OBSERVATIONAL STUDY

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Cefepime Daily Exposure and the Associated Impact on the Change in Sequential Organ Failure Assessment Scores and Vasopressors Requirement in Critically Ill Patients Using Repeated-Measures Mixed-Effect Modeling

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IMPORTANCE: Sepsis and septic shock are major healthcare problems that need early and appropriate management.

OBJECTIVES: To evaluate the association of daily cefepime pharmacokinetic/pharmacodynamic (PK/PD) parameters with change in Sequential Organ Failure Assessment (SOFA) score and vasopressors requirement.

DESIGN, SETTING, AND PARTICIPANTS: This is a retrospective study. Adult ICU patients who received cefepime for Gram-negative pneumonia or bloodstream infection (BSI) and had cefepime concentrations measured were included. Daily cefepime exposure was generated and PK/PD parameters calculated for patients. Repeated-measures mixed-effect modeling was used to evaluate the impact of PK/PD on the outcomes.

MAIN OUTCOMES AND MEASURES: Change in daily SOFA score and vasopressors requirement.

RESULTS: A total of 394 and 207 patients were included in the SOFA and vasopressors analyses, respectively. The mean (±SD) age was 55 years (19) and weight 81 kg (29). For the change in SOFA score, daily SOFA score, mechanical ventilation, renal replacement therapy, and number of vasopressors were included. In the vasopressors analysis, daily SOFA score, day of therapy, and hydrocortisone dose were significant covariates in the final model. Achieving cefepime concentrations above the minimum inhibitory concentration (MIC) ($T_{>MIC}$) for 100% of the dosing interval was associated with 0.006 µg/kg/min decrease in norepinephrine-equivalent dose. Cefepime PK/PD did not have an impact on the daily change in SOFA score.

CONCLUSIONS AND RELEVANCE: Achieving 100% $T_{>MIC}$ was associated with negligible decrease in vasopressors requirement in ICU patients with Gram-negative pneumonia and BSI. There was no impact on the change in SOFA score.

KEYWORDS: cefepime; critical care; organ dysfunction scores; pharmacokinetics; vasoconstrictor agents

Sepsis affects about 1.7 million adults in the United States each year and contributes to 30–50% of hospitalizations (1). Globally, 48.9 million sepsis cases and 11 million sepsis-related deaths were reported in 2017. Studies that reported the microbiologic profiles in hospital-acquired sepsis found that 34–64% of cases were caused by Gram-negative bacteria, and up to one third of cases were caused by drug-resistant bacteria (2).

One of the factors that impacts sepsis outcomes is the site and type of infection (3). Severe pneumonias, including both hospital-acquired pneumonia

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KEY POINTS:

Question: To evaluate the association of daily cefepime pharmacokinetic/pharmacodynamic (PK/PD) parameters with change in Sequential Organ Failure Assessment (SOFA) score and vasopressors requirement.

Findings: Achieving cefepime concentrations above the minimum inhibitory concentration (MIC) ($T_{>MIC}$) for 100% of the dosing interval was associated with 0.006 µg/kg/min decrease in daily vasopressors requirement. There was no impact of cefepime PK/PD target attainment on the change in daily SOFA score.

Meaning: Optimizing cefepime exposure may have negligible-to-no impact on vasopressors requirement and daily SOFA score in critical care.

(HAP) and ventilator-associated pneumonia (VAP), are the most frequently encountered bacterial infection in critical care settings (4). Severe pneumonia is associated with increased duration of mechanical ventilation, length of stay, and mortality rate (5, 6). Mortality due to VAP has been estimated at around 10% (7). In addition to pneumonias, bloodstream infections (BSIs) are associated with significant morbidity and mortality (4, 8). Gram-negative organisms are associated with serious therapeutic problems because of the increased incidence of antimicrobials resistance (6). Patients infected with Gram-negative BSIs may have higher early mortality rates compared to patients with BSIs caused by Gram-positive bacteria (5). Early initiation of appropriate antibacterial therapy may improve patients' outcomes (7).

Beta-lactams, including cefepime, are considered essential for treating infections caused by Gram-negative bacteria. Because beta-lactams are time-dependent agents, the bacterial killing depends on the time the beta-lactam concentration exceeds the bacterial minimum inhibitory concentrations ($T_{>MIC}$) (9). Standard doses of beta-lactams may be inadequate to treat infections in critically ill patients and achieve the pharmacokinetic/pharmacodynamic (PK/PD) targets reported in the literature (10–12). Additionally, critically ill patients may have regular changes in PK parameters which can contribute to unpredictable beta-lactam exposure at standard doses (11). As a result, it is essential to provide adequate exposure to beta-lactam antibiotics, both early and for the whole duration of therapy, to improve patient outcomes using therapeutic drug monitoring (TDM).

Sequential Organ Failure Assessment (SOFA) score may be used to determine the level of organ dysfunction and mortality risk (13), whereas vasopressor requirements may reflect the degree of shock and hypoperfusion in critically ill patients (14). Both can be used as outcome variables in septic patients. Previous studies reported these outcome variables as a snapshot at a certain time point during therapy and/or at the end of therapy. Therefore, the purpose of this study was to evaluate the impact of daily cefepime target attainment on the daily change of SOFA scores and vasopressors requirement in critically ill patients with Gram-negative HAP/VAP or BSI.

MATERIALS AND METHODS

This was an analysis of two previously published datasets which included patients who were admitted to the ICU at University of Florida (UF) Health Shands Hospital between January 2016 and May 2021 (15, 16). Patients were included if they were older than 18 years, had Gram-negative HAP/VAP or BSI confirmed by culture, received cefepime for the treatment of their infection for at least 2 days, and had cefepime plasma concentration measured as part of the usual TDM service. Pregnant women, prisoners, and patients allergic to cefepime were excluded. Data collected included patients' age, sex, weight, calculated creatinine clearance (CrCl) using the Cockcroft-Gault equation, renal replacement therapy (RRT), cefepime dosing information and plasma concentrations, cultures and susceptibility including MICs when available, daily SOFA scores, number of vasopressors administered each day, mean daily vasopressors (epinephrine, norepinephrine, dopamine, phenylephrine, and vasopressin) requirement in µg/kg/min or units/min, total daily dose of systemic steroids in mg/day, and daily mechanical ventilation status (on/off). The mean daily norepinephrine-equivalent dose calculation was based on the following equation (17):

$$\begin{aligned}&\text{Norepinephrine equivalents}\\&(\textit{all in } \mu g/kg/min,\ \textit{except for vasopressin in units/min}) =\\&\text{norepinephrine} + \text{epinephrine} + \text{phenylephrine}/10\\&+ \text{dopamine}/100 + \text{vasopressin} \times 2.5\end{aligned}$$

As per standard of care, patients had their cefepime plasma concentration measured typically in the first 48 hours of therapy, and concentrations were repeated as needed. Clinicians order peak (1 hr after the end of the infusion) and trough (before starting the next dose) samples for patients on intermittent or extended infusion beta-lactams. Patients on continuous infusion may have one to two random samples collected. The quantification of cefepime plasma concentration was done at the Infectious Disease Pharmacokinetics Laboratory at UF using validated liquid chromatography with tandem mass spectrometry assays. The calibration range was 2–100 mg/L and the inter- and intraday precision and accuracy were less than 10% (18). The cefepime doses, concentrations, actual timing, and covariates (baseline weight and daily CrCl) were used to calculate the median posterior predictions for each patient using published nonparametric population PK model (Pmetrics v1.9; Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA) (19, 20). The individual predictions were then imported to Phoenix WinNonlin v8.1 (Certara, St. Louis, MO) and the time the concentration remained above the MIC ($T_{>MIC}$) and above four multiples of the MIC ($T_{>4\times MIC}$) were calculated for each patient on every day of therapy.

Bacteria were identified by standard microbiologic methods using VITEK Mass Spectrometry and VITEK II (bioMérieux, Durham, NC) and MIC quantified. MICs were quantified by E-test only for *Burkholderia cepacia* complex, and previously isolated *Acinetobacter* species and Gram-negative nonfermenters. In the case of polymicrobial infection, the highest MIC was used for the PK/PD calculations. If no MIC reported, the European Committee on Antimicrobial Susceptibility (EUCAST) breakpoint for the bacteria identified was used.

This study was reviewed by the institutional review board at UF and approved as exempt (institutional review board number: 201902910, January 2020, "Clinical experience with a TDM program"). Informed consent was waived.

Statistical Analysis

Continuous data were presented as median and IQR or mean and SD, whereas the categorical data as counts and percentages. A random-intercept, linear, mixed-effects model was applied to determine the impact of PK/PD parameters on the mean daily vasopressors requirement and change in SOFA score. For mean vasopressor requirement analysis, parameters of interest included the day of therapy, type of infection (HAP/VAP or BSI), SOFA score, dose of systemic steroids, and RRT (yes/no) on every day of therapy. For change in SOFA scores, in addition to the parameters included in the vasopressors analysis, the following parameters were added: mechanical ventilation status (on/off) and number of and mean vasopressors requirement on every day of therapy.

A full model was specified using the variables above, excluding the PK/PD parameters, as fixed effects and the subject-specific identifier as a random effect in order to control for subject-specific variation. The reduced model was chosen based on minimizing Akaike's Information Criterion (AIC). The likelihood ratio test was used to detect significant differences in model performance. PK/PD parameters were added to the reduced model as a last step. Multicollinearity was considered acceptable if the variable inflation factor value was less than 10. A p value less than 0.05 was considered statistically significant.

All statistical analyses were conducted with R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) using the lme4 package (21) with models fit using maximum likelihood.

RESULTS

A total of 394 and 207 patients were included in the SOFA and vasopressors analyses, respectively. **Table 1** summarizes patients' demographics. The mean (±SD) age was 55 years (±19) and weight 81 kg (±29). Sixty-one percent of patients were male and 16% received RRT. The mean (±SD) follow-up duration was 11 days (±7). Eighty-five percent of patients had MIC reported for the isolated bacteria; 43% of them had MIC less than or equal to 1 mg/L. Only 15% of patients had no MIC reported for the isolated bacteria, half of them had *Pseudomonas aeruginosa*, and hence, EUCAST breakpoints were used. Daily SOFA score and vasopressor requirement are summarized in **Figures 1** and **2**. Mean (±SD) SOFA score was 7 to 8 (±3 to 4) in the first 25 days of therapy. The mean (±SD) daily vasopressor dose started at 0.13 μg/kg/min (±0.25) and showed more variability over days of therapy than SOFA score, but it dropped slowly over the course

TABLE 1.
Patients Baseline Demographics[a]

Characteristics	Vasopressors Analysis (n = 207)	SOFA Analysis (n = 394)
Age, yr	59 (16)	56 (17)
Sex, male	122 (59)	253 (64)
Weight, kg	85 (30)	83 (29)
Renal replacement therapy	64 (31)	77 (20)
Mechanical ventilation	186 (90)	326 (83)
Baseline SOFA score	9 (3)	8 (3)
Vasopressors starting dose[b]	0.13 (0.25)	0.07 (0.19)
Dataset Hospital-acquired pneumonia/ ventilator-associated pneumonia Bloodstream infection	 151 (73) 56 (27)	 302 (77) 92 (23)
Days of follow-up	12 (8)	11 (6)
Common isolated bacteria[c] *Pseudomonas aeruginosa* *Escherichia coli* *Serratia marcescens* *Klebsiella pneumoniae*	 83 (4) 22 (1) 21 (1) 19 (1)	 169 (4) 35 (2) 37 (1) 36 (1)
No. of cefepime samples	791	459

SOFA = Sequential Organ Failure Assessment.
[a]Data presented as mean (SD) or *n* (%) unless specified.
[b]Reported as norepinephrine-equivalent dose in µg/kg/min.
[c]*n* (median minimum inhibitory concentration).

of therapy. Individual daily cefepime exposure was generated for the entire duration of therapy for all patients. **Figure 3** summarizes the mean and SD PK/PD target attainment daily during therapy.

Table 2 shows the initial and final mixed-effect model for the daily change in SOFA score. The final model included daily SOFA score, mechanical ventilation, RRT, and number of vasopressors. There was no impact of PK/PD target attainment on the change of SOFA score.

Table 3 shows the initial and final mixed-effect model for the daily vasopressor requirement. In addition to the day of therapy, daily SOFA score, and hydrocortisone dose, achieving 100% $T_{>MIC}$ was associated with a statistically, but not clinically, significant decline in the mean daily vasopressors requirement of 0.006 µg/kg/min. Achieving 100% $T_{>4\times MIC}$ was not a significant predictor in this analysis.

DISCUSSION

We presented the impact of cefepime PK/PD on the daily change in SOFA score and the requirement of vasopressors in critically ill patients with Gram-negative bacterial pneumonia and BSI. We used repeated-measures, mixed-effect modeling to investigate this relationship daily (22). Given the longitudinal nature of our data, with daily measurements of both clinical outcomes (i.e., vasopressors requirement and SOFA score) and predictors (i.e., PK/PD target attainment), we employed repeated-measures, mixed-effect modeling. This analytical approach was chosen for its ability to account for intrasubject correlation due to repeated measurements, handle unbalanced datasets (i.e., different numbers of measurements across subjects), and model individual patient trajectories. Specifically, the mixed-effect model was deemed most appropriate to account for the variability in outcomes and predictors for each patient, capturing individual baseline variations and unobserved heterogeneity among patients. Our choice of a random intercept was driven by the need to account for individual differences that are not captured by the fixed effects in the model. $T_{>MIC}$ was a statistically, but not clinically, significant predictor of the decline in daily vasopressors

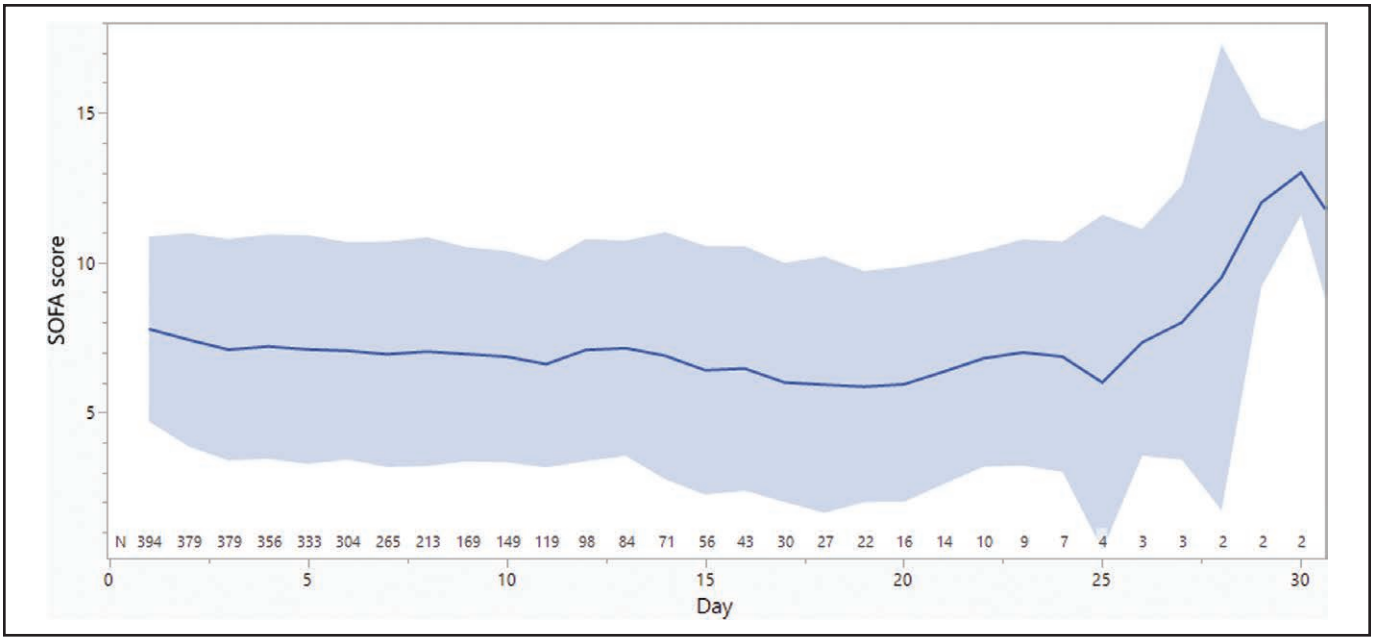

Figure 1. Daily Sequential Organ Failure Assessment (SOFA) scores and vasopressors requirement. The *solid line* represents the mean and the *band* represents the SD.

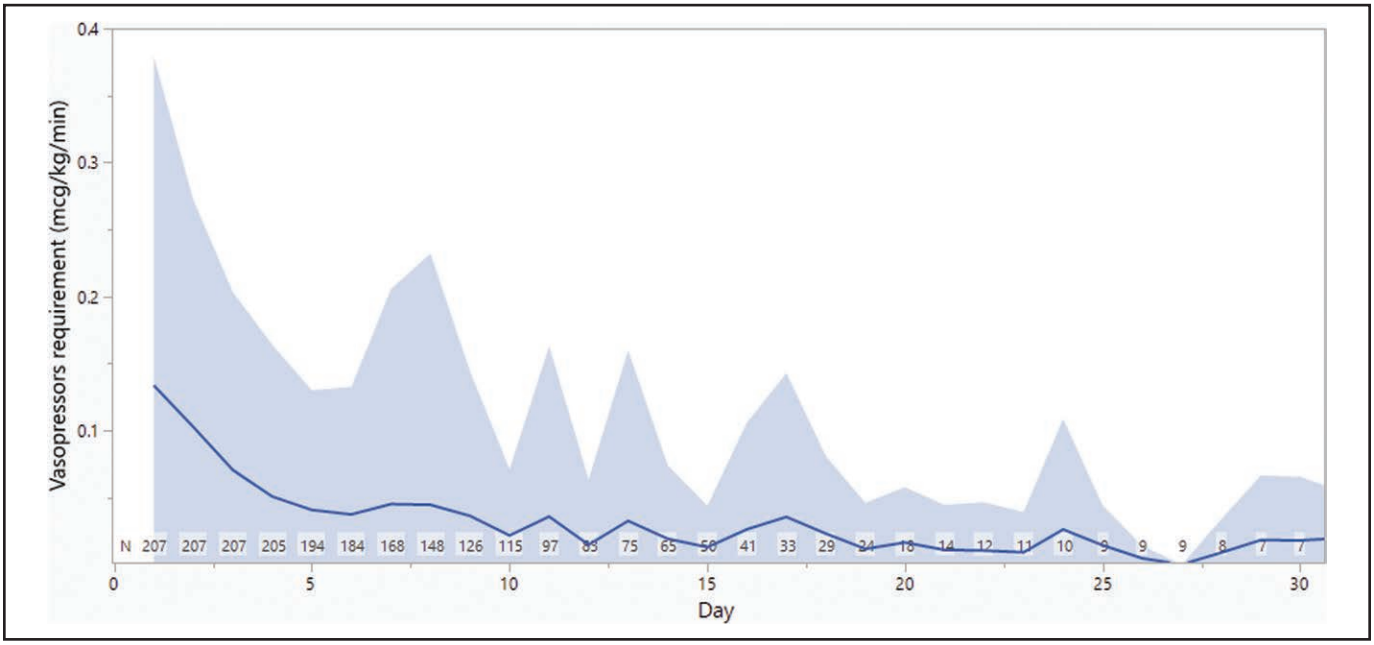

Figure 2. Daily vasopressors requirement. The *solid line* represents the mean and the *band* represents the SD.

requirement, but not change in SOFA score. $T_{>4\times MIC}$ was not a significant predictor in any of the analyses.

In a systematic review and meta-regression which included 87 randomized clinical trials, change in SOFA score was found reliably and consistently associated with mortality (slope = 0.70, $p = 0.004$) and explained 32% of the overall mortality. Although fixed-day SOFA was the most frequently reported outcome in the included trials, it was not significantly associated with mortality (slope = 0.35, $p = 0.08$) and explained 3% of the overall mortality (23). TARGET trial was a multicenter study randomizing septic patients receiving piperacillin/tazobactam continuous infusions to either a TDM-guided arm or a fixed-dose arm. The primary outcome was the mean daily total SOFA score up to day 10. Two hundred forty-nine patients were randomized; 62% had pneumonia. The piperacillin exposure was similar between the study arms; hence

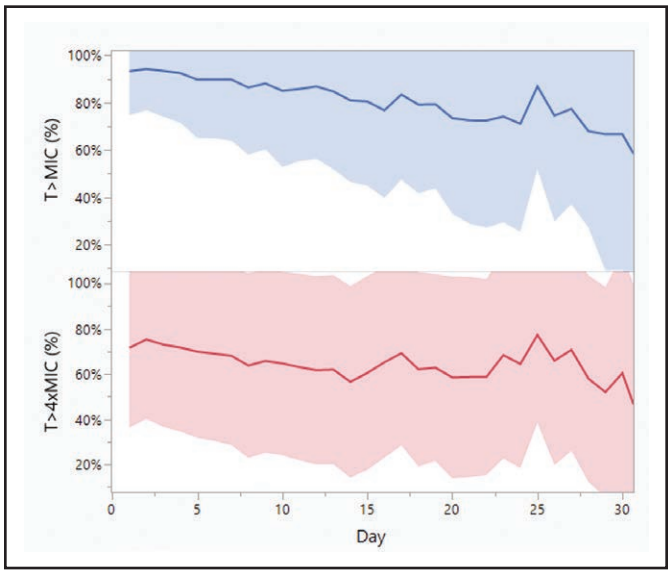

Figure 3. Daily pharmacokinetic/pharmacodynamic target attainment. The *solid line* represents the mean and the *band* represents the SD. $T_{>MIC}$ and $T_{>4\times MIC}$ = time the beta-lactam concentration was above the minimum inhibitory concentration or four multiples of the minimum inhibitory concentration, respectively.

no difference in mean SOFA scores, 28-day mortality, and clinical and microbiologic cure was detected (24, 25). A few other studies looked at the impact of beta-lactam target attainment on the clinical outcomes based on the Acute Physiology and Chronic Health Evaluation (APACHE) score with mixed results regarding the impact of alternative beta-lactam dosing strategies on APACHE scores and potentially lower mortality in patients with higher APACHE scores that achieved appropriate PK/PD targets (26–28). In our study, we evaluated cefepime PK/PD target attainment and the change in the daily SOFA score, rather than comparing the baseline to end-of-therapy SOFA scores. However, our results showed no significant impact of achieving 100% $T_{>MIC}$ on the daily change in SOFA score.

Compared with SOFA score outcome, there were fewer reports published comparing the vasopressors requirement between patients receiving beta-lactam therapy. Richter et al reported a before (intermittent infusion, n = 114) and after (prolonged infusion, n = 290) retrospective study investigating the outcomes associated with beta-lactam infusion strategy. Although mortality was lower in the prolonged infusion arm, there was no difference between the groups in terms of vasopressor dependence at days 0, 2, 4, 7, and 14 (28).

TABLE 2.
Mixed-Effect Model for Change in Sequential Organ Failure Assessment Score[a]

	Initial Model		Final Model	
Predictors	**Coefficient**	***p***	**Coefficient**	***p***
Day of therapy	0.012	**0.0159**	–	–
Current day Sequential Organ Failure Assessment	−0.091	**< 0.0001**	−0.298	**< 0.0001**
No. of vasopressors	0.078	0.41	0.313	**< 0.0001**
Fludrocortisone[b]	-0.625	0.34	–	–
Hydrocortisone[b]	0.001	0.44	–	–
Renal replacement therapy[c]	0.167	**< 0.0001**	0.822	**< 0.0001**
Type of infection[d]	−0.020	0.62	–	–
Mechanical ventilation[c]	−0.150	**< 0.0001**	0.185	**0.0007**
Mean daily vasopressors requirement[e]	0.897	0.14	–	–
100% $T_{>MIC}$[c]	–	–	0.009	0.88
100% $T_{>4\times MIC}$[c]	–	–	0.087	0.055

$T_{>MIC}$ and $T_{>4\times MIC}$ = time the free beta-lactam concentration was above the minimum inhibitory concentration or four multiples of the minimum inhibitory concentration, respectively.

[a]The change in Sequential Organ Failure Assessment was evaluated as the difference between the current and next day's score.

[b]Per 1 mg/d.

[c]Yes compared with no.

[d]Blood vs. pneumonia.

[e]Per 1 µg/kg/min.

Values in boldface font are $p < 0.05$.

TABLE 3.
Mixed-Effect Model for Vasopressor Requirement[a]

	Initial Model		Final Model	
Predictors	**Coefficient**	***p***	**Coefficient**	***p***
Day of therapy	–0.001	**< 0.0001**	–0.002	**0.0002**
Current day Sequential Organ Failure Assessment	0.008	**< 0.0001**	–0.007	**< 0.0001**
Fludrocortisone[b]	0.159	**0.0055**	–	–
Hydrocortisone[b]	0.0004	**< 0.0001**	0.0003	**< 0.0001**
Renal replacement therapy[c]	0.020	**< 0.0001**	–	–
Type of infection[d]	–0.004	0.24	–	–
100% $T_{>MIC}$[c]	–	–	–0.006	**0.0318**
100% $T_{>4\times MIC}$[c]	–	–	0.002	0.38

$T_{>MIC}$ and $T_{>4\times MIC}$ = time the free beta-lactam concentration was above the minimum inhibitory concentration or four multiples of the minimum inhibitory concentration, respectively.

[a]Vasopressors requirement was evaluated as norepinephrine-equivalent dose based on μg/kg/min.

[b]Per 1 mg/d.

[c]Yes compared with no.

[d]Blood vs. pneumonia.

Values in boldface font are $p < 0.05$.

Another retrospective study reported the outcomes in patients receiving meropenem either as extended (n = 52) or intermittent (n = 96) infusion. The ICU mortality was lower, clinical response was higher, and median total vasopressor days were shorter in the extended infusion group (2 vs. 3 days, $p = 0.032$) (29). In our analysis, achieving 100% $T_{>MIC}$ was associated with a marginal decline in daily vasopressors requirement which may not be clinically relevant. Based on these results and previously published work, beta-lactam PK/PD target attainment might be more important for the final therapy outcomes compared with daily changes in vasopressors requirement and SOFA score.

Different cefepime PK/PD targets were reported in the literature. Early preclinical work suggested that bacterial stasis was associated with 30% to 40% $T_{>MIC}$, whereas bactericidal activity was associated with 60% to 70% $T_{>MIC}$ (30–32). Similar targets, 68% and 74% $T_{>MIC}$, were suggested for survival in 180 ICU patients using exposures generated using population PK models (33). Clinically, patients who achieved 100% $T_{>MIC}$ had higher chances of clinical cure and microbiologic eradication and had higher ventilator-free days (34, 35). In our study, we evaluated the daily outcomes associated with achieving 100% $T_{>MIC}$ and $T_{>4\times MIC}$. Only $T_{>MIC}$ was associated with lower daily vasopressors requirement; however, the difference was not clinically significant and unlikely to impact the overall patient outcomes.

Our study has some limitations. First, it was a single-center, retrospective study including mainly patients with Gram-negative bacterial pneumonia treated with cefepime only. Second, we had to use breakpoints for some of the patients to evaluate the PK/PD target attainment which might not have been reflective of the true MICs. Third, cefepime exposure was calculated using population PK which fixes the PK parameters per patient for the entire therapy duration while these parameters may change in an ICU setting. Finally, that PK model was used to generate cefepime exposure in patients receiving RRT although it was not built including such patients. These limitations may be addressed in future studies by robust daily plasma samples collection using prospective study design combined with advanced statistical methods.

CONCLUSIONS

In conclusion, achievement of 100% $T_{>MIC}$ was associated with negligible decline in daily vasopressor requirements in ICU patients receiving cefepime for the treatment of Gram-negative pneumonia or BSI. There was no impact on the daily SOFA score.

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