

Characterizing Cefepime Neurotoxicity: A Systematic Review

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Neurotoxicity due to cefepime has not been well characterized. We performed a systematic review of the literature and included 5 additional cases from our center. Of the 198 cases found, the mean age was 67 years and 87% of patients had renal dysfunction. The most common clinical features were diminished level of consciousness (80%), disorientation/agitation (47%), and myoclonus (40%). It is worth noting that nonconvulsive status epilepticus was relatively common with 31% of cases, whereas only 11% had convulsive seizures. Single-center estimate of incidence was 1 in 480 courses of cefepime. Cefepime neurotoxicity should be considered in older patients with renal dysfunction and new onset encephalopathy, especially if concurrent myoclonus is present. More work is needed to prospectively assess incidence and outcomes related to cefepime neurotoxicity.

Keywords. cefepime; cephalosporins; encephalopathy; seizures.

Cefepime is a fourth-generation cephalosporin antibiotic that was approved for clinical use in 1996 and remains a principal component of parenteral therapy for neutropenic fever and healthcare-associated infections including pneumonia, urinary tract infections, skin and soft tissue infections, and others [1]. Important attributes of this antibiotic include potent broad-spectrum coverage with anti-pseudomonal activity and reasonable stability against certain extended-spectrum β -lactamases. When initially approved, safety data was relatively favorable, and neurotoxicity comprised only 3 seizures reported among more than 2000 participants without clear evidence of causality [2]. However, in the subsequent years, use in critically ill patients was challenged given reports of increased mortality in patients treated with cefepime [3, 4]. Although the US Food and Drug Administration (FDA) did not ultimately conclude that cefepime is unsafe after repeat review of existing data [5], some authors did hypothesize that neurotoxicity, which has been heterogeneously characterized, may be implicated in more morbidity than previously understood [6, 7].

The pathophysiology of cefepime neurotoxicity is thought to be related to inhibition of GABA-A receptors or possibly inhibition of GABA release, which would be consistent with initial report of seizures as well as global encephalopathy or

myoclonus [8, 9]. Although these individual manifestations have been reported in the literature, relatively little is known about how to practically identify cefepime neurotoxicity or how to define the nature of the syndrome. In related studies, incidence has been variably reported between 1% and 15%, perhaps because many clinicians are not attuned to the characteristics of cefepime neurotoxicity [10, 11]. Because early identification and cessation of antibiotic therapy is the only definitive treatment (apart from prevention with stringent attention to renal dosing), recognition of the syndrome is tantamount to prevention of morbidity and mortality associated with cefepime. Our objective is to review the literature and provide clinicians with an evidence-based framework with which to recognize cefepime neurotoxicity. As part of ongoing quality improvement activities, we also reviewed all cases of suspected cefepime neurotoxicity at our center.

METHODS

This systematic review protocol was developed according to specifications outlined by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [12]. Before completing the literature search, inclusion and exclusion criteria as well as analysis methods were registered via PROSPERO (CRD42016045279).

Search Strategy

In conjunction with a biomedical librarian, we searched the Cochrane Library, MEDLINE/PubMed, EMBASE, and Scopus databases for manuscripts from inception through July 2016 using the following search terms: “cefepime” AND (neurotoxicity OR seizures OR “status epilepticus” OR “non-convulsive status epilepticus” OR encephalopathy OR “altered mental status” OR coma OR stupor OR obtundation). References of key manuscripts were additionally searched.

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Inclusion and Quality Criteria

Studies were included if found to describe cefepime specifically and report clinical data related to a neurologic adverse event(s). Manuscripts were excluded if the full manuscript was not published in English, if subjects were less than 18 years of age, or nonhumans (animal subjects). Because our aim was to describe clinical presentations of an adverse event, quality evaluation was focused on obtaining clinical data that could be aggregated rather than on study design of interventional trials. Therefore, we included case reports and case series. Risk of bias assessment was performed according to the Cochrane Collaboration's domain-based tool.

Demographic and clinical data were abstracted from included studies, and our primary outcome categories were created after pilot data abstraction. Diminished level of consciousness was defined as reduced alertness, including drowsiness, stupor, obtundation, or coma. Disorientation/agitation included confusion, delirium, and acute behavioral change. Myoclonus, nonconvulsive status epilepticus (NCSE), seizures, and aphasia all had to be named as such to be categorized as any of the 4. Renal dysfunction was defined as having either acute kidney injury or chronic kidney disease, as ascertained by at least 1 of the following data points: (1) estimated glomerular filtration rate less than 60 mL/minute, (2) serum creatinine greater than 2 mg/dL, or (3) described as having "end-stage renal disease" (ESRD). To tabulate the proportion of patients who received doses of cefepime above the maximum recommended dose for their renal function, we compared doses prescribed, renal function as described above, and the cefepime package insert dose adjustment recommendations [13]. Descriptive statistics were calculated across the sample using Excel (version 15.32).

For the review of cefepime neurotoxicity at our own center, we analyzed cases between January 2013 and June 2016 that were reported to our hospital-wide electronic patient safety network or to our antimicrobial stewardship team. For the internal cases identified, probability scaling was completed using the NARANJO Adverse Drug Reaction Probability Scale [14]. Our antimicrobial pharmacy database was queried for number of courses of cefepime (greater than 2 doses) during the same interval to calculate a lower limit of incidence.

RESULTS

We identified a total of 343 distinct studies and collected individual participant data from 71 studies Figure 1 and Appendix 1. Including the 5 cases of suspected cefepime neurotoxicity encountered at our institution, the number of subjects totaled 198. After probability scaling the internal cases as mentioned above, 80% (4 of 5 cases) were "probable," and 1 case was found to be "possible." Risk of bias assessment yielded frequent reporting bias; as previously mentioned, most studies included were case reports or series, which by nature selectively report a specific outcome. However, we did not find significant selection, performance, or detection bias.

Clinical and demographic data are described in Table 1. Average age of patients with suspected cefepime neurotoxicity was 67 (median age 70) with standard deviation (SD) of 13. Fifty-one percent of cases were women, suggesting that both men and women were relatively equally affected. Most, although not all, patients had renal dysfunction (87%), and approximately one third of subjects had end-stage renal disease (29%). Median reported creatinine was 3 mg/dL, and median cefepime dose per 24 hours was 4 grams (SD = 1.8). This reflected cefepime dosing above the maximum recommendation for renal function in 50% of cases. Mean onset of neurotoxicity symptoms was 5 days (SD = 4) after cefepime initiation. Electroencephalogram (EEG) was performed to aid diagnosis in 81% of cases. Although quantification of this variable was not performed, 2 dominant EEG patterns emerged: triphasic waves consistent with a toxic metabolic encephalopathy and "epileptiform discharges."

The most common clinical manifestations of suspected cefepime neurotoxicity (Figure 2) mimicked delirium or encephalopathy with 80% of cases demonstrating diminished level of consciousness and 47% with disorientation or agitation. However, myoclonus was also a prominent feature exhibited in 40% of cases. It is notable that approximately one third of cases (31%) were found to be nonconvulsive status epilepticus, whereas just 11% of cases involved seizure activity. Only 9% had aphasia.

Although cessation of cefepime was essential to recovery in all non-mortal cases, additional therapy included (1) antiepileptic drugs in 33% and (2) dialysis to reduce cefepime concentrations in 14%. Thirteen percent of subjects died during the same hospital stay in which they experienced neurotoxicity, although this cannot be attributed cefepime toxicity.

Table 1. Demographic and Clinical Characteristics of Cefepime Neurotoxicity

Characteristics	N = 198
Mean age (\pm SD)	67 (\pm 13)
Male sex, % (n)	49% (86 of 170)
Renal dysfunction, % (n) ^a	87% (149 of 171)
ESRD, % (n)	29% (37 of 129)
Median cefepime dose/24 hours, grams (\pm SD)	4 (\pm 1.8)
Dosing above recommended maximum based on renal function ^b	50% (55 of 110)
Mean onset after cefepime start, days (\pm SD)	5 (4)
EEG performed, % (n)	81% (141 of 174)
Treatment	
Antiepileptic drugs used, % (n)	33% (56 of 170)
Dialysis used ^c , % (n)	14% (24 of 171)

Abbreviations: EEG, electroencephalogram; ESRD, end-stage renal disease; SD, standard deviation.

^aIncludes both acute kidney injury and chronic kidney disease.

^bRenal function at time of diagnosis of toxicity if available.

^cExcluding patients who received regularly scheduled maintenance hemodialysis.

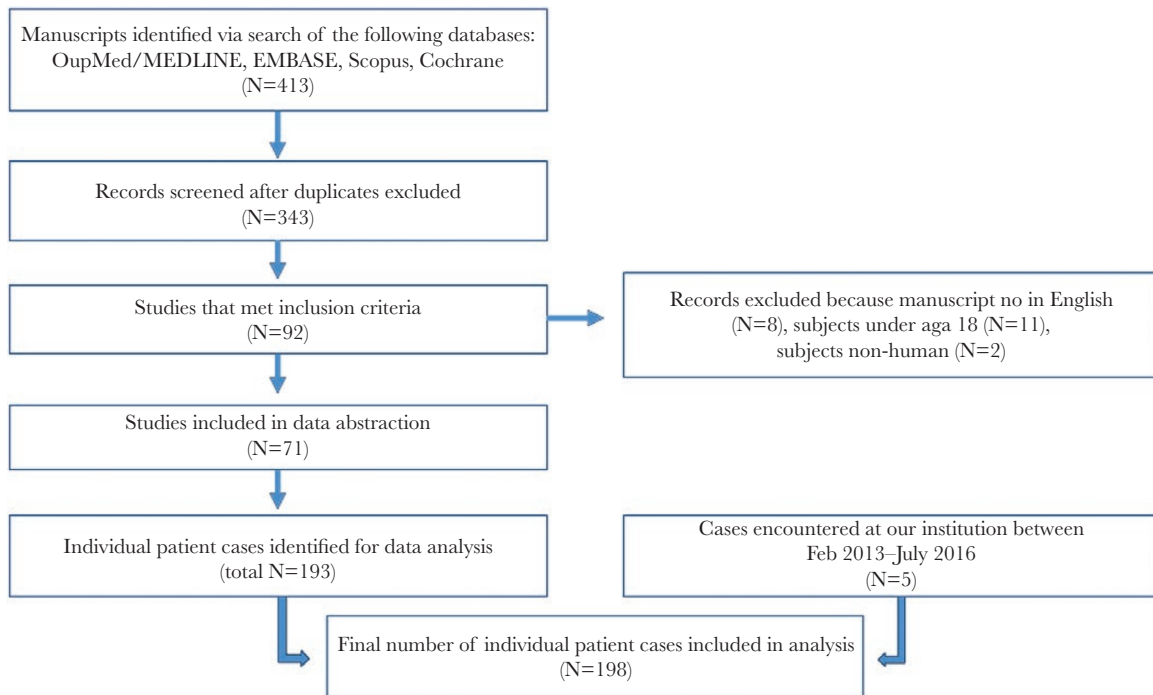


Figure 1. PRISMA flow diagram. This flowchart details our search strategy, inclusion and exclusion criteria, and final cohort size.

Finally, between January 2013 and June 2016 in which 5 cases were diagnosed in our center, there were 2403 courses of cefepime administered to inpatients. This suggests an incidence in our hands of at least 1 in 480 courses.

DISCUSSION

We found that the most commonly reported phenotype/clinical identifiers of cefepime neurotoxicity include older age and renal dysfunction, especially ESRD. Because cefepime is renally cleared

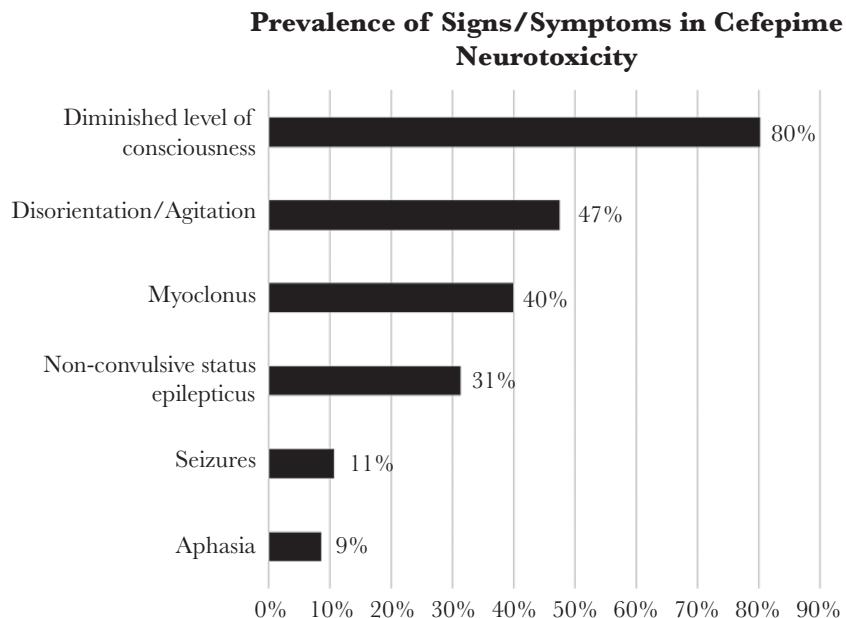


Figure 2. Characterization of cefepime neurotoxicity. Clinical manifestations of cefepime neurotoxicity were tabulated and reported as a percentage of the total cohort (n = 198), from most to least frequently observed.

and can cross the blood-brain barrier, a decrease in glomerular filtration, either acutely or chronically, may lead to inadvertently elevated serum and cerebrospinal fluid (CSF) levels of cefepime, although the maximum tolerable concentration in CSF has not been clearly defined, and the cause of this phenomenon is not known. Proposed mechanisms include its avidity for central nervous system GABA-A receptors, which is higher than that of many β -lactam antibiotics, combined with its high concentration in brain tissue rather than CSF [15–17]. We were surprised to find that only 50% of patients were receiving correctly dose-adjusted cefepime when neurotoxicity was diagnosed. Although consistent with existing data [18, 19], this is remarkable for 2 reasons. First, it is unfortunate that only half of patients received the correct dose based on their renal function. Perhaps this happened because renal function is dynamic, and dose adjustment may not have been made until toxicity was found. Alternatively, the initial dosage may have been calculated in error. Second, we note that the other half of cases developed suspected cefepime neurotoxicity in spite of apparently proper adjustment for renal function. These data did not always allow us to account for the time when renal function was collected in relation to dosing. Therefore, we suspect that providers either underestimated or overestimated the correct dosing. However, as both our data and other reports suggest, there is substantial pharmacokinetic variation within standard dose reduction protocols in which patients have normal renal function and still manifest neurotoxicity [11, 20, 21]. Further work needs to be done to elucidate other pharmacokinetic determinants of relative overdosage.

Regarding clinical presentation, most cases displayed delirium. This finding differs from initial safety data that suggested seizure to be the primary manifestation of neurotoxicity. However, in the last 10 years, several individual reports and qualitative reviews support our quantitative finding that encephalopathy is a hallmark of cefepime neurotoxicity [22–25]. Myoclonus, which we found to be present in almost half of patients, could be an indication for clinicians that there may be a discreet cause or contributor to delirium.

Approximately one third of cases involved NCSE. Although the FDA's Adverse Event Reporting System (AERS) database catalogued 59 cases of NCSE between 1996 and 2012, mainly in older patients with renal dysfunction consistent with our findings, the incidence has not been well reported [11, 26, 27]. It is unfortunate that this entity is generally poorly characterized, and there are insufficient data to understand (1) whether cefepime-related NCSE and nonpileptiform encephalopathy are 2 distinct pathophysiologic and/or clinical entities or (2) whether they represent part of a continuum. Nonconvulsive status epilepticus is generally defined as at least 30 minutes of continuous epileptiform activity accompanied by change in mentation but without major motor manifestations. However, both accurate definition and the implications of NCSE are not well understood, although some suggest that NCSE is a highly morbid condition [28]. This adds impetus

to not only understanding the risk factors for acquisition but also diagnosis and optimal treatment.

Regarding diagnosis, we report that the vast majority of cases used EEG in diagnostic evaluation, although there may be institutional variation in this practice (for instance, only 2 of 5 cases at our center used EEG). However, because EEG is essential to confirmation of NCSE, we assert that EEG is an important diagnostic tool that should be commonly used.

Regarding treatment, we reported that a third of cases were treated with antiepileptic drugs, which included phenytoin, levetiracetam, benzodiazepines, phenobarbital, and valproic acid. If the pathophysiology of toxicity is truly mediated by the GABA receptor, it is possible that benzodiazepines or phenobarbital would be the best pharmacologic choices [29]. However, because of this study design, we are unable to state whether any additional medications may improve outcomes. In addition, other focal neurologic deficits such as seizures and aphasia were reported with reasonable frequency, so although encephalopathy may be the dominant theme, it is clear that cefepime neurotoxicity can be a heterogeneous syndrome.

Finally, we report an incidence at our center of 1 in 480 courses of cefepime. This is a lower limit of incidence because there has not been active surveillance for cefepime-related neurotoxicity at our institution. As clinicians become more aware of this phenomenon, we expect the number of cases identified to increase. As mentioned in the introduction, incidence reporting has been widely variable and sparse, which highlights the need for further prospective study of this topic.

This systematic review allows only limited conclusions to be drawn related to incidence. Likewise, we cannot make any assertions or recommendations about the risk/benefit ratio of using cefepime for various clinical situations, because of our inability to measure incidence among the entire sample. Another limitation is the use of 1 author to abstract data, but the reciprocal benefit is that definitions and protocols specified in Methods and registered with PROSPERO were strictly and consistently adhered to. Finally, as discussed above, reporting bias is an important limitation to acknowledge.

Despite these limitations, this study is an important summary of the evidence to date describing the presentation of cefepime neurotoxicity. To our knowledge, this is the most comprehensive aggregation of clinical data describing these adverse effects that has also used individual patient-level data. The latter feature allowed us to report quantitative findings to create a clinical profile that is widely generalizable in inpatient medicine and directly applicable to patient care. Based on this work, our antimicrobial stewardship program has created a monitoring system to identify patients with a glomerular filtration rate less than 60 mL/min and who are receiving cefepime 2 grams every 8 hours, to alert the inpatient pharmacists and medical teams to evaluate for possible dosage change and monitor for potential neurotoxicity.

In summary, this description of suspected cefepime neurotoxicity should raise clinician awareness and prompt further investigation, especially because our lower limit of incidence suggests that toxicity is not uncommon. Further study is needed to understand nonrenal pharmacokinetic risk factors for acquisition of cefepime neurotoxicity, incidence, and long-term outcomes of cefepime neurotoxicity overall, and especially NCSE.

CONCLUSIONS

Cefepime neurotoxicity should be considered in older patients with renal dysfunction and new onset altered mental status, especially in those with myoclonus. Nonconvulsive status epilepticus may represent up to one third of cases, so prompt EEG may be valuable to differentiate between NCSE and encephalopathy due to other causes. Incidence may approximate at least 1 in 480 courses, but prospective study is necessary to understand the true incidence and outcomes of cefepime neurotoxicity, especially NCSE.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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