Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

# Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study

L. Boschung-Pasquier [1, 2, 3, †], A. Atkinson [2, †], L.K. Kastner [4], S. Banholzer [4], M. Haschke [4], N. Buetti [2, 5], D.I. Furrer [6], C. Hauser [2], P. Jent [2], Y.A. Que [7], H. Furrer [2], B. Babouee Flury [2, *]

[1] Faculty of Medicine, University of Bern, Bern, Switzerland
[2] Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland
[3] Department of Geriatrics and Rehabilitation, Hôpital Fribourgeois Tavel, Tavel, Switzerland
[4] Clinical Pharmacology and Toxicology, Department of General Internal Medicine, Bern University Hospital, University of Bern, Bern, Switzerland
[5] UMR 1137 - IAME Team 5 - DeSCID: Decision SCiences in Infectious Diseases, Control and Care Inserm/University Paris Diderot, Sorbonne Paris Cité, Paris, France
[6] Insel Data Science Center and Insel Data Coordination Lab, Directorate of Teaching and Research, Bern University Hospital, University of Bern, Bern, Switzerland
[7] Department of Intensive Care Medicine, Bern University Hospital, University of Bern, Bern, Switzerland

ARTICLE INFO

*Article history:*
Received 3 March 2019
Received in revised form
27 May 2019
Accepted 19 June 2019
Available online xxx

Editor: W Couet

*Keywords:*
Cefepime
Mortality
Neurotoxicity
Plasma trough concentration
Therapeutic drug monitoring

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 individuals at risk for developing neurotoxic side effects.
*Methods:* Retrospective study including all individuals who underwent cefepime therapeutic drug monitoring (TDM) between 2013 and 2017. Individuals 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, and cerebral and general co-morbidities with the occurrence of neurotoxicity. We also compared the mortality rate during hospitalization in individuals with and without neurotoxicity, and the possible impact of neuroprotective co-medications on outcomes.
*Results:* Cefepime concentrations were determined in 584 individuals. Among 319 individuals with available trough concentrations included, the overall incidence of neurotoxicity was 23.2% (74 of 319 individuals). Higher cefepime plasma trough concentrations were significantly associated with risk of neurotoxicity (no neurotoxicity 6.3 mg/L (interquartile range (IQR) 4.1–8.6) versus with neurotoxicity 21.6 mg/L (IQR 17.0–28.6), p <0.001). Individuals with presumed cefepime neurotoxicity had a significantly lower renal function (estimated glomerular filtration rate 82.0 mL/min/1.73 $m^2$ (IQR 45.0–105.0) versus 35.0 mL/min/1.73 $m^2$ (IQR 23.3–53.3], p <0.001), and significantly higher in-hospital mortality (19 (7.8%) versus 26 (35.1%) individuals, 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 neurological side effects.
*Conclusion:* In individuals with risk factors for cefepime neurotoxicity, such as renal insufficiency, TDM should be systematically performed, aiming at trough concentrations <7.5 mg/L. **L. Boschung-Pasquier, Clin Microbiol Infect 2019;▪:1**
© 2019 The Author(s). Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## Introduction

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

* Corresponding author. B. Babouee Flury, Department of Infectious Diseases, Bern University Hospital, CH-3010 Bern, Switzerland.
*E-mail address:* b.baboueeflury@bluewin.ch (B. Babouee Flury).
† L. Boschung-Pasquier and A. Atkinson contributed equally to this work.

https://doi.org/10.1016/j.cmi.2019.06.028
1198-743X/© 2019 The Author(s). Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article as: Boschung-Pasquier L et al., Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.06.028

Plasma cefepime trough concentrations are highly variable in critically ill individuals, 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 effects with renal insufficiency in individuals 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]. 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 individuals 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 individuals 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. Individuals ≥18 years who (i) were hospitalized between 1 January 2013, when cefepime TDM became routinely available, and 31 December 2017, and (ii) had at least one cefepime plasma concentration available during hospitalization, were included. An Infectious Diseases specialist (BBF) and a specialist in Internal Medicine (LBP) independently reviewed all the medical records of individuals for neurological symptoms and indicators of neurotoxicity (see Supplementary material, Table S1, and definitions below), with additional spot checks by two Infectious Diseases specialists (CH, PJ) on 50 randomly selected medical records. For individuals with presumed neurotoxicity, the clinical and pharmacological data were independently reviewed by three clinical pharmacologists (LK, SB, MH) to confirm the causality assessment and to evaluate the role of potentially confounding co-medications. For each individual, 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 individuals 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 neurological symptoms occurring after three dose intervals of cefepime were documented according to the Common Terminology Criteria for Adverse Events [16] (see Supplementary material, Table S1), 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, coma) occurring under cefepime therapy based on literature reviews and case reports [15,17–19]. A formal causality assessment between cefepime exposure and adverse neurological events was performed using the WHO-Uppsala Monitoring Centre 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 individuals with cefepime trough plasma concentrations ≥5mg/L [21]. In addition, adverse neurological effects of these co-medications, that cannot 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 individuals receiving TDM. Secondary goals were to assess the correlation of (i) renal function, (ii) cefepime cumulative daily doses, (iii) patient age, (iv) co-morbidities and (v) centrally acting co-medications with neurotoxicity (see Supplementary material, Table S2). We additionally reviewed mortality rates in these individuals and cause of death in individuals 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 individuals with an estimated glomerular filtration rate (eGFR) of ≤50 mL/min/1.73 $m^2$ according to the manufacturer's recommendations [21]. Continuous cefepime infusions are not administered. Institutional guidelines suggest application of high doses (2 g every 8 h) for individuals with febrile neutropenia, meningitis or known *Pseudomonas* spp. infections.

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

We only analysed confirmed cefepime plasma trough concentrations, defined as sample collection ≤1 hour before next dose application. The timings of blood collection and previous, as well as subsequent, cefepime administrations 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 stopping cefepime therapy, along with dosage of the drug over the 24 hours preceding the cefepime measurement, were recorded. For individuals with multiple cefepime measurements, we considered the highest cefepime plasma trough concentration for statistical analysis. In individuals with suspected neurotoxicity, we cross-checked the concentrations measured during the occurrence of neurological signs (see Supplementary material, Fig. S1). A detailed description of the methods (e.g. follow up of individuals) is presented in the Supplementary materials.

Renal function of the individuals was assessed using the Chronic Kidney Disease–Epidemiology Collaboration (or CKD-EPI) formula for estimating the glomerular filtration rate (eGFR) on the day of

Please cite this article as: Boschung-Pasquier L et al., Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.06.028

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 Acute Kidney Injury Network 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, and (6) cefepime plasma concentration, along with the following indicator variables: (i) treatment of individual on intensive care unit (ICU) during hospitalization, (ii) general co-morbidities (cardiovascular, pulmonary, diabetes, solid or haematological malignancy), and (iii) neurological co-morbidities (arterial or venous thrombosis/haemorrhage, presence of a tumour, epilepsy, central nervous system 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. The predictive power of the model was internally cross-validated using standard *N*-fold technique using bootstrapped data (see Supplementary material, Appendix S1).

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

## Results

A total of 3793 individuals were treated with cefepime between 2013 and 2017. General consent was available from 1845 individuals. From these, TDM was obtained in 548 and 1138 cefepime concentrations were available for assessment. Among these individuals, 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 (see Supplementary material, Fig. S2).

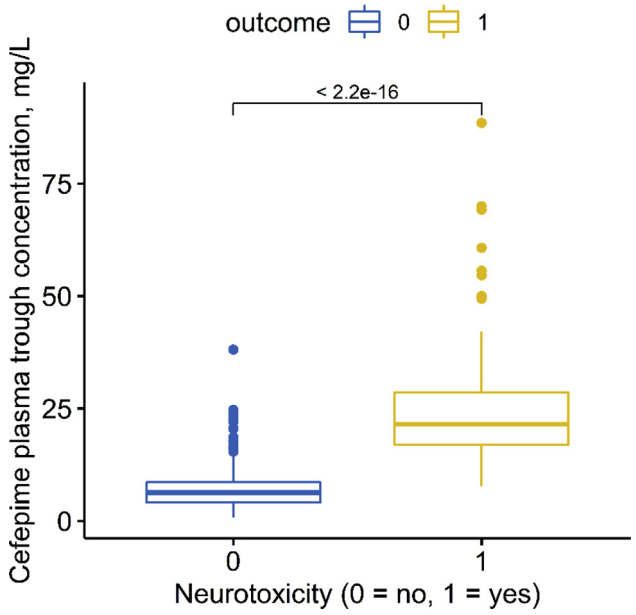


**Fig. 1.** Cefepime plasma trough concentration for individuals with and without presumed cefepime neurotoxicity.

In total 319 individuals were included in the analysis with their respective highest recorded cefepime trough concentration. Seventy-four of the 319 included individuals presented neurological symptoms that were 'possibly' related to cefepime administration according to the formal WHO-Uppsala Monitoring Centre 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 neurological signs was 2 days. In the vast majority of individuals (96%), the cefepime treatment was adapted or stopped after the beginning of the symptoms. Eighty-one per cent of the individuals 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.

**Table 1**
Symptoms and outcome of individuals with presumed cefepime neurotoxicity

| | *n* (%) |
|---|---|
| Overall number of participants | 74 |
| Standardized case causality assessment according to WHO-UMC system | 74 (100) |
| Number of participants with the 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 participants (%) in whom cefepime was: | |
| Stopped | 45 (61) |
| Adapted | 26 (35) |
| Not modified | 3 (4) |
| after the occurrence of suspected neurotoxicity | |
| Number of participants (%) 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 Organization Uppsala Monitoring Centre.

Please cite this article as: Boschung-Pasquier L et al., Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.06.028

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

Regarding the primary outcome of the study, cefepime plasma trough concentrations were significantly higher (21.6 mg/L (interquartile range (IQR) 17.0–28.6) versus 6.3 mg/L (IQR 4.1–8.6), p <0.001) in individuals with suspected cefepime-associated neurotoxicity (Fig. 1). There was no significant association between underlying cerebral co-morbidities and cefepime neurotoxicity. ICU stay during hospitalization and haematological malignancy were highly statistically significant associations for presumed neurotoxicity from the fitted multivariable adjusted logistic models (see Supplementary material, Tables S3 and S4). Fig. S3 (see Supplementary material) depicts the variables that were independently associated with a higher probability of possible neurotoxicity according to the multivariate logistic regression.

No individual 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 (Fig. 2). All participants had neurotoxicity at cefepime trough concentrations ≥38.1 mg/L. Sensitivity and specificity for each of the thresholds defined in Fig. 2 is presented in the supplementary material (Table S5).

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

## 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 individuals with concentrations >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 participant numbers. Huwyler et al. [13] studied 93 hospitalized individuals and stated that no neurotoxicity was seen at any sample concentration (trough, intermediate or steady-state) <35 mg/L. In addition, Lamoth et al. [14] evaluated 30 hospitalized individuals with febrile neutropenia receiving high doses of cefepime. In their study, individuals with cefepime plasma concentrations >22 mg/L had a 50% probability of developing neurological symptoms.

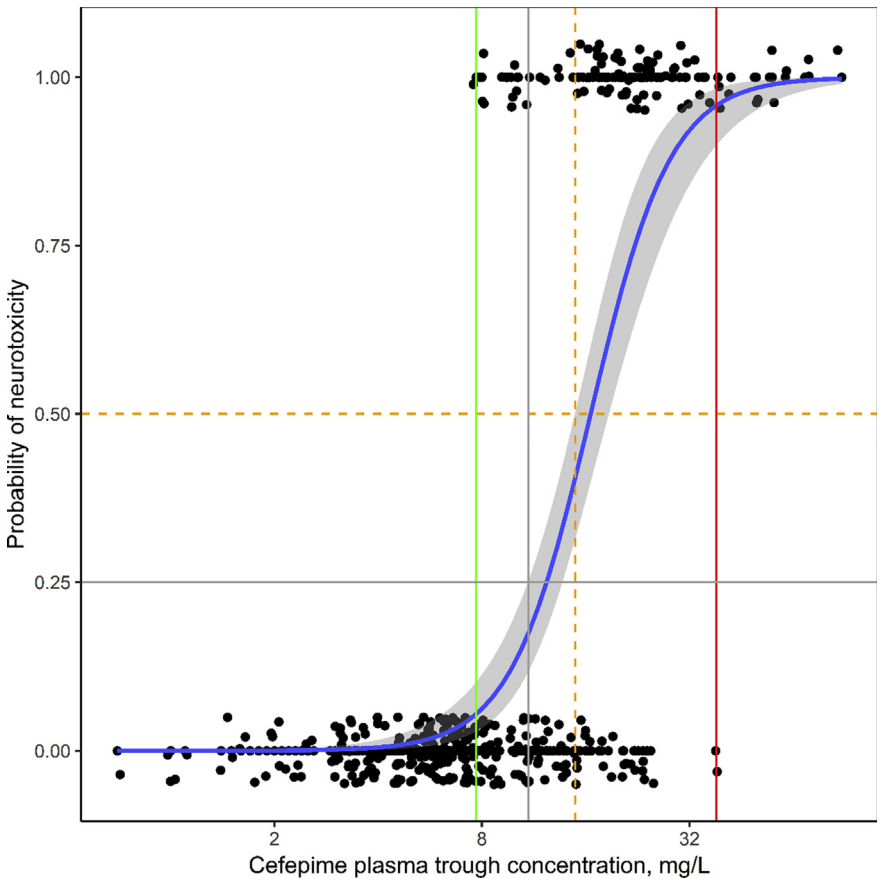


**Fig. 2.** Probability of cefepime-associated neurotoxicity as a function of cefepime plasma trough concentrations; cut-off thresholds for neurotoxicity: (i) 0% neurotoxic below 7.7 mg/L (green solid vertical line), (ii) probability of being neurotoxic = 0.25 at 12 mg/L (grey solid line), (iii) probability 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.

Please cite this article as: Boschung-Pasquier L et al., Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.06.028

**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 | p-value | Multivariate | p-value |
|---|---|---|---|---|
| | OR (95% CI) | | OR (95% CI) | |
| 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/day per 100 mL/min/1.73 $m^2$ eGFR | 1.68 (1.48–1.95) | <0.001 | 1.39 (1.20–1.64) | <0.001 |
| Age, years (10-year 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 hospitalization | 2.45 (1.39–4.52) | 0.003 | 8.23 (2.87–27.48) | <0.001 |
| eGFR, mL/min/1.73 $m^2$ (10 unit steps) | 0.71 (0.63–0.78) | <0.001 | * | * |
| Steady state | 0.19 (0.10–0.34) | <0.001 | N.E. | |
| General co-morbidities | | | | |
| 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 co-morbidities | | | | |
| 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. | — |
| Tumour | 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. | — |

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

To our knowledge, the relationship between cefepime plasma concentrations and neurotoxicity has not been studied in such a large number of individuals. 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 targeting cefepime plasma trough concentrations at <7.5 mg/L to avoid the risk of neurotoxicity in individuals undergoing cefepime therapy.

In our study, 23.2% of participants 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 the result of the increased sensitivity for recognizing potential neurotoxicity by implementing a broader definition based on available literature and prescribing information (i.e. three participants with vertigo) [15,17–19,21]. In addition, the previous studies [13,14] only included individuals that developed signs of neurotoxicity at least 2 days after the start of cefepime treatment. Although penetration of cefepime into the central nervous system is not very high (approx. 5%–10% of serum concentration in individuals with intact blood–brain barrier), concentrations in the cerebrospinal fluid increase within hours after intravenous dosing [27]. In individuals with renal failure, penetration into cerebrospinal fluid may be higher (up to 45%) [28], and very short latency periods of <2 days between start of cefepime treatment and neurological deterioration have been reported [10]. Including individuals that had already developed neurological symptoms after three 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 hospitalization were at substantially higher risk of cefepime-associated neurotoxicity. The latter is in line with the study of Huwyler et al. [13]. Patients in ICU are prone to disruptions of the blood–brain barrier, which might facilitate the central nervous system penetration of cefepime [15]. Furthermore, they have a high frequency of renal impairment.

The highest proportion of individuals with suspected neurotoxicity was seen in those with an eGFR <30 mL/min/1.73 $m^2$. Moreover, the cefepime dose adjusted to the renal function was significantly higher in individuals with presumed cefepime neurotoxicity. These individuals 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

**Table 3**
Cefepime plasma trough levels, doses, presumed cefepime neurotoxicity and death according to renal function among all participants ($n = 319$)

| | eGFR > 90 mL/min/ 1.73$m^2$ | 60 < eGFR ≤ 90 mL/min/ 1.73$m^2$ | 30 < eGFR ≤ 60 mL/min/ 1.73$m^2$ | eGFR <30 mL/min/ 1.73$m^2$ |
|---|---|---|---|---|
| Overall number of participants | 106 | 69 | 87 | 57 |
| Cefepime plasma trough concentration, mg/L, median (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) |
| Adjusted cefepime dose, g/day per 100 mL/min/1.73 $m^2$ eGFR, median (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.

Please cite this article as: Boschung-Pasquier L et al., Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.06.028

[4] and hence to higher probability of cefepime-associated neurotoxicity [13–15,17]. Consequently, we emphasize the importance of closely monitoring renal parameters and cefepime trough concentrations in individuals with eGFR <60 mL/min/1.73 $m^2$.

No statistically significant difference was found in participants with or without neurotoxicity in the use of confounding centrally-active co-medication at cefepime trough concentrations ≥5 mg/L. It should however be taken into consideration that the 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 participants who presented signs of neurotoxicity compared with 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 individual'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. As the causes of death among most individuals with presumed neurotoxicity were non-neurological, 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 were 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 individuals with a delay of at least 2 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 individuals receiving cefepime, but mainly in those receiving high-dose cefepime treatment or with known renal insufficiency. Therefore, the proportion of participants presenting with neurotoxicity in this study probably overestimates the real incidence of neurotoxicity among individuals 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 are required for individuals 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 individuals and to target cefepime trough concentrations ≤7.5 mg/L. However, special attention should be paid to infections with pathogens that require a 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 4–8 mg/L.

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

## Transparency declaration

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

*Funding*

This work was supported by the Swiss National Foundation, Switzerland with grant no. 171259 to Baharak Babouee Flury.

## Acknowledgements

We thank Prof. Dr. phil. nat C. Largiadèr for the advice and help regarding the laboratory methodology.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.06.028.

## References

[1] Harris PN, Ferguson JK. Antibiotic therapy for inducible AmpC β-lactamase-producing Gram-negative bacilli: what are the alternatives to carbapenems, quinolones and aminoglycosides? Int J Antimicrob Agents 2012;40:297–305.
[2] Hilty M, Sendi P, Seiffert SN, Droz S, Perreten V, Hujer AM, et al. Characterisation and clinical features of *Enterobacter cloacae* bloodstream infections occurring at a tertiary care university hospital in Switzerland: is cefepime adequate therapy? Int J Antimicrob Agents 2013;41:236–49.
[3] Siedner MJ, Galar A, Guzman-Suarez BB, Kubiak DW, Baghdady N, Ferraro MJ, et al. Cefepime vs other antibacterial agents for the treatment of *Enterobacter* species bacteremia. Clin Infect Dis 2014;58:1554–63.
[4] Chapuis TM, Giannoni E, Majcherczyk PA, Chioléro R, Schaller MD, Berger MM, et al. Prospective monitoring of cefepime in intensive care unit adult patients. Crit Care 2010;14:R51.
[5] Lipman J, Wallis SC, Rickard C. Low plasma cefepime levels in critically ill septic patients: pharmacokinetic modeling indicates improved troughs with revised dosing. Antimicrob Agents Chemother 1999;43:2559–61.
[6] Wong KM, Chan WK, Chan YH, Li CS. Cefepime-related neurotoxicity in a haemodialysis patient. Nephrol Dial Transplant 1999;14:2265–6.
[7] Smith NL, Freebairn RC, Park MA, Wallis SC, Roberts JA, Lipman J. Therapeutic drug monitoring when using cefepime in continuous renal replacement therapy: seizures associated with cefepime. Crit Care Resusc 2012;14:312–5.
[8] Chatellier D, Jourdain M, Mangalaboyi J, Ader F, Chopin C, Derambure P, et al. Cefepime-induced neurotoxicity: an underestimated complication of antibiotherapy in patients with acute renal failure. Intensive Care Med 2002;28:214–7.
[9] Martínez-Rodríguez JE, Barriga FJ, Santamaria J, Iranzo A, Pareja JA, Revilla M, et al. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. Am J Med 2001;111:115–9.
[10] Sonck J, Laureys G, Verbeelen D. The neurotoxicity and safety of treatment with cefepime in patients with renal failure. Nephrol Dial Transplant 2008;23:966–70.
[11] Sugimoto M, Uchida I, Mashimo T, Yamazaki S, Hatano K, Ikeda F, et al. Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. Neuropharmacology 2003;45:304–14.
[12] Plüss-Suard C, Pannatier A, Kronenberg A, Mühlemann K, Zanetti G. Hospital antibiotic consumption in Switzerland: comparison of a multicultural country with Europe. J Hosp Infect 2011;79:166–71.
[13] Huwyler T, Lenggenhager L, Abbas M, Ing Lorenzini K, Hughes S, Huttner B, et al. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. Clin Microbiol Infect 2017;23:454–9.
[14] Lamoth F, Buclin T, Pascual A, Vora S, Bolay S, Decosterd LA, et al. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. Antimicrob Agents Chemother 2010;54:4360–7.
[15] Payne LE, Gagnon DJ, Riker RR, Seder DB, Glisic EK, Morris JG, et al. Cefepime-induced neurotoxicity: a systematic review. Crit Care 2017;21:276.
[16] National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 5.0. Bethesda, MD: National Cancer Institute; 2017.
[17] Appa AA, Jain R, Rakita RM, Hakimian S, Pottinger PS. Characterizing cefepime neurotoxicity: a systematic review. Open Forum Infect Dis 2017;4. ofx170.
[18] Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacother 2008;42:1843–50.
[19] Lin CJ, Chen SP, Wang SJ, Fuh JL. Cefepime-related encephalopathy in peritoneal dialysis patients. J Chin Med Assoc 2011;74:87–90.
[20] The Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. [Last accessed on 2018 Dec 12].

ARTICLE IN PRESS



Available from: https://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf.
[21] Arzneimittelkompendium der Schweiz. 2018. Basel, Switzerland: HCL Solutions SA; 2018.
[22] Theurillat R, Joneli J, Wanzenried U, Schiess J, Hurni M, Weber T, et al. Therapeutic drug monitoring of cefepime with micellar electrokinetic capillary chromatography: assay improvement, quality assurance, and impact on patient drug levels. J Sep Sci 2016;39:2626–32.
[23] Šesták ová N, Theurillat R, Sendi P, Thormann W. Monitoring of cefepime in human serum and plasma by micellar electrokinetic capillary chromatography: improvement of sample preparation and validation by liquid chromatography coupled to mass spectrometry. J Sep Sci 2017;40:1805–14.
[24] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[25] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
[26] The R Foundation. The R project for statistical computing. Available from: https://stat.ethz.ch/CRAN/.
[27] Lutsar I, Friedland IR. Pharmacokinetics and pharmacodynamics of cephalosporins in cerebrospinal fluid. Clin Pharmacokinet 2000;39:335–43.
[28] Durand-Maugard C, Lemaire-Hurtel AS, Gras-Champel V, Hary L, Maizel J, Prud'homme-Bernardy A, et al. Blood and CSF monitoring of cefepime-induced neurotoxicity: nine case reports. J Antimicrob Chemother 2012;67:1297–9.
[29] Barradell LB, Bryson HM. Cefepime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1994;47:471–505.
[30] Van der Auwera P, Santella PJ. Pharmacokinetics of cefepime: a review. J Antimicrob Chemother 1993;32:103–15.

Please cite this article as: Boschung-Pasquier L et al., Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.06.028