-attainment (Fig. 1a).

Table 1 Antibiotics used in the 343 patients

Antibiotic	*N* (%)	Median 24 h dose administered (IQR) (g)
Piperacillin	107 (31.2)	12 (12–16)
Meropenem	78 (22.7)	3 (3–6)
Amoxycillin	71 (20.7)	4 (3–6)
Ceftriaxone	31 (9.6)	2 (2–4)
Ampicillin	18 (5.2)	12 (6–12)
Cefepime	13 (3.8)	6 (3–6)
Doripenem	13 (3.8)	2 (1.5–3)
Cefazolin	10 (2.9)	4 (3–6)

Target non-attainment: individual antibiotics and major sites of infection

Target non-attainment for piperacillin ($n = 107$), meropenem ($n = 78$) and amoxicillin ($n = 71$) and respiratory tract plus abdominal infections is summarized in Fig. 2.

Factors associated with 100 % $fT_{>MIC}$ target non-attainment for the individual antibiotics included CL_{CR} for all antibiotics [piperacillin OR 1.022 (95 % CI 1.006–1.039), meropenem OR 1.014 (95 % CI 1.001–1.027), amoxicillin OR 1.032 (95 % CI 1.004–1.064)], and the use of extended or continuous infusion for piperacillin OR 0.10 (95 % CI 0.02–0.51).

In patients with abdominal infections no factors associated with target non-attainment could be identified, whereas in patients with respiratory tract infections, again CL_{CR} [OR 1.010 (95 % CI 1.001–1.019)] and the use of extended or continuous infusion [OR 0.273 (95 % CI 0.093–0.805)] were associated with increased target non-attainment.

Discussion

This analysis demonstrates that based on the data from a large group of critically ill patients receiving β-lactam antibiotics, approximately 20 % of patients fail to attain even the most conservative drug exposure targets (antibiotic concentrations above the MIC during 50 % of the dosing interval) during empirical treatment when aiming at adequate concentrations irrespective of the degree of susceptibility. Utilising a higher target (antibiotic concentrations above the MIC throughout the dosing interval), twice this number of patients (>40 %) manifest insufficient drug exposures.

Given that this study included data from 68 ICUs across ten countries, the generalizability of this data is broad. Our findings raise crucial questions as to the validity of current empirical β-lactam dosing strategies, with the critical care environment significantly altering the 'normal' PK/PD profile. As illustrated by the distribution of doses employed, most clinicians are utilising these agents in agreement with current recommendations,

Table 2 Patient characteristics: all patients, and according to PK/PD target attainment

	All patients ($n = 343$)	Patients not reaching 50 % $T >$ MIC ($n = 66$)	Patients reaching 50 % $T >$ MIC ($n = 277$)	p	Patients not reaching 100 % $T >$ MIC ($n = 142$)	Patients reaching 100 % $T >$ MIC ($n = 201$)	p
Age (years)	60 (47–73)	*52 (39–65)*	63 (49–75)	<0.001	55 (40–66)	64 (51–76)	<0.001
Male gender	218 (63.6 %)	27 (40.1 %)	97 (35.0 %)	0.382	86 (60.6 %)	132 (65.7 %)	0.376
Body mass index (kg/m^2)	25.9 (23.4–29.1)	25.2 (23.1–28.0)	26.0 (23.4–29.3)	0.249	25.3 (23.7–29.0)	25.9 (23.3–29.4)	0.945
APACHE II score at admission	18 (13–24)	15 (8–21)	19 (14–25)	0.001	16 (10–23)	19 (15–25)	<0.001
SOFA on day of sampling	5 (2–8)	3 (1–6)	6 (3–9)	<0.001	3 (2–6.5)	6 (3–9)	<0.001
Cockroft-Gault CL_{CR} (mL/min)	91 (54–141)	119 (84–164)	82 (48–124)	<0.001	118 (86–169)	70 (42–108)	<0.001
Interval between start AB and sampling (days)	2 (1–5)	2 (1–4)	3 (1–5)	0.141	2 (0.75–5)	2.5 (1–5)	0.327
Antibiotic dose administered (daily dose in mg/kg)							
Piperacillin	184 (139–226)	171 (117–224)	185 (140–227)	0.376	173 (139–215)	195 (139–229)	0.180
Meropenem	43 (29–61)	45 (43–48)	42 (29–63)	0.211	45 (42–60)	40 (28–61)	0.851
Amoxicillin	60 (44–75)	56 (43–73)	62 (45–75)	0.897	58 (46–72)	71 (40–82)	0.589
Ratio of administered dose to DD_{ICU}	1.00 (1.00–1.50)	1.00 (0.94–1.50)	1.00 (1.00–1.50)	0.957	1.17 (1.00–1.50)	1.00 (1.00–1.33)	0.182
Trauma as admission diagnosis	44 (12.8 %)	12 (18.2 %)	32 (11.6 %)	0.119	32 (22.5 %)	12 (5.9 %)	<0.001
Surgery in the 24 h prior to antibiotic dose sampled	78 (22.7 %)	19 (28.8 %)	59 (21.3 %)	0.197	41 (28.9 %)	37 (18.4 %)	0.024
RRT	33 (9.6 %)	1 (1.5 %)	32 (11.6 %)	0.013	2 (1.4 %)	31 (15.4 %)	<0.001
AB administered using extended or continuous infusion	86 (25.1 %)	7 (10.6 %)	79 (28.5 %)	0.03	18 (12.7 %)	68 (33.8 %)	<0.001
AB for treatment of infection	259 (75.5 %)	38 (57.6 %)	221 (79.8 %)	<0.001	97 (68.3 %)	162 (80.6 %)	0.016

MIC minimal inhibitory concentration, *APACHE* acute physiology and chronic health evaluation, CL_{CR} creatinine clearance, *SOFA* sequential organ failure assessment, *AB* antibiotic, DD_{ICU} daily dose in intensive care unit patients, *RRT* renal replacement therapy

Table 3 Multivariate analysis, with PK/PD target non-attainment as the dependent variable

	p value	Odds ratio	95 % CI	
			Lower	Upper
Factors associated with not reaching concentrations above the MIC during at least 50 % of the dosing interval				
Age (per year)	0.151	0.983	0.960	1.006
Interval between start AB and sampling (per day)	0.086	0.905	0.807	1.014
APACHE II score on admission (per point)	0.879	0.996	0.952	1.043
SOFA on the day of AB sampling (per point)	0.069	0.908	0.818	1.008
Cockroft-Gault CL_{CR} (per mL/min)	0.173	1.004	0.998	1.010
Trauma as an admission diagnosis	0.947	0.968	0.368	2.543
Surgery in the previous 24 h	0.681	0.828	0.337	2.034
Extended/continuous infusion (vs. intermittent)	0.027	0.340	0.131	0.882
Prophylaxis indication	0.067	2.088	0.949	4.595
Hosmer–Lemeshow goodness of fit, $p = 0.928$				
Factors associated with not reaching concentrations above the MIC during 100 % of the dosing interval				
Age (per year)	0.656	0.995	0.975	1.016
Interval between start AB and sampling (per day)	0.101	0.932	0.856	1.014
APACHE II score on admission (per point)	0.425	1.015	0.978	1.054
SOFA on the day of AB sampling (per point)	0.733	0.986	0.909	1.069
Cockroft-Gault CL_{CR} (per mL/min)	0.000	1.012	1.006	1.019
Ratio antibiotic dose to DD_{ICU}	0.338	0.977	0.991	1.003
Trauma as an admission diagnosis	0.056	2.596	0.977	6.899
Surgery in the previous 24 h	0.068	2.105	0.946	4.682
Extended/continuous infusion (vs. intermittent)	0.000	0.252	0.118	0.538
Prophylaxis indication	0.834	0.926	0.452	1.898
Hosmer–Lemeshow goodness of fit, $p = 0.225$				

AB antibiotic, *APACHE* acute physiology and chronic health evaluation, *CL_{CR}* creatinine clearance, *SOFA* sequential organ failure assessment

albeit guidelines that are derived from non-critically ill patients, which often fail to consider the unique physiology encountered within the ICU [17, 18]. As such, 'one size fits all', is unlikely to be an effective approach to β-lactam antibiotic dosing in this setting.

In the overall study population, use of intermittent infusion was the most significant factor associated with target non-attainment, both for 50 % and 100 % $fT_{>MIC}$. The type of infusion was such a significant covariate in the model that it eliminated the effects of other variables. When considering only patients receiving intermittent administration only, other factors, such as recent surgery and the interval between the start of the antibiotic and the sampling date, became statistically significant as determinants of target non-attainment. Specifically in these patients, the use of extended or continuous infusion could be used to increase antibiotic exposure.

Extended or continuous infusion has been demonstrated to increase target attainment in other studies, most of which involved dosing simulations [19–21]. This study confirms the important PK/PD effect of these infusion strategies, as illustrated by the striking influence in our multivariate model. In this respect, empiric extended or continuous infusion appears to be a very attractive means to counter the PK/PD variability observed in critically ill patients, although important clinical questions remain. Simulation data indeed demonstrate that extended and continuous infusion results in increased target attainment, while recent publications also describe improved clinical outcomes. Dulhunty et al. reported that, compared to intermittent dosing, continuous infusion resulted in statistically significant higher plasma concentrations of meropenem on day 3 of therapy, but this was not statistically significant for piperacillin [22]. They also found increased clinical cure rates in patients treated with continuous infusion [22]. Systematic reviews, however, could not unequivocally demonstrate any clinical superiority of extended or continuous infusion strategies although these analyses have also included non-critically ill patients which may have obscured any therapeutic advantages [23–25]. Although we did not have data on the use of a loading dose at the start of therapy when extended infusion was used, this is a logical and necessary component and may also have contributed to improved target attainment.

Kidney function appears to be an equally important determinant, if maintaining adequate concentrations throughout the dosing interval is considered necessary. CL_{CR} influenced the probability of achieving 100 % $fT_{>MIC}$, with higher values reducing this likelihood. This was remarkably consistent across the most frequently used antibiotics as well as in the group of patients with respiratory tract infections. β-Lactam antibiotics are cleared renally from the circulation, with markedly higher clearances—as might be observed in patients with augmented renal clearance (ARC)—being associated with

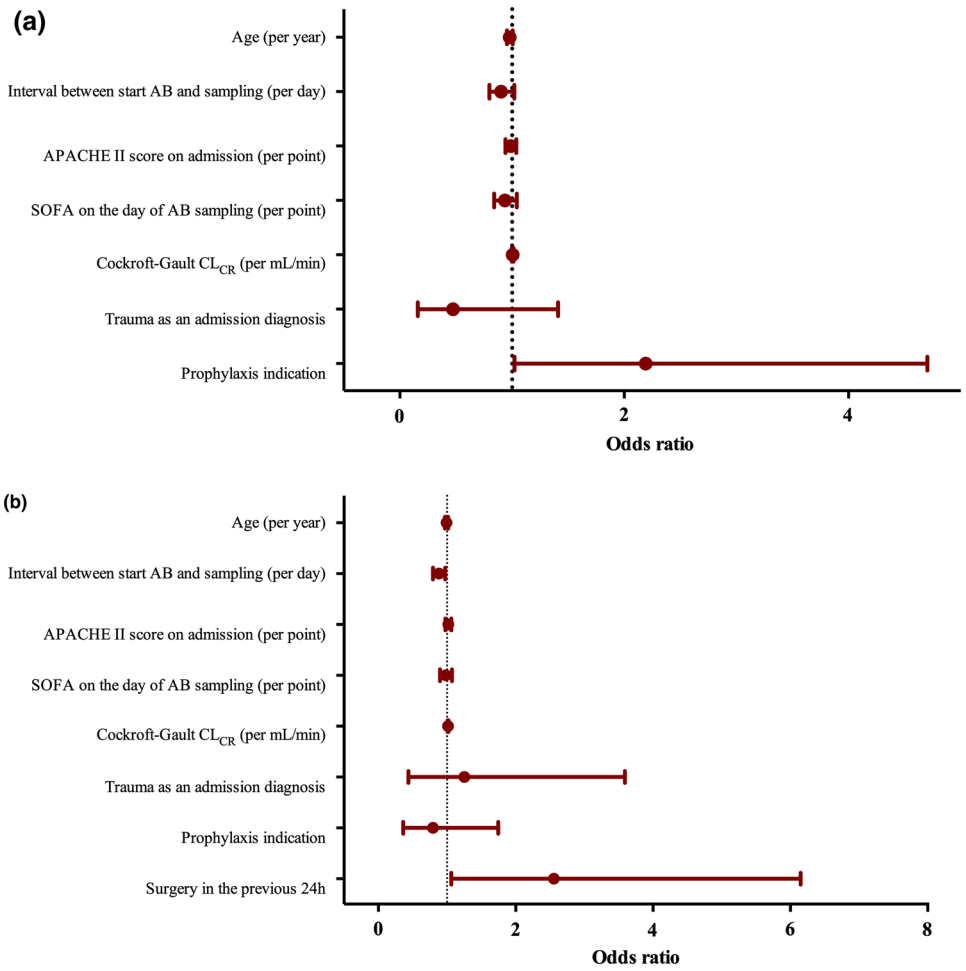

Fig. 1 Multivariable analysis with target non-attainment as the dependent variable in patients treated with intermittent infusion. **a** Odds ratio (with 95 % confidence interval) of factors associated with not reaching concentrations above the MIC during at least 50 % of the dosing interval (Hosmer–Lemeshow goodness of fit, $p = 0.542$). **b** Odds ratio (with 95 % confidence interval) of factors with not reaching concentrations above the MIC during 100 % of the dosing interval (Hosmer–Lemeshow goodness of fit, $p = 0.272$)

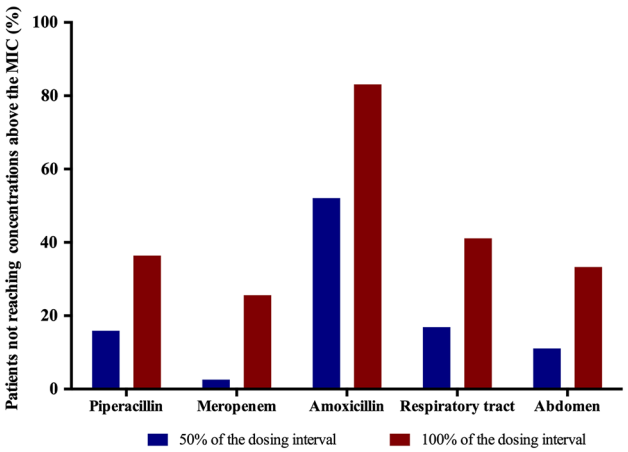

Fig. 2 Target non-attainment according to antibiotic administered most frequently (>50 patients) and major sites of infection

lower antibiotic exposure [5]. Of note, this was an important covariate in both the overall population, and in patients treated with intermittent administration only. ARC is a frequent finding in the ICU [26, 27], and has been linked to specific patient populations such as burns or trauma [28, 29]. A recent study highlighted young age and trauma as independent risk factors as well as a SOFA score of 4 or less [30]. In our study, CL_{CR} did not influence mid-dose target attainment, which is not necessarily a contradictory finding, because elimination of the drug will probably exert a more profound effect on the PK profile in the elimination phase of the dosing interval which is typically in the second half.

Although this study confirms the influence of dosing strategies and renal elimination on β-lactam antibiotic PK/PD target non-attainment, other factors were also identified. These include recent surgery and the interval between starting the antibiotic and sampling. There are a number of reasons why recent surgery affects antibiotic concentrations: intraoperative blood and fluid loss, perioperative fluid loading, systemic inflammation as a result of the surgical trauma, and increased circulating antidiuretic hormone levels [31].

The observation that the interval between starting antibiotic therapy and sampling influences antibiotic

concentrations in those patients receiving intermittent dosing is interesting. It follows that patients may be more likely to be underdosed at the beginning of treatment, with subsequent accumulation leading to higher concentrations—and potentially toxicity—in the steady state phase. Taccone et al. found that early concentrations of β-lactam antibiotics were often insufficient, although higher targets were used in that study [32]. This suggests a potential role for 'front loading' in the early days of treatment, with subsequent dose adaptation—likely downward—at a later stage [33]. The exact reason for this remains unclear, but changes in the volume of distribution of β-lactam antibiotics will certainly play a role. Furthermore, the observed increases in antibiotic concentrations may reflect an improvement in pathophysiology of the patient, with lower clearances when the infection is resolving [34]. Front loading may be clinically highly valuable as the bacterial inoculum is likely highest on day 1 of therapy and optimised drug dosing is likely to have a greater impact on patient outcome at this time.

In this study we evaluated two different PK/PD targets—50 % and 100 % $fT_{>MIC}$, and employed 'worst-case' MIC values, based on EUCAST cut-off levels, that represent only part of the epidemiological spectrum. Whereas the first target has been universally accepted on the basis of convincing animal data, the higher 100 % $fT_{>MIC}$ remains controversial. Data, however, are accumulating that greater β-lactam drug exposure is associated with improved outcomes in critically ill patients [1, 3, 13, 19].

We wish to declare the following limitations of this work. Despite sampling times being standardised across the study population, the dose, dosing interval and infusion strategy were not, and although severity of illness and other variables were considered, we may still have missed important elements that determine antibiotic concentrations. Also a detailed analysis of other factors that could have influenced antibiotic concentrations such as the primary diagnosis, differences in individual organ dysfunction, fluid administration or albumin concentrations was not possible. We did not collect samples throughout the course of the disease, and the within-patient variability remains unexplored. Measures of renal function employed a commonly used estimate (Cockcroft-Gault formula), although its accuracy in the critically ill—particularly those with ARC—remains questionable. Finally, our primary interest was in β-lactam PK in this setting, although the role of the causative microorganism, and its susceptibility, is equally important when effects on bacteriological and clinical outcomes are considered.

Although only 20 % of patients did not achieve the most conservative PK/PD targets, improved methods to identify these patients are still required. Even in patients who receive continuous or extended infusion, target attainment may be inadequate [9] and further research is needed to further improve antibiotic exposure in these patients—notably when less susceptible or borderline resistant microorganisms are involved. In these cases, it may be that dose adjustment based on therapeutic drug monitoring results is the only approach that will ensure a higher proportion of patients achieve target beta-lactam exposures [35–39].

In conclusion, when simulating an empirical setting where a broad range of pathogens at the susceptibility breakpoint is targeted, we found that target attainment using conventional β-lactam antibiotic dosing was generally inadequate, on the basis of data obtained in the DALI study. Although several factors play a role, use of intermittent infusion resulted in a 3- to 4-fold increase in the likelihood of not reaching the desired PK/PD targets. Renal clearance was another important determinant, with fewer patients reaching concentrations above the MIC during the whole dosing interval, when CL_{CR} was high. Recent surgery and the interval between starting drug administration and sampling are two additional clinical characteristics associated with low antibiotic concentrations, both of which mandate further investigation.

Acknowledgments This project has received funding from the European Society of Intensive Care Medicine's European Critical Care Research Network (ESICM ECCRN), and the Royal Brisbane and Women's Hospital Foundation. Jason Roberts is funded in part by a National Health and Medical Research Council of Australia Research Fellowship (NHMRC APP1048652).

Conflicts of interest The authors declare that they have no conflict of interest.

Appendix: Participating investigators

Author name	Affiliation
Jason A. Roberts	Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia Royal Brisbane and Women's Hospital, Brisbane, Australia
Jeffrey Lipman	Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia Royal Brisbane and Women's Hospital, Brisbane, Australia
Therese Starr	Royal Brisbane and Women's Hospital, Brisbane, Australia
Steven C. Wallis	Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia
Sanjoy Paul	Queensland Clinical Trials & Biostatistics Centre, School of Population Health, The University of Queensland, Brisbane, Australia

Appendix continued

Author name	Affiliation
Antonio Margarit Ribas	Hospital Nostra Senyora de Meritxell, Escaldes-Engordany, Andorra
Jan J. De Waele	Ghent University Hospital, Ghent, Belgium
Luc De Crop	Ghent University Hospital, Ghent, Belgium
Herbert Spapen	Universitair Ziekenhuis Brussels, Brussels, Belgium
Joost Wauters	Universitair Ziekenhuis Gasthuisberg, Leuven, Brussels
Thierry Dugernier	Clinique Saint Pierre, Ottignies, Belgium
Philippe Jorens	Universitair Ziekenhuis Antwerpen, Edegem, Belgium
Ilse Dapper	Algemeen Ziekenhuis Monica, Deurne, Belgium
Daniel De Backer	Erasme University Hospital, Brussels, Belgium
Fabio S. Taccone	Erasme University Hospital, Brussels, Belgium
Jordi Rello	Vall d'Hebron Institut of Research, Universitat Autonoma de Barcelona, Spain Centro de Investigación Biomedica En Red- Enfermedades Respiratorias (CibeRes)
Laura Ruano	Vall d'Hebron Institut of Research, Universitat Autonoma de Barcelona, Spain Centro de Investigación Biomedica En Red- Enfermedades Respiratorias (CibeRes)
Elsa Afonso	Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut of Research, Universitat Autonoma de Barcelona, Spain Centro de Investigación Biomedica En Red- Enfermedades Respiratorias (CibeRes)
Francisco Alvarez-Lerma	Hospital Del Mar, Parc Salut Mar, Barcelona, Spain
Maria Pilar Gracia-Arnillas	Hospital Del Mar, Parc Salut Mar, Barcelona, Spain
Francisco Fernández	Centro Médico Delfos, Barcelona
Neus Feijoo	Hospital General de L'Hospitalet, Barcelona, Spain
Neus Bardolet	Hospital General de L'Hospitalet, Barcelona, Spain
Assumpta Rovira	Hospital General de L'Hospitalet, Barcelona, Spain
Pau Garro	Hospital General de Granollers, Barcelona, Spain
Diana Colon	Hospital General de Granollers, Barcelona, Spain
Carlos Castillo	Hospital Txagorritxu, Vitoria, Spain
Juan Fernado	Hospital Txagorritxu, Vitoria, Spain
Maria Jesus Lopez	Hospital Universitario de Burgos, Burgos, Spain
Jose Luis Fernandez	Hospital Universitario de Burgos, Burgos, Spain
Ana Maria Arribas	Hospital Universitario de Burgos, Burgos, Spain
Jose Luis Teja	Hospital Universitario Marques de Valdecilla, Santander, Spain
Elsa Ots	Hospital Universitario Marques de Valdecilla, Santander, Spain
Juan Carlos Montejo	Hospital Universitario 12 de Octubre, Madrid, Spain
Mercedes Catalan	Hospital Universitario 12 de Octubre, Madrid, Spain
Isidro Prieto	Hospital Ramon y Cajal, Madrid, Spain

Appendix continued

Author name	Affiliation
Gloria Gonzalo	Hospital Ramon y Cajal, Madrid, Spain
Beatriz Galvan	Hospital Universitario La Paz, Madrid, Spain
Miguel Angel Blasco	Hospital Universitario Severo Ochoa, Madrid, Spain
Estibaliz Meyer	Hospital Universitario Severo Ochoa, Madrid, Spain
Frutos Del Nogal	Hospital Universitario Severo Ochoa, Madrid, Spain
Loreto Vidaur	Hospital Universitario de Donostia, Donostia, Spain
Rosa Sebastian	Hospital Universitario de Donostia, Donostia, Spain
Pila Marco Garde	Hospital Universitario de Donostia, Donostia, Spain
Maria del Mar Martin Velasco	Hospital Universitario Nuestra Señora de Candelaria, Spain
Rafael Zaragoza Crespo	Hospital Universitario Dr. Peset, Spain
Mariano Esperatti	Institut Clínic del Tòrax, Hospital Clinic, IDIBAPS, Barcelona, Spain Centro de Investigación Biomedica En; Red- Enfermedades Respiratorias (CibeRes)
Antoni Torres	Institut Clínic del Tòrax, Hospital Clinic, IDIBAPS, Barcelona, Spain Centro de Investigación Biomedica En Red- Enfermedades Respiratorias (CibeRes)
Philippe Montravers	Centre Hospitalier Universitaire Bichat-Claude Bernard, AP-HP, Université Paris VII, Paris, France
Olivier Baldesi	Centre Hospitalier Pays D Aix, Aix en Provence, France and AzuRea Group
Herve Dupont	Centre Hospitalier Universitaire d'Amiens, Amiens, France
Yazine Mahjoub	Centre Hospitalier-Universitaire d'Amiens, Amiens, France and AzuRea Group
Sigismond Lasocki	Centre Hospitalier-Universitaire d'Angers, Angers, France
Jean Michel Constantin	Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France and AzuRea Group
Jean François Payen	Centre Hospitalier-Universitaire Grenoble, Grenoble France and AzuRea Group
Claude Martin	Hopital Nord, Marseille, France; AzuRea Group, France
Jacques Albanese	Hopital Nord, Marseille, France and AzuRea Group
Yannick Malledant	Hôpital Pontchaillou, Rennes, France
Julien Pottecher	University Hospital, Strasbourg, France and AzuRea Group
Jean-Yves Lefrant	Centre Hospitalier-Universitaire Nimes, Nimes France and AzuRea Group
Samir Jaber	Hospitalier-Universitaire Montpellier, Montpellier, France and AzuRea Group
Olivier Joannes-Boyau	Centre Hospitalier-Universitaire Bordeaux, Bordeaux, France and AzuRea Group
Christophe Orban	Centre Hospitalier-Universitaire Nice, Nice, France and AzuRea Group
Marlies Ostermann	St Thomas' Hospital, London, UK
Catherine McKenzie	St Thomas' Hospital, London, UK
Willaim Berry	St Thomas' Hospital, London, UK
John Smith	St Thomas' Hospital, London, UK
Katie Lei	St Thomas' Hospital, London, UK

Appendix continued

Author name	Affiliation
Francesca Rubulotta	Charing Cross Hospital, Imperial Healthcare NHS Trust, London, UK
Anthony Gordon	Charing Cross Hospital, Imperial Healthcare NHS Trust, London, UK
Stephen Brett	Hammersmith Hospital, Imperial Healthcare NHS Trust, London, UK
Martin Stotz	St Mary's Hospital, Imperial Healthcare NHS Trust, London, UK
Maie Templeton	St Mary's Hospital, Imperial Healthcare NHS Trust, London, UK
Andrew Rhodes	St George's Hospital, St George's Healthcare NHS Trust, London, UK
Claudia Ebm	St George's Hospital, St George's Healthcare NHS Trust, London, UK
Carl Moran	St George's Hospital, St George's Healthcare NHS Trust, London, UK
Kirsi-Maija Kaukonen	Helsinki University Central Hospital, Helsinki, Finland
Ville Pettilä	Helsinki University Central Hospital, Helsinki, Finland
George Dimopoulos	Attikon University Hospital, Athens, Greece
Despoina Koulenti	Attikon University Hospital, Athens, Greece
Aglaia Xristodoulou	Attikon University Hospital, Athens, Greece
Vassiliki Theodorou	University Hospital of Alexandroupolis, Alexandroupolis, Greece
Georgios Kouliatsis	University Hospital of Alexandroupolis, Alexandroupolis, Greece
Stylianos Fotakis	University Hospital of Alexandroupolis, Alexandroupolis, Greece
Georgios Anthopoulos	251 Air Force General Hospital of Athens, Athens, Greece
George Choutas	251 Air Force General Hospital of Athens, Athens, Greece
Thanos Rantis	251 Air Force General Hospital of Athens, Athens, Greece
Stylianos Karatzas	General Hospital of Athens 'Hippokrateion', Athens, Greece
Margarita Balla	General Hospital of Athens 'Hippokrateion', Athens, Greece
Metaxia Papanikolaou	General Hospital of Athens 'Hippokrateion', Athens, Greece
Pavlos Myrianthefs	'Aghioi Anargyroi' Hospita, Athens, Greece
Alexandra Gavala	'Aghioi Anargyroi' Hospita, Athens, Greece
Georgios Fildisis	'Aghioi Anargyroi' Hospita, Athens, Greece
Antonia Koutsoukou	Sotiria General Hospital, Athens, Greece
Magdalini Kyriakopoulou	Sotiria General Hospital, Athens, Greece
Kalomoira Petrochilou	Sotiria General Hospital, Athens, Greece
Maria Kompoti	'Thriassio' General Hospital of Eleusi, Athen, Greece
Martha Michalia	'Thriassio' General Hospital of Eleusi, Athen, Greece
Fillis-Maria Clouva-Molyvdas	'Thriassio' General Hospital of Eleusi, Athen, Greece
Georgios Gkiokas	Aretaieion University Hospital, Athens, Greece
Fotios Nikolakopoulos	Aretaieion University Hospital, Athens, Greece
Vasiliki Psychogiou	Aretaieion University Hospital, Athens, Greece
Polychronis Malliotakis	University Hospital Herakleion, Crete, Greece
Evangelia Akoumianaki	University Hospital Herakleion, Crete, Greece
Emmanouil Lilitsis	University Hospital Herakleion, Crete, Greece
Vassilios Koulouras	University Hospital of Ioannina, Ioannina, Greece
George Nakos	University Hospital of Ioannina, Ioannina, Greece
Mihalis Kalogirou	University Hospital of Ioannina, Ioannina, Greece
Apostolos Komnos	General Hospital of Larisa, Larisa, Greece
Tilemachos Zafeiridis	General Hospital of Larisa, Larisa, Greece
Achilleas Chovas	General Hospital of Larisa, Larisa, Greece
Kostoula Arvaniti	General Hospital of Thessaloniki 'G. Papageorgiou', Thessaloniki, Greece
Dimitrios Matamis	General Hospital of Thessaloniki 'G. Papageorgiou', Thessaloniki, Greece
Christos Chaintoutis	General Hospital of Thessaloniki 'G. Papageorgiou', Thessaloniki, Greece
Christina Kydona	General Hospital of Thessaloniki 'Hippokrateion', Thessaloniki, Greece
Nikoleta Gritsi-Gerogianni	General Hospital of Thessaloniki 'Hippokrateion', Thessaloniki, Greece
Tatiana Giasnetsova	General Hospital of Thessaloniki 'Hippokrateion', Thessaloniki, Greece
Maria Giannakou	Ahepa University Hospital, Thessaloniki, Greece
Ioanna Soultati	Ahepa University Hospital, Thessaloniki, Greece
Ilias Chytas	Ahepa University Hospital, Thessaloniki, Greece
Eleni Antoniadou	General Hospital 'G. Gennimatas', Thessaloniki, Greece
Elli Antipa	General Hospital 'G. Gennimatas', Thessaloniki, Greece
Dimitrios Lathyris	General Hospital 'G. Gennimatas', Thessaloniki, Greece
Triantafyllia Koukoubani	General Hospital of Trikala, Trikala, Greece
Theoniki Paraforou	General Hospital of Trikala, Trikala, Greece
Kyriaki Spiropoulou	General Hospital of Trikala, Trikala, Greece
Vasileios Bekos	Naval Hospital of Athens, Athens, Greece
Anna Spring	Naval Hospital of Athens, Athens, Greece
Theodora Kalatzi	Naval Hospital of Athens, Athens, Greece
Hara Nikolaou	'Aghia Olga-Konstantopouleion' General Hospital, Athens, Greece
Maria Laskou	'Aghia Olga-Konstantopouleion' General Hospital, Athens, Greece
Ioannis Strouvalis	'Aghia Olga-Konstantopouleion' General Hospital, Athens, Greece
Stavros Aloizos	General Hospital of Athens 'NIMITS', Athens, Greece
Spyridon Kapogiannis	General Hospital of Athens 'NIMITS', Athens, Greece
Ourania Soldatou	General Hospital of Athens 'NIMITS', Athens, Greece
Matteo Bassetti	Azienda Ospedaliera Universitaria Santa Maria della Misericordia, Udine, Italy
Chiara Adembri	Azienda Ospedaliero Universitaria Careggi, Florence, Italy
Gianluca Villa	Azienda Ospedaliero Universitaria Careggi, Florence, Italy
Antonio Giarratano	Università degli Studi di Palermo, Palermo, Italy
Santi Maurizio Raineri	Università degli Studi di Palermo, Palermo, Italy

Appendix continued

Author name	Affiliation
Andrea Cortegiani	Università degli Studi di Palermo, Palermo, Italy
Francesca Montalto	Università degli Studi di Palermo, Palermo, Italy
Maria Teresa Strano	Università degli Studi di Palermo, Palermo, Italy
V. Marco Ranieri	San Giovanni-Battista Molinette, Turin, Italy
Claudio Sandroni	Catholic University School of Medicine, Rome, Italy
Gennaro De Pascale	Catholic University School of Medicine, Rome, Italy
Alexandre Molin	University of Genoa, Genoa, Italy
Paolo Pelosi	University of Genoa, Genoa, Italy
Luca Montagnani	Universitaria San Martino, Genova, Italy
Rosario Urbino	Universitaria S.Giovanni Battista della Città di Torino, Turin, Italy
Ilaria Mastromauro	Universitaria S.Giovanni Battista della Città di Torino, Turin, Italy
Francesco G. De Rosa	Universitaria S.Giovanni Battista della Città di Torino, Turin, Italy
V. Marco Ranieri	Universitaria S.Giovanni Battista della Città di Torino, Turin, Italy
Teresa Cardoso	Hospital de Santo António, Porto, Portugal
Susana Afonso	Hospital de St António dos Capuchos, Lisbon, Portgual
João Gonçalves-Pereira	Hospital de São Francisco Xavier, Lisbon, Portugal
João Pedro Baptista	Hospital de Universidade de Coimbra, Coimbra, Portugal
Murat Akova	Hacettepe University School of Medicine, Ankara, Turkey
Arife Özveren	Hacettepe University School of Medicine, Ankara, Turkey

References

1. McKinnon PS, Paladino JA, Schentag JJ (2008) Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T > MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 31:345–351
2. Muller AE, Punt N, Mouton JW (2013) Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. J Antimicrob Chemother 68:900–906
3. Li C, Du X, Kuti JL, Nicolau DP (2007) Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 51:1725–1730
4. Antonelli M, Bonten M, Cecconi M, Chastre J, Citerio G, Conti G, Curtis JR, Hedenstierna G, Joannidis M, Macrae D, Maggiore SM, Mancebo J, Mebazaa A, Preiser JC, Rocco P, Timsit JF, Wernerman J, Zhang H (2013) Year in review in Intensive Care Medicine 2012. II: Pneumonia and infection, sepsis, coagulation, hemodynamics, cardiovascular and microcirculation, critical care organization, imaging, ethics and legal issues. Intensive Care Med 39:345–364
5. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, Lipman J, Roberts JA (2012) Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142:30–39
6. Ulldemolins M, Roberts JA, Wallis SC, Rello J, Lipman J (2010) Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: special emphasis on unbound pharmacokinetics. J Antimicrob Chemother 65:1771–1778
7. van Loon HJ, Vriens MR, Fluit AC, Troelstra A, van der Werken C, Verhoef J, Bonten MJM (2005) Antibiotic rotation and development of gram-negative antibiotic resistance. Am J Respir Crit Care Med 171:480–487
8. Carlier M, Noe M, De Waele JJ, Stove V, Verstraete AG, Lipman J, Roberts JA (2013) Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients. J Antimicrob Chemother 68:2600–2608
9. Carlier M, Carrette S, Roberts JA, Stove V, Verstraete AG, Hoste E, Decruyenaere J, Depuydt P, Lipman J, Wallis SC, De Waele JJ (2013) Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 17:R84
10. Timsit JF, Citerio G, Bakker J, Bassetti M, Benoit D, Cecconi M, Curtis JR, Hernandez G, Herridge M, Jaber S, Joannidis M, Papazian L, Peters M, Singer P, Smith M, Soares M, Torres A, Vieillard-Baron A, Azoulay E (2014) Year in review in Intensive Care Medicine 2013: iii. sepsis, infections, respiratory diseases, pediatrics. Intensive Care Med 40:471–483
11. Carlier M, De Waele JJ (2013) Identifying patients at risk for augmented renal clearance in the ICU—limitations and challenges. Crit Care 17:130
12. Hites M, Taccone FS, Wolff F, Cotton F, Beumier M, De Backer D, Roisin S, Lorent S, Surin R, Seyler L, Vincent JL, Jacobs F (2013) Case-control study of drug monitoring of beta-lactams in obese critically ill patients. Antimicrob Agents Chemother 57:708–715
13. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J (2014) DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 58:1072–1083

14. Roberts JA, De Waele JJ, Dimopoulos G, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J (2012) DALI: defining antibiotic levels in intensive care unit patients: a multi-centre point of prevalence study to determine whether contemporary antibiotic dosing for critically ill patients is therapeutic. BMC Infect Dis 12:152
15. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
16. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707–710
17. Lipman J, Udy AA, Roberts JA (2011) Do we understand the impact of altered physiology, consequent interventions and resultant clinical scenarios in the intensive care unit? The antibiotic story. Anaesth Intensive Care 39:999–1000
18. Udy AA, Roberts JA, Lipman J (2013) Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Med 39:2070–2082
19. Lodise TP Jr, Lomaestro B, Drusano GL (2007) Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 44:357–363
20. Shea KM, Cheatham SC, Wack MF, Smith DW, Sowinski KM, Kays MB (2009) Steady-state pharmacokinetics and pharmacodynamics of piperacillin/tazobactam administered by prolonged infusion in hospitalised patients. Int J Antimicrob Agents 34:429–433
21. Crandon JL, Ariano RE, Zelenitsky SA, Nicasio AM, Kuti JL, Nicolau DP (2011) Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Med 37:632–638
22. Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Lipman J (2013) Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis 56:236–244
23. Kasiakou SK, Lawrence KR, Choulis N, Falagas ME (2005) Continuous versus intermittent intravenous administration of antibacterials with time-dependent action: a systematic review of pharmacokinetic and pharmacodynamic parameters. Drugs 65:2499–2511
24. Roberts JA, Paratz J, Paratz E, Krueger WA, Lipman J (2007) Continuous infusion of beta-lactam antibiotics in severe infections: a review of its role. Int J Antimicrob Agents 30:11–18
25. Tamma PD, Putcha N, Suh YD, Van Arendonk KJ, Rinke ML (2011) Does prolonged beta-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials. BMC Infect Dis 11:181
26. Grootaert V, Willems L, Debaveye Y, Meyfroidt G, Spriet I (2012) Augmented renal clearance in the critically ill: how to assess kidney function. Ann Pharmacother 46:952–959
27. Udy AA, Baptista JP, Lim NL, Joynt GM, Jarrett P, Wockner L, Boots RJ, Lipman J (2014) Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Crit Care Med 42:520–527
28. Udy A, Boots R, Senthuran S, Stuart J, Deans R, Lassig-Smith M, Lipman J (2010) Augmented creatinine clearance in traumatic brain injury. Anesth Analg 111:1505–1510
29. Udy AA, Putt MT, Boots RJ, Lipman J (2011) ARC–augmented renal clearance. Curr Pharm Biotechnol 12:2020–2029
30. Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J (2013) Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients. Crit Care 17:R35
31. Adnan S, Paterson DL, Lipman J, Kumar S, Li J, Rudd M, Roberts JA (2012) Pharmacokinetics of beta-lactam antibiotics in patients with intra-abdominal disease: a structured review. Surg Infect (Larchmt) 13:9–17
32. Taccone FS, Laterre PF, Dugernier T, Spapen H, Delattre I, Wittebole X, De Backer D, Layeux B, Vincent JL, Wallemacq P, Jacobs F (2010) Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care 14:R126
33. Goncalves-Pereira J, Paiva JA (2013) Dose modulation: a new concept of antibiotic therapy in the critically ill patient? J Crit Care 28:341–346
34. Gous AG, Dance MD, Lipman J, Luyt DK, Mathivha R, Scribante J (1995) Changes in vancomycin pharmacokinetics in critically ill infants. Anaesth Intensive Care 23:678–682
35. De Waele JJ, Carrette S, Carlier M, Stove V, Boelens J, Claeys G, Leroux-Roels I, Hoste E, Depuydt P, Decruyenaere J, Verstraete AG (2014) Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. Intensive Care Med 40:380–387
36. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, Lipman J (2010) Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents 36:332–339
37. Scaglione F (2002) Can PK/PD be used in everyday clinical practice. Int J Antimicrob Agents 19:349–353
38. Blondiaux N, Wallet F, Favory R, Onimus T, Nseir S, Courcol RJ, Durocher A, Roussel-Delvallez M (2010) Daily serum piperacillin monitoring is advisable in critically ill patients. Int J Antimicrob Agents 35:500–503
39. Connor MJJ, Salem C, Bauer SR, Hofmann CL, Groszek J, Butler R, Rehm SJ, Fissell WH (2011) Therapeutic drug monitoring of piperacillin-tazobactam using spent dialysate effluent in patients receiving continuous venovenous hemodialysis. Antimicrob Agents Chemother 55:557–560