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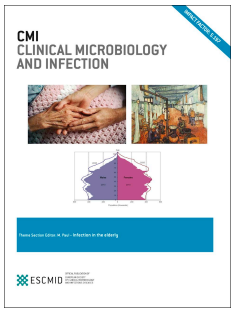

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Cefepime Neurotoxicity: Thresholds and Risk Factors. A Retrospective Cohort Study

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Key words: cefepime, neurotoxicity, plasma trough concentration, therapeutic drug monitoring, mortality

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Abstract

Objectives

Toxic serum cefepime trough concentrations are not well defined in the current literature. We aimed to define a more precise plasma trough concentration threshold for this antibiotic's neurological toxicity and to identify patients at risk for developing neurotoxic side effects.

Methods

Retrospective study including all patients who underwent cefepime therapeutic drug monitoring (TDM) between 2013 and 2017. Patients with cefepime concentrations other than trough were excluded. The primary outcome was to assess the incidence of neurotoxicity and its relationship with cefepime plasma trough concentrations. Secondary outcomes were the relationship of renal function, cefepime daily dose, age, cerebral and general comorbidities with the occurrence of neurotoxicity. We also compared the mortality rate during hospitalisation in patients with and without neurotoxicity, and the possible impact of neuroprotective co-medications on the outcomes.

Results

Cefepime concentrations were determined in 584 patients. Among 319 patients with available trough concentrations included, the overall incidence of neurotoxicity was 23.2% (74 of 319 patients). Higher cefepime plasma trough concentrations were significantly associated with risk of (no neurotoxicity 6.3 mg/L [IQR 4.1, 8.6] vs with neurotoxicity 21.6 mg/L [IQR 17.0, 28.6], $p < 0.001$). Patients with presumed cefepime neurotoxicity had a significantly lower renal function (eGFR 82.0 ml/min/1.73m^2 [IQR 45.0, 105.0] vs 35.0 ml/min/1.73m^2 [IQR 23.3, 53.3], $p<0.001$), and significantly higher in-hospital mortality (19 (7.8%) vs 26 (35.1%) patients, $p<0.001$).No neurotoxic side effects were seen below a trough concentration of 7.7 mg/L. Levels ≥ 38.1 mg/L always led to neurologic side effects.

Conclusion

In patients with risk factors for cefepime neurotoxicity, such as renal insufficiency, TDM should be systematically performed, aiming at trough concentrations below 7.5 mg/L.

Introduction

Cefepime serves as a treatment of choice in AmpC producers that do not harbour extended-spectrum beta-lactamase enzymes (ESBLs), or carbapenemases which are able to hydrolyse the drug [1-3].

Plasma cefepime trough concentrations are highly variable in critically ill patients, and those with renal failure are at risk of drug accumulation [4, 5]. The neurotoxic effects of cefepime were first reported in 1999 [6], and some case reports have emphasized the relationship of neurological side effect with renal insufficiency in patients receiving cefepime treatment [7-10]. The pathophysiology of cefepime neurotoxicity is thought to be related to concentration-dependent GABA-A receptor modulation [11].

Switzerland is among the major consumers of cefepime per capita in Europe [12]. In order to monitor and prevent toxicity of cefepime, Swiss hospitals have started to offer therapeutic drug monitoring (TDM) [13, 14] – our hospital starting in 2013.

Specific therapeutic ranges, however, are still missing. Case series observing smaller numbers of patients with cefepime-associated neurotoxicity have failed to determine any concentration thresholds [15]. Two studies – both retrospective - were conducted to define a threshold at which cefepime trough concentrations are associated with an increased risk of neurotoxicity, and suggested these to be at 20 mg/L and 15-20 mg/L respectively [13, 14]. Both studies however examined only a small number of trough concentrations.

The objectives of the present study were to define more stringent therapeutic ranges for cefepime and to identify patients at risk for developing cefepime-associated neurotoxicity.

Methods

Study design, population and setting

This single-centre retrospective cohort study was conducted at the University Hospital of Bern, Switzerland, a 1000-bed tertiary care centre. Patients ≥18 yearsi) hospitalised between 1st January 2013, when cefepime TDM became routinely available, and 31st December 2017, and ii) who had at least one cefepime plasma concentration available during hospitalisation, were included. An Infectious Diseases (ID) specialist (BBF) and a specialist in Internal Medicine (LBP) independently reviewed all patient's medical records for neurological symptoms and indicators of neurotoxicity (see **Table S1**, supplementary material and definitions below) , with additional spot checks by two ID specialists (CH, PJ) on 50 randomly selected medical records. For patients with presumed neurotoxicity, the clinical and pharmacological data was independently reviewed by three clinical pharmacologists (LK, SB, MH) in order to confirm the causality assessment and to evaluate the role of potentially confounding co-medications. For each patient, demographic features and characteristics were collected. Data on time of cefepime application and concentration measurement were cross-checked. Specific attention was paid to the development of neurotoxicity in patients with known underlying structural or functional cerebral impairments.

The study was approved by the ethics committee of the canton of Bern (KEK No 2018-00330).

Definitions and outcomes

Potential neurotoxicity and/or neurologic symptoms occurring after three dose intervals of cefepime were documented according to the Common Terminology Criteria for Adverse Events [16] (**Table S1**, supplementary material), with the absence of any plausible alternative cause/co-medication for the symptoms. We additionally documented possible adverse

neurological effects based on the occurrence of neurological signs (altered mental status, depressed concentration of consciousness, confusion, aphasia, asterixis, myoclonus, dystonia, seizure, non-convulsive status epilepticus [NCSE], coma) occurring under cefepime therapy based on literature reviews and case reports [15, 17-19]. A formal causality assessment between cefepime exposure and adverse neurologic events was performed using the WHO-UMC system [20], with trough levels closest to the symptoms being double-checked .The presence of potentially confounding medications that might have prevented convulsions (such as anticonvulsants, propofol and benzodiazepines) was examined for all patients with cefepime trough plasma concentrations ≥ 5mg/L [21, 27, 28]. In addition, adverse neurologic effects of these co-medications, that can not be distinguished from cefepime-associated neurotoxicity (e.g. altered mental status) were taken into account, and symptom improvement after stopping cefepime (i.e. positive de-challenge) was checked.The primary aim of this study was to assess the incidence of neurotoxicity and its relationship with cefepime plasma trough concentrations in patients receiving TDM. Secondary goals were to assess the correlation of i) renal function, ii) cefepime cumulative daily doses, iii) patient age, iv) comorbidities and v) centrally acting co-medications with neurotoxicity (see **Table S2**. We additionally reviewed mortality rates in these patients and cause of death in patients with presumed cefepime neurotoxicity.

Cefepime trough concentration measurements and estimation of creatinine clearance

At our hospital, cefepime is given three times a day with dosing adjustment for patients with an eGFR of ≤ 50 ml/min/1.73m^2 according to the manufacturer's recommendations [21]. Continuous cefepime infusions are not administered. Institutional guidelines suggest application of high doses (2g every 8h) for patients with febrile neutropenia, meningitis or known *Pseudomonas* spp infections.

Sample preparation and analysis was performed as previously described [22, 23]. Samples from patients with sulfamethoxazole co-application were excluded from the study (n=4) due to potential interference.

We only analysed confirmed cefepime plasma trough concentrations, defined as sample collection ≤ 1h before next dose application. The timing of blood collection and previous, as well as subsequent, cefepime administration were carefully cross-checked. In addition to plasma concentrations that were not confirmed trough concentrations, all results with unclear timing of cefepime application or concentration measurement were excluded.

Dates of starting and stoping cefepime therapy, along with dosage of the drug over the 24 hours preceding the cefepime measurement were recorded. For patients with multiple cefepime measurements, we considered the highest cefepime plasma trough concentration for statistical analysis. In patients with suspected neurotoxicity, we cross-checked the concentrations measured during the occurrence of neurological signs (see **Figure S1** supplementary material) . A detailed description of the methods (e.g. follow-up of patients) is presented in the supplementary materials.

Renal function of the patients was assessed using the CKD-EPI formula for estimating the glomerular filtration rate (eGFR) on the day of cefepime concentration measurement [24]. If not available, the value of the closest day was considered. We also evaluated whether renal function was stable or not, based on the AKIN definition [25].

Statistical Analysis

For comparison between those with and without neurotoxicity, the chi-squared test was used for categorical variables, and the Mann-Whitney-Wilcoxon test for continuous variables. Univariate and multivariate logistic regression models were fitted with neurotoxicity as dependent variable. The independent variables consisted of : 1) age, 2) sex, 3) kidney

function, 4) cefepime treatment duration until plasma trough concentration measurement, 5) adjusted cefepime dose, 6) cefepime plasma concentration, along with the following indicator variables : i) treatment of patient on intensive care unit (ICU) during hospitalisation, ii) general comorbidities (cardiovascular, pulmonary, diabetes, solid or haematological malignancy), and iii) neurologic comorbidities (arterial or venous thrombosis / haemorrhage, presence of a tumour, epilepsy, CNS infection, dementia, cognitive impairment, other brain diseases). The final adjusted multivariate model was determined by forwards and then backwards variable selection using the Akaike Information Criteria (AIC). The predictive power of the model was internally cross-validated using standard *N*-fold technique using bootstrapped data. (see supplementary material, model validation, **Figure M1**).

Subgroup analyses were performed to identify whether there was a significant difference in confounding co-medication between patients with and without adverse neurological effects. Results were considered significant at a p-value ≤ 0.05. The statistical analysis was performed using the R statistical software [26].

Results

3793 patients were treated with cefepime between 2013 and 2017. General consent was available from 1845 patients. Of these, TDM was obtained in 548 and 1138 cefepime concentrations were available for assessment. Among these patients, 265 were excluded, mainly because of inadequate/uncertain timing of the blood sampling, co-application of sulfamethoxazole (possible interference with cefepime concentration analysis) or lack of adequate neurological assessment (**Figure S2**, supplementary material).

In total 319 patients were included in the analysis with their respective highest recorded cefepime trough concentration. Seventy-four of the 319 included patients presented neurologic symptoms that were “possibly” related to cefepime administration according to

the formal WHO-UMC causality assessment. The most frequently encountered symptoms were confusion/agitation/hallucinations and reduced consciousness, including coma (**Table 1**). The median time from cefepime start to the development of neurologic signs was 2 days. In the vast majority of patients (96%), the cefepime treatment was adapted or stopped after the beginning of the symptoms. Eighty-one percent of the patients recovered at least partially from their symptoms, and required a median time of 2 days after therapy adaptation or cessation for the symptoms to improve or disappear.

There was no significant difference in receiving at least one potentially confounding centrally active co-medication between the two groups of patients (71/171 vs 28/74, p=0.69) (**Table S4**, supplemental material).

Regarding the primary outcome of the study, cefepime plasma trough concentrations were significantly higher (21.6 mg/L [IQR 17.0,28.6] vs 6.3 mg/L[IQR 4.1, 8.6] , p <0.001) in patients with suspected cefepime-associated neurotoxicity (**Figure 1**). There was no significant association between underlying cerebral comorbidities and cefepime neurotoxicity. ICU stay during hospitalisation and haematological malignancy were highly statistically significant associations for presumed neurotoxicity from the fitted multivariable adjusted logistic models (**Tables S3** and **4)**. **Figure S3** (supplementary material) depicts the variables that were independently associated with a higher probability of possible neurotoxicity according to the multivariate logistic regression.

No patient developed possible neurotoxicity at cefepime plasma trough concentrations < 7.7 mg/L. The probability of neurotoxicity from the fitted logistic regression model was 25% for cefepime concentrations ≥ 12 mg/L , 50% for cefepime concentrations ≥ 16 mg/L (**Figure 2)**All patients had neurotoxicity at cefepime trough concentrations ≥ 38.1 mg/L . Sensitivity and specificity for each of the thresholds defined in Figure 2 is presented in **Table S5**, supplementary material.

Patients with presumed cefepime neurotoxicity had a significantly lower eGFR (35.0 ml/min/1.73m^2 [IQR 23.3,53.3]) when compared to patients without neurologic symptoms (82.0 ml/min/1.73m^2 [IQR 45.0,105.0]), p<0.001 (**Tables S3** and **Table 2**). Moreover, renal function was less frequently stable, and the cefepime dose adjusted to renal clearance was significantly higher, in patients with presumed neurotoxicity. As expected, cefepime trough concentrations were inversely correlated with renal function (**Figure S4**, supplementary material). The highest proportion of patients with presumed cefepime neurotoxicity (31/57, 54%) and in-hospital mortality (14/57,25%) was seen in patients with an eGFR < 30mL/min/1.73m^2 (**Table 3).** In-hospital mortality was significantly higher in patients with presumed cefepime neurotoxicity (7.8% vs 35.1%, p <0.001) (**Table S4**). The most frequent causes of death in these patients were their underlying conditions and infections (**Table S4**, supplementary material).

Discussion

In our study we found that there was no risk of developing neurotoxicity with cefepime plasma trough concentrations < 7.7 mg/L. However, all patients with concentrations above 38.1 mg/L, presented with neurological symptoms. The relationship between cefepime plasma concentrations and risk of neurotoxicity has been evaluated in two other studies with substantially smaller patient numbers. Huwyler et al. [13] studied 93 hospitalised patients and stated that no neurotoxicity was seen at any sample concentration (trough, intermediate or steady-state) below 35mg/L. In addition, Lamoth et al.[14] evaluated 30 hospitalised patients with febrile neutropenia receiving high doses of cefepime. In their study, patients with cefepime plasma concentrations > 22 mg/L had a 50% probability of developing neurologic symptoms.

To our knowledge, the relationship between cefepime plasma concentrations and neurotoxicity has not been studied in such a large number of patients. In our cohort, the 50% probability of developing presumed neurotoxicity was reached at a lower concentration (≥ 16 mg/L) than previously reported. Based on our current results, we would advise to target cefepime plasma trough concentrations at < 7.5 mg/L to avoid the risk of neurotoxicity in patients undergoing cefepime therapy.

In our study 23.2% developed symptoms consistent with neurotoxicity. This is similar to the study of Lamoth et al. (20%) [14], but substantially higher than in the study of Huwyler et al.(11%) [13]. This difference might be due to the increased sensitivity for recognizing potential neurotoxicity by implementing a broader definition based on available literature and prescribing information (*i.e.* 3 patients with vertigo) [15, 17-19, 21]. In addition, the previous studies [13, 14] only included patients that developed signs of neurotoxicity at least ≥ 2 days after start of cefepime treatment. Although penetration of cefepime into the central nervous system is not very high (approx. 5-10% of serum concentration in patients with intact blood brain barrier), concentrations in the cerebrospinal fluid (CSF) increase within hours after intravenous dosing [27]. In patients with renal failure, penetration into CSF may be higher (up to 45%) [28], and very short latency periods of less than two days between start of cefepime treatment and neurological deterioration have been reported [10]. Including patients that had already developed neurological symptoms after 3 dose intervals of cefepime increased the sensitivity of detecting adverse neurological effects in our study.

Patients with haematological malignancy and those who needed intensive care during hospitalisation, were at substantially higher risk of cefepime associated neurotoxicity. Latter is in line with the study of Huwyler et al. [13]. ICU patients are prone to disruptions of the blood-brain barrier, which might facilitate the CNS penetration of cefepime [15]. Furthermore, they have a high frequency of renal impairment.

The highest proportion of patients with suspected neurotoxicity was seen in those with an eGFR < 30ml/min/1.73m^2. Moreover, the cefepime dose adjusted to the renal function was significantly higher in patients with presumed cefepime neurotoxicity. These patients also had higher cefepime plasma trough concentrations. As elimination of cefepime is primarily mediated by glomerular filtration in the kidneys [29, 30], reduced creatinine clearance has been shown to lead to drug accumulation [4] and thus higher probability of cefepime-associated neurotoxicity [13-15, 17]. Consequently, we emphasize the importance of closely monitoring renal parameters and cefepime trough concentrations in patients with eGFR <60mL/min/1.73m2.

No statistically significant difference was found in those with or without neurotoxicity in the use of confounding centrally-active co-medication at cefepime trough concentrations ≥ 5mg/L. It should however be taken into consideration that central effects of these agents are dose-dependent. Due to the retrospective character of this study, doses of administered co-medications were not considered.

Surprisingly, we found no statistically significant association between underlying structural or functional cerebral impairments and the development of neurotoxicity; The incidence of neurotoxicity might be unrecognized and the causality is difficult to assign either to the underlying condition or cefepime treatment [15].

Mortality was significantly higher in patients who presented signs of neurotoxicity compared to those without. To our knowledge, there is no other study with a similar design addressing this issue. Whether cefepime neurotoxicity had an impact on the patient's outcome remains to be determined. Cefepime neurotoxicity is strongly associated with higher cefepime plasma concentrations due to declining renal function. Renal failure is a marker for more severe illness, e.g. multi-organ failure and severe sepsis. Since the causes of death among patients

with presumed neurotoxicity were non-neurologic in the majority of the cases, cefepime neurotoxicity may not be causally related to mortality, but rather be associated with more severe illness leading to lower eGFR.

This study is limited by its retrospective nature and data was not specifically collected to depict the incidence of cefepime-induced neurotoxicity. However, we increased sensitivity for recognizing potential neurotoxicity by implementing a broader definition based on available literature and prescribing information. In addition, we did not only include patients with a delay of at least two days after start of the antibiotic, which may have increased sensitivity for detecting early manifestations of neurotoxicity, especially in those with renal failure. However, at our institution, TDM is not routinely performed in all patients receiving cefepime, but mainly in those receiving high-dose cefepime treatment or with known renal insufficiency. Therefore, the proportion of patients presenting with neurotoxicity in this study probably overestimates the real incidence of neurotoxicity among patients treated with cefepime.

Although we have taken into account many confounding parameters, plasma trough concentrations do not reflect pharmacodynamics and toxicodynamic interactions caused by individual and environment-related factors, which might be a limitation of this testing method.

In conclusion, particular caution and a high index of suspicion of neurotoxicity is required for patients with renal insufficiency, multi morbidity and those in ICU care who are treated with cefepime. We advise implementing TDM as a routine tool to guide therapy in those patients and to target cefepime trough concentrations $\leq$ 7.5mg/L. However, special attention should be paid to infections with pathogens that require higher dosage of cefepime in order to

prevent treatment failure and/or resistance evolution such as infections with *pseudomonas aeruginosa* that harbour cefepime MICs of 4- 8mg/L.

Further prospective studies investigating the development of cefepime neurotoxicity in patients with cerebral comorbidities are needed in order to assess whether the use of cefepime is safe in these patients. Furthermore, we envisage externally validating the thresholds presented here using data from other hospitals in a further study.

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Conflicts of interest

All authors declare no conflict of interest related to this study.

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Table 1. Symptoms and Outcome of Patients with presumed Cefepime Neurotoxicity

	N (%)
Overall number of patients	74
Standardised case causality assessment according to WHO-UMC	74 (100)
Number of patients with following symptoms	
- Confusion, agitation, hallucinations	46 (62)
- Reduced consciousness, coma	32 (43)
- Myoclonus	6 (8)
- Vertigo	3 (4)
- Flapping tremor	2 (3)
- Ataxia	2 (3)
- Seizure, non-convulsive status epilepticus	2 (3)
- Aphasia	1 (1)
- Dystonia / dyskinesia	1 (1)
Median time from first cefepime dose to symptom presentation, days [range]	2 [1, 14]
Number of patients (%) in whom cefepime was	
- Stopped	45 (61)
- Adapted	26 (35)
- Not modified	3 (4)
After the occurrence of suspected neurotoxicity	
Number of patients (%) with symptom improvement or resolution after stop of cefepime	60 (81)
Median time to improvement or recovery after treatment adaptation, days [range]	2 [1, 19]

WHO-UMC: World Health Organisation Uppsala Monitoring Centre

Table 2: Univariable and Multivariable Logistic Regression with the Variable for presumed Cefepime Neurotoxicity as Indicator Variable; Final Model for the Multivariate adjusted model.

	Univariate		**Multivariate**	
	Odds Ratio [95% confidence interval]	p-value	Odds Ratio [95% confidence interval]	p-value
Cefepime plasma trough concentration, mg/L	1.31 [1.24, 1.40]	< 0.001	1.33 [1.23, 1.45]	< 0.001
Cefepime treatment duration until plasma trough concentration measurement, days	0.99 [0.92, 1.05]	0.7	n.s	-
Adjusted cefepime dose, g/d per 100mL/min/1.73m2 eGFR	1.68 [1.48, 1.95]	<0.001	1.39 [1.20, 1.64]	<0.001
Age, years (10 yr steps)	1.46 [1.18, 1.83]	<0.001	n.s.	-
Male sex	0.71 [0.41, 1.24]	0.2	n.s.	-
ICU stay during hospitalisation	2.45 [1.39, 4.52]	0.003	8.23 [2.87, 27.48]	< 0.001
eGFR, mL/min/1.73m^2 (10 unit steps)	0.71 [0.63, 0.78]	< 0.001	*	*
- Steady state	0.19 [0.10, 0.34]	< 0.001	n.E.	
General comorbidities				
- Overall	1.61 [1.23, 2.12]	<0.001	n.E.	-
- Cardiovascular	2.06 [1.18, 3.68]	0.01	n.s.	-
- Pulmonary	1.84 [1.08, 3.23]	0.03	3.41 [1.28, 10.07]	0.02
- Diabetes	1.47 [0.84, 2.54]	0.2	n.s.	-
- Solid cancer	0.96 [0.46, 1.90]	0.9	n.s.	-
- Haematological cancer	2.06 [0.96, 4.25]	0.06	6.27 [1.62, 25.30]	0.008
Cerebral comorbidities				
- Overall	0.89 [0.60, 1.25]	0.5	n.E.	-
- Arterial or venous thrombosis, haemorrhage	0.55 [0.25, 1.11]	0.1	n.s.	-
- Tumor	1.22 [0.33, 3.68]	0.8	n.s.	-
- Epilepsy	1.35 [0.47, 3.47]	0.6	n.s.	-
- Infection	0.82 [0.23, 2.32]	0.7	n.s.	-
- Dementia, cognitive impairment	4.61 [0.99, 23.86]	0.05	n.s.	-
- Other	0.48 [0.11, 1.44]	0.2	n.s.	-

n.s, not significant at the 5% concentration; n.E., not estimated, yr, year; eGFR, estimated glomerular filtration rate; ICU, intensive care unit * collinear with cefepime trough concentration excluded from final model (tested using Farrar-Glauber test)

Table 3: Cefepime Plasma Trough Levels, Doses, presumed Cefepime Neurotoxicity and Death according to Renal Function among all Patients (n = 319)

	eGFR > 90mL/min	60 < eGFR ≤ 90mL/min	30 < eGFR ≤ 60mL/min	eGFR <30mL/min
Overall number of patients	106	69	87	57
Median cefepime plasma trough concentration, mg/L [IQR]	5.6 [3.4, 7.7]	7.2 [5.3, 11.1]	11.6 [6.1, 21.9]	16.3 [7.1, 26.2]
Median adjusted cefepime dose, g/d per 100mL/min/1.73m2 eGFR [IQR]	3.0 [2.6, 4.9]	3.6 [2.9, 4.5]	4.7 [3.3, 6.3]	7.1 [4.4, 10.5]
Neurotoxicity (%)	4 (4%)	11 (16%)	28 (32%)	31 (54%)
Hospital mortality (%)	9 (9%)	3 (4%)	19 (22%)	14 (25%)

eGFR, estimated glomerular filtration rate; IQR, interquartile range

Figure 1. Cefepime Plasma Trough Concentration for Patients with and without presumed Cefepime Neurotoxicity

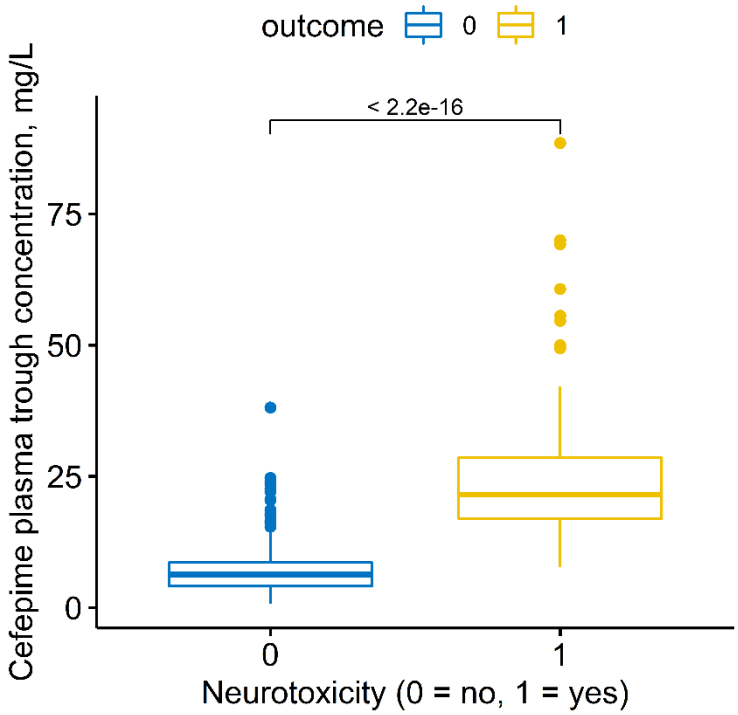

Figure 2. Probability of Cefepime associated Neurotoxicity as a Function of Cefepime Plasma Trough Concentrations; Cut-off Thresholds for Neurotoxicity i.) 0% Neurotoxic below 7.7 mg/L (Green Solid Vertical Line), ii.) Probability of being Neurotoxic = 0.25 at 12 mg/L (Grey Solid Line), and iii.) Probability of being Neurotoxic = 0.5 at 16 mg/L (Dashed Orange Lines), and iv.) 100% Neurotoxic above 38.1 mg/L (Solid Red Line); vertically jittered Data points to ease Readability.