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Continuous versus intermittent infusion of cefotaxime in critically ill patients: a randomized controlled trial comparing plasma concentrations

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Background: In critical care patients, reaching optimal β-lactam concentrations poses challenges, as infections are caused more often by microorganisms associated with higher MICs, and critically ill patients typically have an unpredictable pharmacokinetic/pharmacodynamic profile. Conventional intermittent dosing frequently yields inadequate drug concentrations, while continuous dosing might result in better target attainment. Few studies address cefotaxime concentrations in this population.

Objectives: To assess total and unbound serum levels of cefotaxime and an active metabolite, desacetylcefotaxime, in critically ill patients treated with either continuously or intermittently dosed cefotaxime.

Methods: Adult critical care patients with indication for treatment with cefotaxime were randomized to treatment with either intermittent dosing (1 g every 6 h) or continuous dosing (4 g/24 h, after a loading dose of 1 g). We defined a preset target of reaching and maintaining a total cefotaxime concentration of 4 mg/L from 1 h after start of treatment. CCMO trial registration number NL50809.042.14, Clinicaltrials.gov NCT02560207.

Results: Twenty-nine and 30 patients, respectively, were included in the continuous dosing group and the intermittent dosing group. A total of 642 samples were available for analysis. In the continuous dosing arm, 89.3% met our preset target, compared with 50% in the intermittent dosing arm. Patients not reaching this target had a significantly higher creatinine clearance on the day of admission.

Conclusions: These results support the application of a continuous dosing strategy of β-lactams in critical care patients and the practice of therapeutic drug monitoring in a subset of patients with higher renal clearance and need for prolonged treatment for further optimization, where using total cefotaxime concentrations should suffice.

Introduction

Infection in ICUs is an important problem, leading to high antimicrobial consumption and substantial morbidity and mortality. In a large, international point-prevalence study, more than half of patients were considered to have an infection, while 71% were receiving antibiotics.[1] In the critically ill, β-lactams are the most prescribed group of antibiotics.[2]

To achieve the best clinical outcome, timely administration of appropriate antibiotics is critical in ICU patients with severe infections.[3–6] To avoid treatment failure and emergence of antibiotic resistance, correct dosing is equally important.[7,8] With β-lactams, the bactericidal effect depends on the time the unbound serum concentration exceeds the MIC of the causative microorganism.[9] Although, for cephalosporins, preclinical studies show a bactericidal effect for 60%–70% $fT_{>MIC}$, clinical data involving the critically ill suggest a more aggressive approach to achieve a minimum target of 100% $fT_{\geq MIC}$ is needed to ensure optimal clinical cure in this vulnerable population.[9,10] Optimal dosing in the

individual ICU patient poses challenges as critical illness is associated with pharmacokinetic (PK) and pharmacodynamic (PD) differences compared with the non-critically ill.[9,11] This patient group is typically prone to infections with microorganisms associated with higher MICs.[12] Conventional dosing can lead to subtherapeutic levels due to augmented renal clearance in the case of renally cleared drugs and an increase in the patient's volume of distribution in the case of hydrophilic drugs, such as β-lactams.[9] Recently, a large multinational PK point-prevalence study including eight β-lactams showed that less than half of the patients reached a predefined preferred PK/PD target. Patients treated for infections in this study who did not achieve a target of 50% $fT_{>MIC}$ were 32% less likely to have a positive clinical outcome.[13] Conversely, renal dysfunction can result in elevated antibiotic concentrations and/or accumulation of metabolites.[14] Cefotaxime, however, seems to have a high threshold for (neuro)toxicity.[10] The complex PK changes in the critically ill are outlined in detail in several reviews.[9,14,15]

Based on their time-dependent profile, continuous as opposed to intermittent dosing of β-lactams seems a logical alternative in the ICU population. This concept is supported by PK studies showing better target attainment using a continuous dosing approach.[16–18]

In critical care units throughout the Netherlands, β-lactams are also widely employed in the context of selective decontamination of the digestive tract (SDD). In an environment with low levels of antimicrobial resistance, its use is associated with a reduction in ICU and hospital mortality and ICU-acquired bacteraemia.[19] The SDD approach includes 4 days of preemptive treatment with a cephalosporin, such as cefotaxime.[2]

To date, only two observational studies on cefotaxime dosing in comparable critical care populations are available, both of which evaluated intermittent dosing.[20,21] As cefotaxime is widely prescribed, more knowledge about its PK in ICU patients is important to ensure best efficacy of the drug. Therefore, the aim of this study was to ascertain which dosing regimen of cefotaxime results in the most rapid and persistent target attainment in critically ill patients. We defined our target as a total (bound and unbound) cefotaxime concentration of at least 4 mg/L, to be reached within 1 h after start of treatment and to be maintained during treatment. Both total (bound and unbound) concentrations and unbound concentrations of cefotaxime and its active metabolite desacetylcefotaxime were evaluated.

Patients and methods

Study design and patient population

This randomized controlled single-centre study was conducted in a tertiary referral hospital in the Netherlands between November 2015 and June 2016. The study was approved by the Medical Ethics Board of this hospital (ethics approval number METc 2014/468, CCMO trial registration number NL50809.042.14, Clinicaltrials.gov NCT02560207). Enrolment with deferred consent was used. Written consent was obtained from the patient or next of kin.

Patients aged ≥18 years were eligible for inclusion. It was possible to start cefotaxime (Sandoz B.V., Almere, The Netherlands) per protocol as part of SDD if a patient had an anticipated mechanical ventilation for >48 h and ICU stay of >72 h. The duration of treatment was 4 days, or shorter if the patient was discharged and transferred to a ward within that period, as SDD including cefotaxime was discontinued on discharge. Exclusion criteria were: inability to acquire written informed consent; contra-indication for cefotaxime, such as cephalosporin allergy; no indication for placement of an arterial line; and use of renal replacement therapy or extracorporeal life support. Patients were randomized by a research nurse using a secure web application service provided by the Trial Coordination Center of this hospital. After randomization, patients were treated with either intermittent dosing (1 g every 6 h) or continuous dosing (4 g/24 h, after a loading dose of 1 g infused over 40 min) using a syringe pump (Alaris® GH perfusor; CareFusion, Rolle, Switzerland). Target attainment was the primary endpoint of this study and was based on the cefotaxime MIC breakpoint for Enterobacterales of 1 mg/L, as defined by EUCAST.[22] Consequently, we defined target unbound cefotaxime levels to be at least 1 mg/L. Since 25%–40% of cefotaxime is bound to plasma proteins, and to allow for a safety margin due to variability in tissue penetration in ICU patients,[14,23] total target (protein-bound and unbound) cefotaxime levels were defined as 4 mg/L and higher, at any given timepoint during treatment.

Data collection

Blood samples were drawn from an indwelling arterial catheter, placed for routine monitoring. In patients randomized for continuous administration, 2 mL blood samples were drawn on Day 1 at 0 min, then at 40 min from start of infusion of the loading dose, i.e. immediately after completion of the loading dose. Subsequent samples were drawn at 1, 2, 4, 8, 12 and 24 h after start of administration on Day 1. During the subsequent days of continuous infusion, samples were drawn every 12 h, until the end of treatment on Day 4. In patients randomized for intermittent dosing, 2 mL blood samples were drawn on Day 1 at 0 min, directly after infusion at 40 min, 1, 2, 4, 8, 12 and 24 h after start of administration on Day 1. After that, trough and peak levels were obtained once daily just before and 40 min after bolus infusion, respectively, until the end of treatment. Samples were centrifuged and serum was frozen at −80°C, until analysis. Patient characteristics included demographic and clinical data, assessment of severity of illness reflected by the APACHE IV score and laboratory investigations. Baseline was considered start of cefotaxime treatment.

PK analysis

Plasma concentrations of cefotaxime (total and unbound) and both total and unbound concentrations of its active metabolite desacetylcefotaxime were determined at the laboratory of the Department of Clinical Pharmacy and Pharmacology of University Medical Center Groningen by means of a validated analytical method using LC-MS/MS. In brief, cefotaxime and desacetylcefotaxime were analysed by means of an isotope dilution method. As internal standard, a stable isotope of cefotaxime was used. LC-MS/MS equipment (Thermo Fisher Scientific, Waltham, USA) consisted of a Vanquish UPLC pump, autosampler, column compartment and Quantiva triple quadrupole mass spectrometer. Total cefotaxime and desacetylcefotaxime concentrations were measured after protein precipitation of the samples; free cefotaxime and desacetylcefotaxime were measured after temperature-controlled ultrafiltration of the samples using Nanosep 30K Omega Centrifugal Devices (Pall Life Sciences, Portsmouth, UK) and measuring cefotaxime and desacetylcefotaxime in the ultrafiltrate. The lower limit of quantitation of both cefotaxime and desacetylcefotaxime was 1 mg/L and the method was linear up to 200 mg/L for cefotaxime and up to 100 mg/L for desacetylcefotaxime. The assay complied with the criteria for bioanalytical method development as issued by the EMA.[24] Target attainment was assessed by comparing measured concentrations with our preset target as described above; target attainment was thus defined by reaching a target of at least 4 mg/L for total cefotaxime and at least 1 mg/L for unbound cefotaxime within 1 h after start of treatment, and maintaining this target thereafter.

Statistical analysis

Target attainment was presented as percentage of time above target per subject and the percentage reaching the target at group level. Continuous parameters such as age, weight, height, length of stay (LOS) and duration of mechanical ventilation were collected and depicted in absolute figures and medians, including IQR. Non-normally distributed continuous variables were compared by Mann–Whitney *U*-test for unpaired data. Categorical data, which were depicted as proportions, were compared using the χ^2 test or Fisher's exact test (two-sided; type I, 5%). PK analysis was performed with and without correction for outliers and apparent permutations (trough level taken as peak level and vice versa). Outliers, assumed to have been caused by procedural shortcomings such as sampling during bolus infusion, were defined as higher than 3× the IQR above Q3 and lower than 3× below Q1. SPSS v 23.0 (IBM Corp., Armonk, NY, USA) and Minitab® 18.1 (©2017 Minitab, Inc.) were used for statistical analyses and graphics.

Power calculation

Based on available literature on β-lactam antibiotics, we expected continuous dosing to result in adequate drug levels in 80% of patients, compared with 40% of patients in the intermittent group.[17] Therefore, our sample size (taking into account an absolute effect size of 40%, an alpha of 0.05 and a beta of 0.8) was 23 patients per group. Correcting for potential dropout, we aimed for 30 patients per group.

Results

Demographic data and clinical characteristics

Two-hundred and eight patients were deemed eligible for inclusion. Of these, 128 were excluded from randomization; 111 because admission occurred out of office hours and a research nurse was not available, 12 because inclusion criteria were not met and 5 were missed at screening. Eighty ICU patients were screened for eligibility and were randomized for treatment with continuous or intermittent dosing. Consent could not be obtained from 11 patients, 5 patients were excluded because of breach of protocol, such as wrong dosing, 2 patients died shortly after admittance, 1 patient had no indication for an arterial line, 1 patient received cefotaxime only very briefly and 1 patient did not receive cefotaxime. We thus included 59 patients for analysis; 29 in the continuous dosing arm and 30 in the intermittent dosing arm. Patient characteristics are shown in Table 1. Of the total group, most of the patients were middle-aged and male, with a median LOS in the ICU of 6 days and with a median APACHE IV score of 70. Weight and BMI were significantly different between the continuous and intermittent groups, with the heavier patients in the intermittent group.

PK data

After correction for outliers (n=15), 627 samples from 59 patients could be analysed (327 samples from 29 patients and 300 samples from 30 patients in the continuous group and the intermittent group, respectively); 271 and 247 samples were available from 1 h after start of treatment in the continuous group and the intermittent group, respectively. The median number of samples per patient was 11 (IQR=9–14) for the continuous group and 10 (IQR=7–13) (not significant) for the intermittent group (Table S1, available as Supplementary data at *JAC* Online). For total cefotaxime concentrations, the target of 4 mg/L was reached within 1 h after start of treatment and maintained thereafter in 89.3% of patients in the continuous versus 50% of patients in the intermittent arm (P=0.003) (Figure 1 and Table S2). From 1 h after start of treatment, 266 of 271 (98.2%) available samples in the continuous group had a cefotaxime concentration ≥4 mg/L, versus 194 of 247 (78.5%) samples in the intermittent group (P<0.0001). For unbound cefotaxime concentrations, the target of 1 mg/L was reached and maintained in 96.4% of patients in the continuous arm versus 71.4% in the intermittent arm (P=0.025) (Figure 2 and Table S3). Comparing all available concentration measurements from 1 h after start of treatment per group, median total cefotaxime, unbound cefotaxime, total desacetylcefotaxime and unbound desacetylcefotaxime concentrations were all significantly higher in the continuous group compared with the intermittent group (Figures 1–3 and Table S4). In patients not reaching our predefined target, creatinine clearance on ICU admittance was significantly higher than in patients who did reach this target. APACHE IV score, albumin concentration or BMI on ICU admittance were not associated with target attainment (Table 2).

Discussion

Our randomized controlled study assessing total and unbound cefotaxime, as well as total and unbound desacetylcefotaxime concentrations in a heterogeneous group of ICU patients, showed that continuous dosing of cefotaxime in adult critical care patients will lead to better PK target attainment compared with intermittent dosing.

Our results are in line with available literature.[17,25] In a prospective, double-blind, randomized controlled trial, Dulhunty *et al.*[17] compared PK and clinical outcome in 60 patients with severe sepsis allocated to treatment with a β-lactam antibiotic (piperacillin/tazobactam, meropenem or ticarcillin/clavulanate) through either continuous or intermittent dosing. Plasma antibiotic concentration exceeded a predefined MIC (based on breakpoints for *Pseudomonas aeruginosa*; free plasma antibiotic concentrations of 16 mg/L for piperacillin and ticarcillin, 2 mg/L for meropenem) in 82% of patients in the continuous arm versus 29% in the intermittent arm. Survival and ICU-free days did not significantly differ between the groups. As a wide array of targets and dosing schedules are employed, comparing PK studies on β-lactam dosing is complex. However, overall, as summarized in a recent review by Veiga and Paiva,[25] continuous dosing seems to result in better PK results compared with intermittent dosing. Moreover, a better clinical outcome using prolonged or continuous infusion in the critically ill is suggested in several recent meta-analyses.[26–29] A large multicentre randomized controlled trial powered on mortality comparing continuous with intermittent dosing of β-lactams is currently recruiting patients.[30] To date, only a few studies on cefotaxime dosing in comparable cohorts of ICU patients have been published. Seguin *et al.*[20] assessed plasma and peritoneal levels of cefotaxime and its metabolite in 11 patients with secondary peritonitis treated with 4 g of cefotaxime daily through continuous infusion, following a bolus of 2 g. Although wide interpatient variation was found, this regimen provided a peritoneal concentration of >5× MIC for the recovered Enterobacteriaceae and the susceptibility breakpoint of cefotaxime for facultative Gram-negative microorganisms. In a prospective, open-label, non-randomized setting, Abhilash *et al.*[21] examined plasma concentrations of

Table 1. Demographic data and clinical characteristics

Variable	total	continuous	intermittent	*P*
Number of patients	59	29	30	
Male/female, *n*/*n* (%/%)	39/20 (66/34)	20/9 (69/31)	19/11 (63/37)	0.648
Age (years), median (IQR)	67 (56–77)	67 (60.5–74)	66.5 (45.25–78.25)	0.808
Height (cm), median (IQR)	175 (170–185)	175 (171–185)	175 (168.25–185)	0.503
Weight (kg), median (IQR)	82 (74–97)	77 (70–93.50)	85.50 (75.75–101.25)	0.05
BMI (kg/m^2), median (IQR)	26.6 (24.5–30.9)	25.4 (22.7–28.9)	28.9 (24.5–32.2)	0.04
LOS in the ICU at the start of cefotaxime treatment (days), median (IQR)	1 (0–1)	1 (0–1.5)	1 (0–1)	0.315
Duration of cefotaxime (days), median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.106
Patient category, *n* (%)	59 (100)	29 (100)	30 (100)	0.362
medical	17 (28.8)	7 (24.1)	10 (33.3)	
surgical	20 (33.9)	9 (31)	11 (36.7)	
trauma	4 (6.8)	1 (3.4)	3 (10)	
neurological	6 (10.2)	5 (17.2)	1 (3.3)	
other	12 (20.3)	7 (24.1)	5 (16.7)	
Acute/planned admission, *n*/*n* (%/%)	15/44 (25.4/74.6)	9/20 (31/69)	6/24 (20/80)	0.33
APACHE IV score, median (IQR)	70 (53–93)	71 (57.5–95.5)	67.5 (49.5–90.75)	0.422
Vasopressor use—yes/no, *n*/*n* (%/%)	31/28 (53/47)	16/13 (55/45)	15/15 (50/50)	0.446
Fluid resuscitation—yes/no, *n*/*n* (%/%)	35/24 (59/41)	19/10 (66/34)	16/14 (53/47)	0.246
Mechanical ventilation—yes/no, *n*/*n* (%/%)	50/9 (85/15)	24/5 (83/17)	26/4 (87/13)	0.478
Serum albumin (g/L), median (IQR)	30 (26–35)	30 (26–34)	30.5 (26–36)	0.470
Serum creatinine (μmol/L), median (IQR)	81 (70–107)	84 (68–107)	80.5 (70–109)	0.617
Serum ALT (U/L), median (IQR)	27 (13–57)	21 (11.5–51.5)	37.5 (20.75–63.75)	0.089
Urinary creatinine 24 h (mmol/24 h), median (IQR)	9 (7–13)	9 (6.1–12.5)	10 (7.75–14)	0.186
Creatinine clearance (mL/min), median (IQR)	80 (49–112)	75 (42.5–99.5)	84 (56.5–134.25)	0.214
LOS in the ICU (days), median (IQR)	6 (4–10)	6 (4–10.5)	6.5 (3–10.25)	0.483
ICU mortality, *n* (%)	10 (16.9)	4 (13.8)	6 (20)	0.731
Hospital mortality, *n* (%)	11 (18.6)	5 (17.2)	6 (20)	1.000

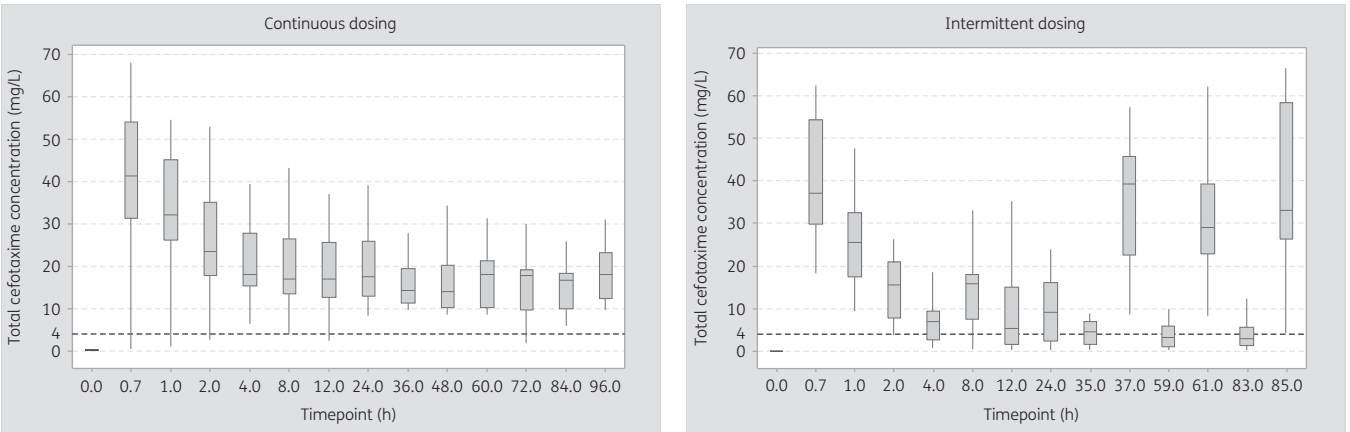

Figure 1. Boxplot of total cefotaxime concentration, per timepoint, per treatment group.

cefotaxime in 30 critically ill patients treated with 1 g of cefotaxime three times daily infused over 30 min. Cefotaxime levels were found to be below the MIC and <5× MIC for the isolated microorganisms in 16.7% and 43.3% of patients, respectively.

The patients in our cohort who did not reach our target had higher creatinine clearance. Augmented renal clearance is a recognized risk factor for underdosing of β-lactams.[31,32]

Strengths of our study are that we used a randomized controlled design and recruited typical 'real-life' ICU patients. We used dense sampling to allow for a precise assessment of the difference in target attainment. Furthermore, we also assessed unbound concentrations and the active metabolite desacetylcefotaxime to explore differences in drug metabolism. However, as the antibacterial activity of desacetylcefotaxime is 4–8-fold less than

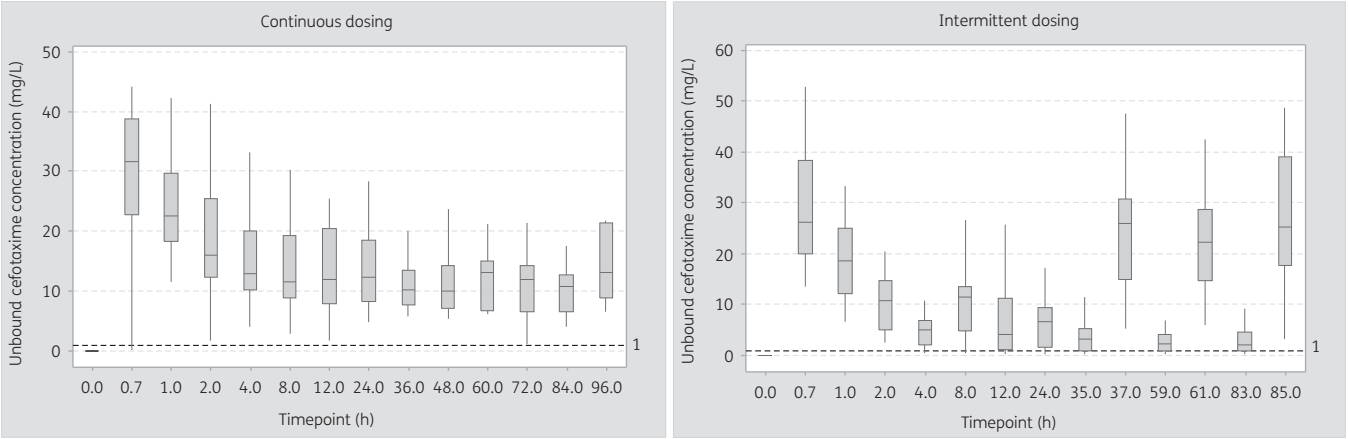

Figure 2. Boxplot of unbound cefotaxime concentration, per timepoint, per treatment group.

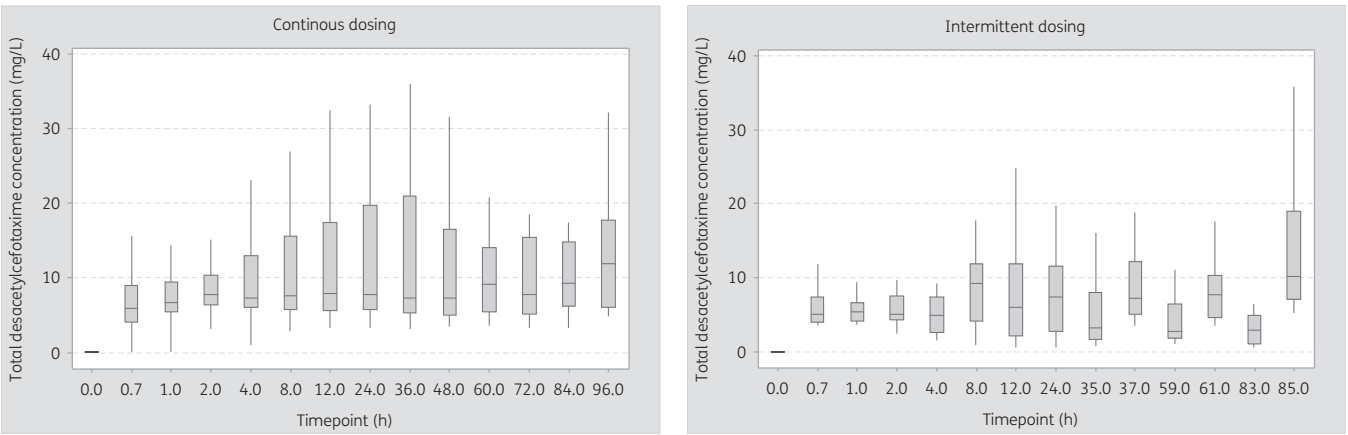

Figure 3. Boxplot of total desacetylcefotaxime concentration, per timepoint, per treatment group.

Table 2. Baseline characteristics in patients who did and did not reach and maintain a total cefotaxime target concentration of ≥4 mg/L

Baseline characteristic	Target reached (n=39)	Target not reached (n=17)	P^a
Albumin (g/L), median (IQR)	29 (26–34)	32 (28–39.5)	0.112
APACHE IV score, median (IQR)	73 (54–97)	61 (43.5–91.5)	0.121
BMI (kg/m^2), median (IQR)	25.7 (24.5–30.3)	27.5 (23.5–33.8)	0.354
Creatinine clearance (mL/min), median (IQR)	65 (30–99)	114 (84–173)	0.000

Data on target attainment available for 28 of 29 (96.6%) patients in the continuous group and for 28 of 30 (93.3%) patients in the intermittent group.
[a]Calculated based on Mann–Whitney *U*-test, two-sided.

cefotaxime and its contribution to the total concentration is low, we chose not to integrate the desacetylcefotaxime concentrations in the analysis of total cefotaxime concentration.[33] In our cohort, we did not find accumulation of desacetylcefotaxime (Table S4). As expected, comparing the two treatment arms, results from the total and unbound concentrations of cefotaxime and desacetylcefotaxime were comparable, with higher median concentrations in the continuous dosing arm. As the free fraction percentage of cefotaxime appeared to have a low range in our cohort of heterogeneous critical care patients (Table S4), measurements of total cefotaxime concentrations for therapeutic drug monitoring (TDM) purposes should suffice. While not yet a standard procedure in many centres, the use of TDM in optimization by personalizing antibiotic dosing of β-lactams in the critical care population is gaining ground.[10,25,34,35] Although evidence for a reduction in mortality is lacking thus far,[34] the use of TDM has proven to lead to better PK target attainment[36] and might be especially useful in patients with high PK variability such as those with higher renal clearance[10,25] who are to be treated for a longer period of time; in our cohort, with a median treatment period of 4 days, TDM would hardly be feasible.

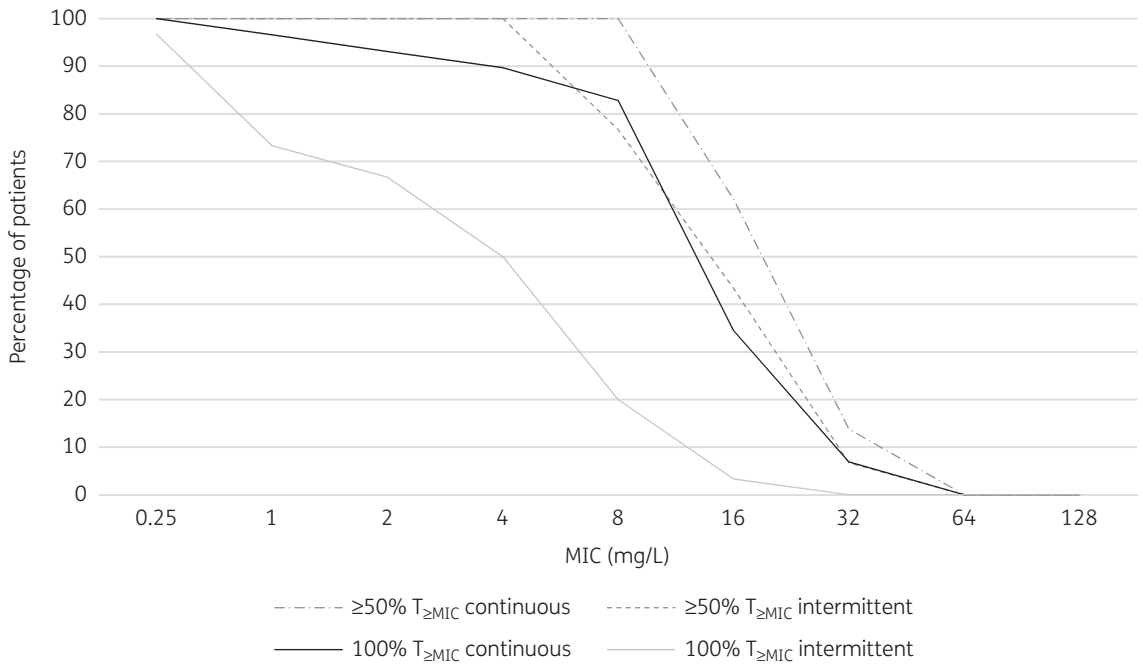

Figure 4. Target attainment, per MIC, per treatment group and target.

Higher dosing in this category could be an alternative strategy to obtain better target attainment when TDM is not available.[10]

This study also has some limitations. Although, for β-lactams, a %$fT_{>MIC}$ between 40% and 70% for a bactericidal effect is described in earlier *in vivo* studies,[7] and different targets have been assessed,[13] a target of an unbound concentration of at least 4× the MIC for 100% of the time is considered optimal and this target is advocated in several recent publications.[6,10,25] Based on these recommendations, our target (100% $fT_{>MIC}$) can be considered somewhat conservative. Applying the strictest target of 100% $fT_{>4\times MIC}$ to our data, 82.4% versus 23.3% of patients would reach this target from 1 h after start of treatment in the continuous and intermittent arms, respectively (Table S5). Inclusion was feasible during office hours only. This might have created a selection bias for the study population, but not for allocation to the treatment arms. As this study was carried out in a single-centre setting and patients with renal replacement therapy or extracorporeal life support were excluded, our results might not be generalizable to all critical care patients. After careful consideration of the small sample size and heterogeneous nature of the population, we chose not to include clinical outcome, as we felt the results would not be supported by an adequately powered study. A large randomized controlled trial with clinical outcome as endpoint is on its way.[30] Baseline characteristics such as creatinine clearance and serum albumin concentration were evaluated at start of treatment and not over time. The baseline weight and BMI were significantly higher in the intermittent-dosing treatment group. Obesity as a risk factor for underdosing is recognized in some studies,[37–39] but not supported by other publications.[40,41] In our study, we did not find such an association. Some results were excluded from analysis, as they were identified as outliers, and some results were apparent permutations. Results of an analysis including these data points did not alter our main results (Tables S6–S10 and Figure S1). As cefotaxime was prescribed as preemptive antimicrobial treatment in the context of SDD, we used a presumptive MIC as issued by EUCAST. Target non-attainment would occur more often in the intermittent group at higher MIC targets (Tables S5 and S11 and Figure 4).

Conclusions

In our cohort of 59 patients, continuous dosing resulted in higher median total and unbound cefotaxime and desacetylcefotaxime levels, and our predefined target was met more often in the continuous dosing group. Patients who did not reach this target had higher creatinine clearance. Our study endorses a continuous dosing strategy of β-lactams in the challenge to optimize control of infectious problems in the vulnerable critical care population. In a selected patient subgroup with augmented renal clearance, higher dosing is indicated. TDM based on total cefotaxime concentrations could further optimize treatment in cases where prolonged treatment is indicated.

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Transparency declarations

None to declare.

Author contributions

H.A., W.B., W.D., J.-W.C.A. and J.G.Z. contributed to the conception and design of the study protocol. H.A., W.B., W.D. and J.G.Z. coordinated the study and the data collection. H.A. and W.B. wrote the first draft of the manuscript. K.v.H. performed the pharmacokinetic analyses. W.B., D.J.T. and J.-W.C.A. supervised the pharmacokinetic analyses and contributed to the analysis and interpretation of these data. H.A. performed the analysis of clinical parameters, W.B. and H.A. performed pharmacokinetic analysis. J.-W.C.A., D.J.T., W.D. and J.G.Z. supervised data collection and data analysis and revised the manuscript. K.v.H., W.D., D.J.T., J.-W.C.A. and J.G.Z. revised the manuscript. All authors made a substantial contribution to the manuscript and read and approved the final manuscript.

Supplementary data

Tables S1 to S11 and Figure S1 are available as Supplementary data at *JAC* Online.

References

1 Vincent JL, Rello J, Marshall J *et al*. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323–9.

2 de Smet AM, Kluytmans JA, Cooper BS *et al*. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009; **360**: 20–31.

3 Kumar A, Roberts D, Wood KE *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; **34**: 1589–96.

4 Ferrer R, Martin-Loeches I, Phillips G *et al*. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med* 2014; **42**: 1749–55.

5 Garnacho-Montero J, Ortiz-Leyba C, Herrera-Melero I *et al*. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. *J Antimicrob Chemother* 2008; **61**: 436–41.

6 Abdul-Aziz MH, Driver E, Lipman J *et al*. New paradigm for rapid achievement of appropriate therapy in special populations: coupling antibiotic dose optimization rapid microbiological methods. *Expert Opin Metab Toxicol* 2018; **14**: 693–708.

7 Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. *Nat Rev Microbiol* 2004; **2**: 289–300.

8 Thomas JK, Forrest A, Bhavnani SM *et al*. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob Agents Chemother* 1998; **42**: 521–7.

9 Roberts JA, Abdul-Aziz MH, Lipman J *et al*. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis* 2014; **14**: 498–509.

10 Guilhaumou R, Benaboud S, Bennis Y *et al*. Optimization of the treatment with β-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics (Societe Francaise de Pharmacologie et Therapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Societe Francaise d'Anesthesie et Reanimation—SFAR). *Crit Care* 2019; **23**: 104.

11 Goncalves-Pereira J, Povoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams. *Crit Care* 2011; **15**: R206.

12 Hanberger H, Garcia-Rodriguez JA, Gobernado M *et al*. Antibiotic susceptibility among aerobic gram-negative bacilli in intensive care units in 5 European countries. French and Portuguese ICU Study Groups. *JAMA* 1999; **281**: 67–71.

13 Roberts JA, Paul SK, Akova M *et al*. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 2014; **58**: 1072–83.

14 Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med* 2009; **37**: 840–51.

15 Scaglione F, Paraboni L. Pharmacokinetics/pharmacodynamics of antibacterials in the intensive care unit: setting appropriate dosing regimens. *Int J Antimicrob Agents* 2008; **32**: 294–301.

16 Abdul-Aziz MH, Sulaiman H, Mat-Nor MB *et al*. β-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open labelled randomised controlled trial of continuous versus intermittent β-lactam infusion in critically ill patients with severe sepsis. *Intensive Care Med* 2016; **42**: 1535–45.

17 Dulhunty JM, Roberts JA, Davis JS *et al*. Continuous infusion of β-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. *Clin Infect Dis* 2013; **56**: 236–44.

18 Abdul-Aziz MH, Lipman J, Akova M *et al*. Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. *J Antimicrob Chemother* 2016; **71**: 196–207.

19 Plantinga NL, de Smet A, Oostdijk EAN *et al*. Selective digestive and oropharyngeal decontamination in medical and surgical ICU patients: individual patient data meta-analysis. *Clin Microbiol Infect* 2018; **24**: 505–13.

20 Seguin P, Verdier MC, Chanavaz C *et al*. Plasma and peritoneal concentration following continuous infusion of cefotaxime in patients with secondary peritonitis. *J Antimicrob Chemother* 2009; **63**: 564–7.

21 Abhilash B, Tripathi CD, Gogia AR *et al*. Variability in plasma concentration of cefotaxime in critically ill patients in an intensive care unit of India and its pharmacodynamic outcome: a nonrandomized, prospective, open-label, analytical study. *J Pharmacol Pharmacother* 2016; **7**: 15–21.

22 EUCAST. Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 9.0, 2019. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf.

23 Tangden T, Ramos Martin V, Felton TW *et al*. The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections. *Intensive Care Med* 2017; **43**: 1021–32.

24 EMA. Guideline on Bioanalytical Method Validation. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf.

25 Veiga RP, Paiva JA. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of β-lactam antibiotics in critically ill patients. *Crit Care* 2018; **22**: 233.

26 Roberts JA, Abdul-Aziz MH, Davis JS *et al*. Continuous versus intermittent β-lactam infusion in severe sepsis: a meta-analysis of individual patient data from randomized trials. *Am J Respir Crit Care Med* 2016; **194**: 681–91.

27 Rhodes NJ, Liu J, O'Donnell JN *et al*. Prolonged infusion piperacillin-tazobactam decreases mortality and improves outcomes in severely ill patients: results of a systematic review and meta-analysis. *Crit Care Med* 2018; **46**: 236–43.

28 Falagas ME, Tansarli GS, Ikawa K *et al*. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. *Clin Infect Dis* 2013; **56**: 272–82.

29 Yang H, Zhang C, Zhou Q *et al*. Clinical outcomes with alternative dosing strategies for piperacillin/tazobactam: a systematic review and meta-analysis. *PLoS One* 2015; **10**: e0116769.

30 Lipman J, Brett SJ, De Waele JJ *et al*. A protocol for a phase 3 multicentre randomised controlled trial of continuous versus intermittent β-lactam antibiotic infusion in critically ill patients with sepsis: BLING III. *Crit Care Resusc* 2019; **21**: 63–8.

31 Udy AA, Lipman J, Jarrett P *et al*. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? *Crit Care* 2015; **19**: 28.

32 Carlier M, Carrette S, Roberts JA *et al*. 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* 2013; **17**: R84.

33 Grayson ML, Crowe SM, McCarthy JS *et al*. Part 2 Cephalosporins and related drugs. In: ML Grayson, ed. *Kucer's The Use of Antibiotics*. 6th edn. CRC Press, 2010: 324.

34 Jager NG, van Hest RM, Lipman J *et al*. Therapeutic drug monitoring of anti-infective agents in critically ill patients. *Expert Rev Clin Pharmacol* 2016; **9**: 961–79.

35 Parker SL, Sime FB, Roberts JA. Optimizing dosing of antibiotics in critically ill patients. *Curr Opin Infect Dis* 2015; **28**: 497–504.

36 de Waele JJ, Carrette S, Carlier M *et al*. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. *Intensive Care Med* 2014; **40**: 380–7.

37 Jung B, Mahul M, Breilh D *et al*. Repeated piperacillin-tazobactam plasma concentration measurements in severely obese versus nonobese critically ill septic patients and the risk of under- and overdosing. *Crit Care Med* 2017; **45**: e470–8.

38 Alobaid AS, Brinkmann A, Frey OR *et al*. What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients? *J Antimicrob Chemother* 2016; **71**: 696–702.

39 Chung EK, Cheatham SC, Fleming MR *et al*. Population pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese and nonobese patients. *J Clin Pharmacol* 2015; **55**: 899–908.

40 Hites M, Taccone FS, Wolff F *et al*. Case-control study of drug monitoring of β-lactams in obese critically ill patients. *Antimicrob Agents Chemother* 2013; **57**: 708–15.

41 Alobaid AS, Hites M, Lipman J *et al*. Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: a structured review. *Int J Antimicrob Agents* 2016; **47**: 259–68.