https://doi.org/10.31925/farmacia.2025.6.11 **ORIGINAL ARTICLE**

PREDICTORS OF CEFTAZIDIME PK/PD INDEX TARGET VALUES AND TOXIC PLASMA LEVELS IN ADULT HOSPITALISED PATIENTS

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Manuscript received: October 2025

Abstract

The effectiveness of antibiotics in systemic bacterial infections depends not only on microbial sensitivity, but also on achieving adequate concentrations in tissues. This study aimed to identify predictors of achieving target pharmacokinetic/pharmacodynamic (PK/PD) values for ceftazidime and factors associated with toxic plasma concentrations. A cross-sectional observational study was conducted on hospitalised patients treated with ceftazidime for systemic bacterial infections at the University Clinical Centre Kragujevac (UKCK), Serbia, in 2024, as part of routine therapeutic drug monitoring. A total of 59 adult patients were included, each with at least two measurements of ceftazidime concentration per dosing interval. Forty-four patients achieved the target PK/PD value of fT above MIC, while 22 had toxic plasma concentrations. Male patients were less likely to achieve the target fT above MIC (adjusted OR = 0.07 [0.009 - 0.464]). Advanced age, elevated serum creatinine, and higher daily doses were associated with toxic concentrations. To ensure optimal efficacy and safety, ceftazidime dosing should be individualised based on sex, age, and renal function.

Rezumat

Eficacitatea antibioticelor în infecțiile bacteriene sistemice depinde nu numai de sensibilitatea microbiană, ci și de atingerea concentrațiilor adecvate în țesuturi. Această cercetare a avut ca scop identificarea factorilor predictivi pentru atingerea valorilor farmacocinetice/farmacodinamice (PK/PD) țintă pentru ceftazidimă și a factorilor asociați cu concentrații plasmatice toxice. Un studiu observațional transversal a fost realizat pe pacienți spitalizați tratați cu ceftazidimă pentru infecții bacteriene sistemice la Centrul Clinic Universitar Kragujevac (UKCK), Serbia, în 2024, ca parte a monitorizării terapeutice de rutină a medicamentelor. Au fost incluși în total 59 de pacienți adulți, fiecare cu cel puțin două determinări ale concentrației de ceftazidimă *per* interval de administrare. Patruzeci și patru de pacienți au atins valoarea PK/PD țintă de fT peste MIC, în timp ce 22 au prezentat concentrații plasmatice toxice. Pacienții de sex masculin au avut o probabilitate mai mică de a atinge valoarea țintă fT peste MIC (OR_ajustat = 0,07 [0,009 - 0,464]). Vârsta înaintată, creatinina serică crescută și dozele zilnice mai mari au fost asociate cu concentrații toxice. Pentru a asigura eficacitatea și siguranța, doza de ceftazidimă trebuie individualizată în funcție de sex, vârstă și funcția renală.

Keywords: ceftazidime, therapeutic drug monitoring, toxic plasma concentrations, pharmacokinetic/pharmacodynamic index

Introduction

The effectiveness of antibiotics in treating systemic bacterial infections depends not only on the susceptibility of the causative microorganisms but also on the attainment of adequate antibiotic concentrations within tissues [1]. Simultaneously, it is crucial to avoid concentrations that may exert toxic effects on human cells. Pharmacokinetic/pharmacodynamic (PK/PD) indices represents the quantitative relationship between antibiotic exposure and antibacterial effect. For β-lactams such as ceftazidime, the key PK/PD index is the percentage of the dosing interval during which concentration of free drug (unbound for plasma proteins) remain above the Minimal Inhibitory Concentration

- MIC (fT > MIC), which correlates well with antimicrobial effect [2].

Numerous studies examined the factors that affect achieving or failing to achieve therapeutic plasma concentrations, as well as the development of potentially harmful levels [3-5]. Variability in plasma drug concentrations can result from several factors. These include differences among individuals in drug absorption and distribution, variability in how drugs are processed and eliminated, the presence of other health conditions such as renal, cardiac, or liver insufficiency, physiological alterations such as obesity, and polypharmacy [6, 7]. In critically ill patients suffering from systematic bacterial infections timely identifications of sepsis, coupled with the prompt and appropriate administration of antibiotics, is essential for improving survival outcomes. However, the effective delivery of antibiotic therapy may be influenced by pathophysiological changes associated with the primary illness, as well as by medical interventions such as therapeutic procedures or mechanical support that are employed in the management of these patients [8, 9].

Ceftazidime, a beta-lactam antibiotic, is primarily utilized for the treatment of severe Gram-negative bacterial infections. For beta-lactam agents like ceftazidime, the most predictive PK/PD parameter is the duration for which the free (unbound) plasma concentration remains above the minimum inhibitory concentration (fT > MIC). [10]. This index measures the percentage of the dosing interval when the unbound antibiotic concentration is above the MIC. A total plasma concentration of ceftazidime greater than 80 mg/L at the end of the dosing interval, in the final hour, is viewed as potentially toxic [11]. In clinical situations, target tissue concentrations may not be reached, or toxic levels could occur, especially if dosing is not adjusted for renal function and drug clearance capacity [12].

The aim of this study was to investigate predictors of achieving target values of pharmacokinetic/ pharmacodynamic (PK/PD) index relevant for ceftazidime, as well as factors associated with toxic plasma concentrations of the same drug.

Materials and Methods

The study was designed as a cross-sectional observational study in hospitalised patients treated for systemic bacterial infection with ceftazidime. The study was conducted at the University Clinical Centre Kragujevac (UKCK), Serbia, during the year 2024, when routine therapeutic monitoring of ceftazidime concentrations was carried out.

The study was reviewed and approved by the study Ethics Committee of the University Clinical Centre Kragujevac (Ethics Committee number 01/23-209).

The study population consisted of hospitalised patients over the age of 18, treated for at least 48 hours in the hospital, who had a diagnosis of systemic bacterial infection and were treated with ceftazidime in monotherapy, and then their blood plasma ceftazidime concentration was measured at least twice during the dosing interval after the patient had established a steady-state. Exclusion criteria were: patients in the terminal stage of malignant diseases, patients who died before the expiration of 24 hours from the moment of ceftazidime measurement, patients in whom there was a laboratory error in the measurement of concentrations observed by the biochemist, and patients with incomplete medical documentation. The sample of patients was of "convenience" type, where all patients without exception in whom ceftazidime concentration was measured, and which met the inclusion criteria and did not meet the exclusion criteria, were taken into account.

Two blood samples were collected during the same dosing interval after achieving steady state (after five ceftazidime half-lives have passed from start of the therapy). The first sample was drawn 30 minutes after the end of the 30-minutes infusion (representing post-distribution peak concentration). The second sample was drawn 4 hours after end of the i.v. infusion, during the same dosing interval, representing a lower concentration.

In the study, two dependent variables of a categorical nature were singled out: achievement of the target therapeutic value of the PK/PD index fT above MIC and the occurrence of a toxic concentration of ceftazidime in the plasma at the end of the dosing interval. The fT above MIC index is calculated as the percentage of the dose interval in which the concentration of the antibiotic is above the MIC, while the toxic concentration at the end of the dose interval (last hour) was accounted if the total concentration of ceftazidime in the blood plasma was greater than 80 mg/L. Serum concentrations of ceftazidime were measured by enzyme immunoassay (EIA) using apparatus DRG Hybrid XL and reagents produced by DRG-BioCheck, Germany. Ceftazidime was administered in individual doses of 0.5 to 4 g, using intermittent intravenous infusion lasting one hour. Of the confounding variables, age, sex, smoking status, body weight, body height, serum creatinine level and daily dose of ceftazidime were monitored; data on confounding variables were collected from patients' medical histories.

The size of the study sample was calculated on the basis of the hypothesis that the daily dose is a significant predictor of achieving the therapeutic value of fT above MIC index and toxic values of plasma concentration of ceftazidime. The test on the basis of which the calculation was carried out was multivariate logistic regression, and the input parameters

in the calculation are: probability of statistical error of the first type 0.05, target statistical power of the study 0.8, expected Odds ratio 2, R2 = 0.6, distribution of the value of the daily dose that is not normal, but without specification, and the probability of 0.2 that the target value of the dependent variable was reached in case of a positive value of the predictor. The calculation was carried out using Gpower software version 3.1.9.7. [13] Based on the above data and procedures, the minimum required number of patients is 55.

A classical pharmacokinetic approach was used to estimate the concentration-time curve between the two measured points. Specifically, a non-compartmental pharmacokinetic formulas were used to reconstruct plasma concentrations of unbound drug during the steady-state. With the reconstructed plasma concentrations in time, both time within the dosing interval when plasma concentrations were above the MIC and the dosing interval could have been read from the graph. The ratio between these two values is fT > MIC index.

The data were first processed with descriptive statistics. After checking the normality of the data distribution of continuous variables using the Kolmogorow Smirnov test, those continuous variables that had a normal distribution were described with the mean value and standard deviation, while the remaining continuous variables were described with the median and interquartile range. Categorical variables are listed with frequency and percentages. We then compared groups defined by outcome using the Student's T test for normally distributed continuous variables and the Mann Whitney U test for non-normally distributed variables. Categorical values were compared using the Chi-square test or Fisher's test in the case of frequencies of less than 5 patients. Finally, we conducted uni- and multi-variate analysis using logistic regression, where the dependent variables were the achievement of the target value of fT above MIC and toxic concentrations of ceftazidime, and the predictors were all the variables monitored in the study. All calculations were carried out using the SPSS program version 26. The limit value of the probability of the null hypothesis taken for the purposes of this study was 0.05, but it was corrected by Bonferroni in the univariate analysis.

Results and Discussion

The study included a total of 59 adult hospitalized patients receiving ceftazidime, who had their ceftazidime concentration measured at least twice during the dosing interval. Details about the demographic and other characteristics of the entire study sample are given in Table I. Based on the results of the study, the sample was first divided into subgroups, namely 44 patients who achieved the therapeutic value of PK/PD index fT above MIC, and 15 of them who did not achieve that value. Details of the univariate analysis of the differences between these two groups are shown in Table II. The same sample was then divided into two groups, but this time based on the appearance of toxic concentrations of ceftazidime in the plasma at the end of the dosing interval, namely 22 patients with toxic concentrations and 37 of them who did not reach toxic levels of the drug in the plasma. Univariate analysis of the differences between these two groups is shown in Table III. The results of univariate and multivariate logistic regressions where the dependent variables were the achievement of the target therapeutic value of fT above MIC index or toxic plasma concentration of the drug are shown in Table IV. Both multivariate logistic regression models were obtained by the Backward deletion method, where the probability of the Omnibus test was less than 0.05, the probability of the Hosmer Lemeshow test was greater than 0.05, and the percentage of variability of the dependent variables explained by the models was in both cases greater than 0.4. Multicollinearity was assessed using the variance inflation factor (VIF), and all predictors included in the final model had VIF < 2, indicating no significant collinearity. Confidence intervals (95% CI) were reported for all odds ratios.

In order to promote antibiotic stewardship and optimize appropriate antibiotic dispensing not only in terms of achieving favourable therapeutic outcomes but also in ensuring cost-effective decision-making, it is essential to consider the variability in PK/PD parameters of antibiotics [14].

The objective of this study was to identify predictors associated with achieving the target PK/PD index for ceftazidime, as well as to examine factors contributing to toxic plasma concentrations of the drug. The key findings demonstrate that the majority of patients (74.6%) attained the therapeutic target of maintaining free drug concentrations above the minimum inhibitory concentration for susceptible bacteria (fT > MIC). However, 37.3% of patients developed toxic drug levels by the end of the dosing interval.

Patients who failed to reach the therapeutic fT > MIC target were more frequently male, younger, taller, had lower serum creatinine levels, and were more often smokers. In contrast, those who achieved therapeutic concentrations were also more likely to develop toxic plasma levels, indicating a potential overlap between drug efficacy and toxicity due to accumulation. Notably, all patients with toxic plasma concentrations had reached the therapeutic target, whereas none of the patients with subtherapeutic levels exhibited signs of toxicity. Given that antimicrobials are a major class of drugs associated with toxicity [15], these findings highlight the critical importance of close pharmacokinetic monitoring in clinical practice.

Table I

Characteristics of the study sample (n = 59)

Variable	Value*
Body weight (kg)	77.2 ± 13.4
Height (cm)	170.0 [15.0]
Daily dose (g)	4.0 [3.0]
Serum creatinine (µM/L)	85.0 [97.0]
Age (years)	67.0 [13.0]
Sex (m/f)	26/33 (44.1%/55.9%)
Smokers (yes/no)	18/41 (30.5%/69.5%)
Toxic serum concentration (yes/no)	22/37 (37.3%/62.7%)
Therapeutic level of fT above MIC (yes/no)**	44/15 (74.6%/25.4%)

* mean ± standard deviation if normally distributed, median [interquartile range] if not normally distributed, frequency (percent) if categorical variable; ** fT above MIC – percent of dose interval when free plasma concentration of ceftazidime was above minimal inhibitory concentration for sensitive bacteria

Table II

Univariate comparison of the patients grouped according to achievement of therapeutic value of fT above MIC

Variable***	Patients achieving therapeutic values of fT above MIC* (n = 44)	Patients not achieving therapeutic values of fT above MIC (n = 15)	p**
Body weight (kg)	74.9 ± 12.7	84.0 ± 13.4	0.823
Height (cm)	170. 0 [14.5]	180.0 [12.0]	0.018
Daily Dose (g)	4. 0 [2.5]	4.0 [2.0]	0.257
Serum creatinine (µM/L)	98.5 [97.0]	68.0 [25.0]	0.024
Age (years)	68.0 [8.8]	60.0 [19.0]	0.018
Sex (m/f)	14/30 (31.8%/68.2%)	12/3 (80%/20%)	0.002
Smokers (yes/no)	10/34 (22.7%/77.3%)	8/7 (53.3%/46.7%)	0.026
Toxic plasma concentration (yes/no)	22/22 (50%/50%)	0/15 (0%/100%)	0.000

* fT above MIC – percent of dose interval when free plasma concentration of ceftazidime was above minimal inhibitory concentration for sensitive bacteria; ** threshold p value corred by Bonferroni method to 0.007; *** mean ± standard deviation if normally distributed, median [interquartile range] if not normally distributed, frequency (percent) if categorical variable

Table III

Univariate comparison of the patients grouped according to acquiring toxic plasma concentrations

Variable***	Patients acquiring toxic concentrations (n = 22)	Patients not acquiring toxic concentration (n = 37)	p**
Body weight (kg)	71.0 ± 13.2	80.1 ± 12.2	0.721
Height (cm)	169. 5 [9.8]	175.0 [14.0]	0.055
Daily Dose (g)	4. 0 [2.0]	4.0 [3.0]	0.477
Serum creatinine (µM/L)	103.5 [154.0]	80.0 [66.0]	0.100
Age (years)	69.5 [7.8]	65.0 [16.5]	0.015
Sex (m/f)	7/15 (31.8%/68.2%)	19/18 (51.4%/48.6%)	0.144
Smokers (yes/no)	4/18 (18.2%/81.8%)	14/23 (37.8%/62.2%)	0.149
Patients achieving therapeutic levels of fT above MIC (yes/no)	22/0 (100%/0%)	22/15 (59.5%/40.5%)	0.000

* fT above MIC – percent of dose interval when free plasma concentration of ceftazidime was above minimal inhibitory concentration for sensitive bacteria; ** threshold p value corred by Bonferroni method to 0.007; *** mean ± standard deviation if normally distributed, median [interquartile range] if not normally distributed, frequency (percent) if categorical variable

Patients who did not achieve the therapeutic target of free drug concentration above the minimum inhibitory concentration (fT > MIC) were found to be significantly taller than those who met the target. Increased height is commonly associated with a larger volume of distribution, which for hydrophilic agents such as ceftazidime, may result in lower plasma concentrations if dosing adjustments are not made accordingly. This pharmacokinetic consideration likely explains the diminished target attainment observed in taller individuals. The association between greater height and reduced target attainment likely reflects height acting as a proxy for overall body size, as ceftazidime is hydrophilic and distributes primarily according to lean body mass and total body weight rather than height alone [15-17].

Serum creatinine levels were significantly elevated in patients who achieved the therapeutic threshold. Given that ceftazidime is primarily eliminated via renal excretion, reduced renal clearance in patients with higher creatinine levels may lead to slower drug elimination and prolonged exposure above the MIC. This finding underscores the critical role of renal function in influencing antibiotic exposure [18].

Table IV

Multivariate analysis of predictors of achieving fT above MIC therapeutic levels and of acquiring toxic plasma concentrations

Outcome	Predictor	OR crude (95% CI)*	p	OR adjusted (95% CI)	p
Achieving therapeutic levels of fT above MIC	Sex	0.117 (0.028 - 0.480)	0.003	0.07 (0.009 - 0.464)	0.006
Acquiring toxic plasma concentrations	Age	1.054 (0.999 - 1.111)	0.054	1.093 (1.007 - 1.187)	0.033
	Serum creatinine	1.003 (0.999 - 1.006)	0.139	1.009 (1.002 - 1.015)	0.007
	Daily Dose	1.115 (0.789 - 1.574)	0.537	2.659 (1.301 - 5.437)	0.007

* OR – odds ratio; CI – confidence interval

Age was also significantly associated with target attainment, with patients reaching the PK/PD target being older than those who did not. Although the absolute difference in median age was modest, this association may reflect age-related declines in renal function, which can occur even in the presence of normal serum creatinine due to reduced muscle mass [18]. Consequently, older patients may exhibit prolonged drug retention, thereby increasing the likelihood of achieving effective concentrations [6, 18]. Smoking status emerged as an additional significant factor. A considerably higher proportion of smokers were noted among patients who failed to reach therapeutic levels. Smoking is known to induce various metabolic and physiological alterations, including modified drug clearance and tissue distribution [19]. These effects may contribute to decreased ceftazidime exposure in smokers, potentially compromising PK/PD efficacy.

Multivariate analysis refined the univariate findings by identifying sex as the sole independent predictor of achieving therapeutic fT > MIC levels. Specifically, the likelihood of reaching the pharmacodynamic target was significantly lower in male patients, as demonstrated by both univariate and multivariate models. As shown in Table II, 80% of patients who failed to reach the therapeutic threshold were male, compared to only 31.8% among those who achieved it. This suggests that male sex is independently associated with a reduced probability of attaining PK/PD targets, potentially due to sex-related differences in volume of distribution, free drug fraction, glomerular filtration rate, or other pharmacokinetic parameters [20]. These findings underscore the importance of accounting for sex-based variability in drug exposure and support the implementation of individualised dosing strategies when prescribing β-lactam antibiotics such as ceftazidime.

Age, serum creatinine levels, and daily dose were found to be significant predictors of the risk factors for developing toxic plasma concentrations. An increased risk of toxicity was substantially correlated with both advanced age and elevated serum creatinine, both of which are signs of diminished renal function. With renal plasma flow declining by about 2% annually, this is in line with known age-related declines in renal clearance [21, 22]. Furthermore, the risk of toxic accumulation was significantly raised by a higher daily ceftazidime dosage [23]. These findings emphasise the need for dose modifications, especially in older patients, and support the crucial role that renal function plays in directing dosing decisions.

These findings have significant clinical implications. Negative side effects like neurotoxicity and nephrotoxicity can be brought on by toxic plasma concentrations of ceftazidime, which can lengthen hospital stays and raise medical expenses [24-26]. Therefore, balancing efficacy and safety requires early identification of patients at risk through routine therapeutic drug monitoring and dosing regimen adjustments.

Several factors, including age, smoking status, body height, and serum creatinine, were not included in the multivariate model even though they were substantially linked to target attainment in univariate analyses. This could be a result of sample size and statistical power limitations, and it implies that although these factors might influence drug exposure variability, their independent predictive value merits more research in larger cohorts.

Several limitations of this study should be noted. The relatively small sample size may limit the ability to apply the findings broadly and reduce the power to detect subtle predictors. Additionally, the study design did not consider all possible confounding factors, such as other health conditions, other medications, or genetic factors that could affect ceftazidime pharmacokinetics. Moreover, plasma drug concentrations were measured at specific times, which might not fully reflect changes over the dosing interval. Future studies with larger, more diverse groups and more frequent sampling are needed to support these findings.

When we compare our results with previous literature, identifying male sex and renal function as key factors matches earlier pharmacokinetic studies on β-lactam antibiotics [20, 27]. However, the novel association with smoking status highlights an area for further exploration, as limited data currently exist on how smoking influences ceftazidime pharmacodynamics.

Conclusions

This study emphasises the need for personalised dosing strategies for ceftazidime. It considers factors such as patient sex, age, kidney function, and smoking status to improve treatment results and

reduce toxicity risks. Improved monitoring of how the drug behaves in the body and adjusting doses based on these factors are suggested in clinical practice to promote better use of antibiotics and ensure patient safety. Future research should aim to confirm these factors in larger groups and create practical dosing guidelines for clinicians.

Acknowledgement

This work was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Contract no. 451-03-137/2025-03/200111).

Conflict of interest

The authors declare no conflict of interest.

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