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Cefepime-Induced Neurotoxicity Presenting with Nonconvulsive Status Epilepticus Admitted as a Stroke Alert

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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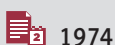
Patient: Female, 72-year-old
Final Diagnosis: Cefepime-induced neurotoxicity
Symptoms: Aphasia
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Unusual or unexpected effect of treatment

Background: Cefepime-induced neurotoxicity has been described in intensive care units (ICUs) and neuro ICU settings, occurring in patients started on ceftazidime for management of severe infections and sepsis. Most cases occur within 1 to 10 days after starting the drug. We publish a case that occurred on the general medical ward of a patient who had been on cefepime therapy for 4 weeks prior to admission. The aim of this study was to improve the knowledge of this serious condition to general internists as our patient was being managed on the general medical ward.

Case Report: A 72-year-old female on prolonged intravenous antibiotics for sacral and pelvic osteomyelitis presented with acute encephalopathy and aphasia in the setting of an acute kidney injury. Due to the acute focal neurologic deficit, she was initially admitted as a stroke alert. After a negative magnetic resonance imaging (MRI) of the brain, an electroencephalogram (EEG) was pursued and showed nonconvulsive status epilepticus (NCSE). NCSE was likely a result of cefepime therapy in the setting of an acute kidney injury.

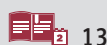
Conclusions: Cefepime-induced neurotoxicity should be suspected in any patient on cefepime therapy who develops acute changes in mental status, myoclonus, or evidence of seizures. Risk factors for the disease include older age, renal dysfunction, critical illness, and inappropriate dosing based upon renal function. A high index of suspicion is required and delays in diagnosis are common as there are frequently multiple possible causes for altered mental status in systemically ill patients requiring treatment with broad-spectrum antibiotics.

MeSH Keywords: Aphasia • Cephalosporins • Epilepsy, Generalized • Neurotoxicity SyndromesFull-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/921643>

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Background

Initial use of broad-spectrum antibiotics has well documented uses in the Emergency Department and critical care setting in patients with severe sepsis and septic shock [1]. However, continuation of broad-spectrum antibiotics without appropriate antimicrobial stewardship can have severe consequences including antimicrobial resistance, nosocomial infections, increased costs, and severe side effects [2]. Neurologic complications of antibiotics are overall rare but well documented [3]. Challenges can include separating neurologic sequelae of the antibiotic from delirium due to worsening of the infection, metabolic abnormalities that develop due to the underlying illness, or other medications started during hospitalization. While using a prolonged course of antibiotics, it is important to both closely monitor renal and liver function which may affect drug pharmacokinetics and dosing. In addition, clinicians should be aware of the rare and dangerous complications of the drugs being prescribed.

We present a case of cefepime-induced neurotoxicity that was unique in our review of the literature. Most cases of cefepime-induced neurotoxicity begin within 1 to 10 days of starting the drug [4]. Our case started after 4 weeks of receiving intravenous cefepime for pelvic osteomyelitis. As a result, the initial sepsis and critical illness from the infection had already resolved. This patient presented with an acute encephalopathy and aphasia leading to an initial stroke evaluation in the emergency department. The negative stroke evaluation led to admission to the general medicine service for management of delirium and a possible urinary tract infection (UTI) based upon a positive urinalysis (UA). This resulted in delayed recognition of this serious condition. We aim to both describe characteristics of cefepime-induced neurotoxicity and to also describe clinical characteristics of nonconvulsive status epilepticus (NCSE) that the internist should be aware as a potential clue to cefepime toxicity.

Case Report

A 72-year-old female with a history of a stage IV sacral wound and pelvic osteomyelitis, insulin dependent diabetes, and a chronic indwelling Foley catheter presented to the emergency department with confusion and aphasia. She was sent from a nursing home with the report that she was no longer communicating verbally and was having difficulty following commands compared to an earlier assessment. It had been more than 4 hours since she had been observed at her baseline. The patient was staying in a nursing facility to receive intravenous antibiotics and rehabilitation for her osteomyelitis. Previously, she had been living independently in the community, completing her activities of daily living (ADLs) independently and had

no prior history of dementia. Her blood glucose was 61 mg/dL prior to arrival and her mental status did not improve with dextrose. Her other past medical and surgical history included diabetes, hypertension, Roux-en-Y gastric bypass, and a prior history of coronary artery disease. Her medications included cefepime 2 grams intravenous every 8 hours and daptomycin 400 mg intravenous every 24 hours for ongoing treatment of pelvic osteomyelitis, insulin via an insulin pump, aspirin, prasugrel, pantoprazole, lisinopril, and metoprolol succinate.

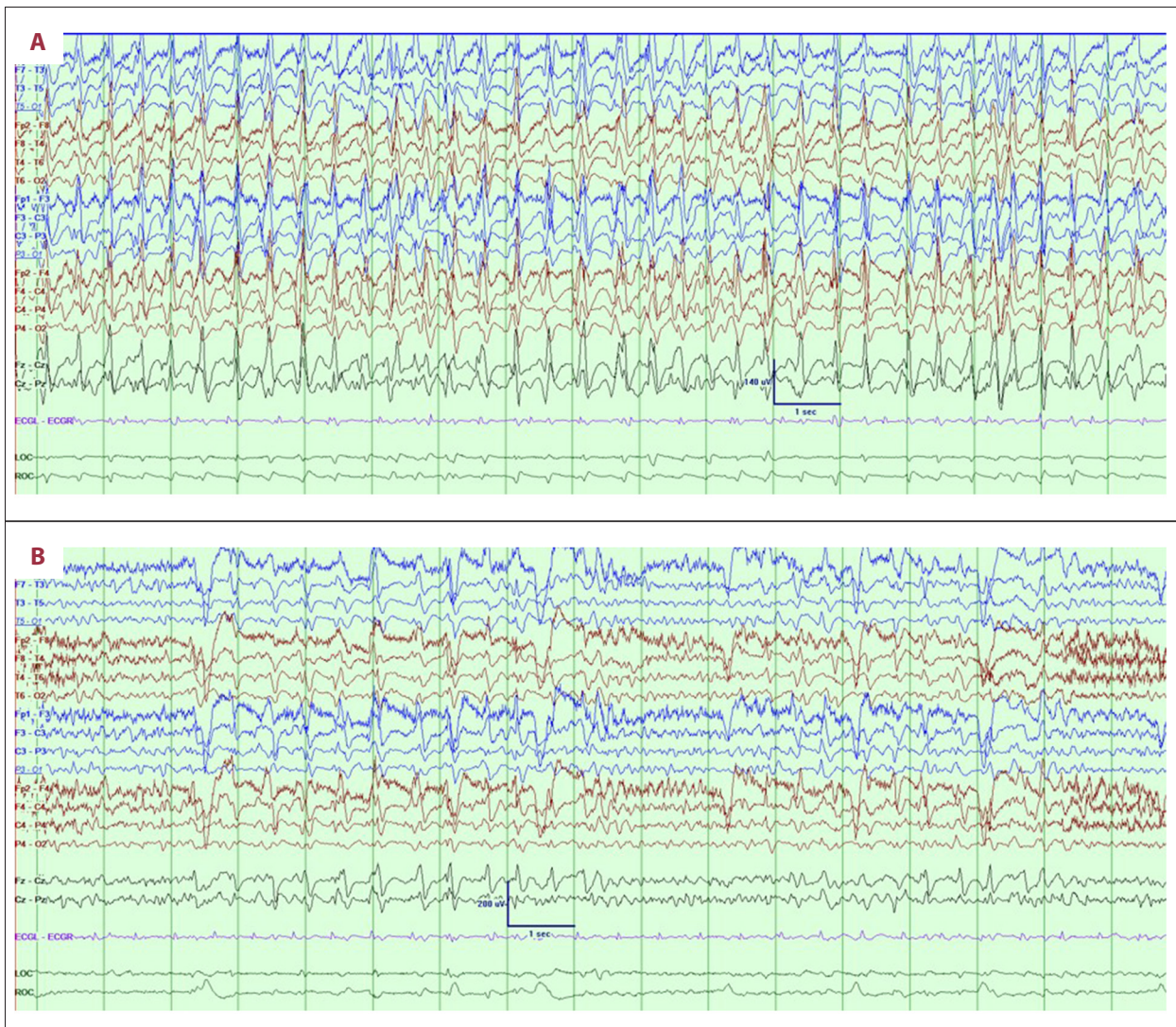
On emergency department arrival, the patient was afebrile, pulse was 72 beats per minute, respiratory rate was 18 breaths per minute, blood pressure was 175/67 mmHg and oxygen saturation was 97% breathing on 2 L/minute by nasal cannula. Body weight was 77.2 kg. She was awake and moving all extremities spontaneously but was non-verbal. She would open and move her eyes spontaneously and to voice but could not consistently follow commands. Glasgow Coma Scale was 10 on admission (eye 4, verbal 2, motor 4). Neurologic examination was limited by cooperation which made it difficult to assess for motor strength, presence of pronator drift, and asterixis. The examination was positive for receptive and expressive aphasia. The patient was able to withdraw to painful stimuli in all extremities, reflexes were symmetric throughout, there was no clonus or Babinski's sign, pupils were equally reactive and there was no facial droop. No convulsions or myoclonic jerks were noted. The cardiovascular and pulmonary examinations were normal. Abdominal examination revealed multiple well healed surgical scars but was otherwise benign.

Laboratory tests on arrival were notable for an elevated serum creatinine of 1.2 mg/dL with a blood urea nitrogen (BUN) of 53 mg/dL when compared to baseline of 0.8 mg/dL. Using a modified Cockcroft-Gault equation to account for weight, the creatinine clearance was 45 mL/minute, however the true glomerular filtration rate (GFR) was likely lower given the presence of an acute kidney injury. Sodium, glucose, and other electrolytes were within normal limits. Complete blood count showed a normal white count 7.2 k/uL, chronic anemia with a hemoglobin of 11.2 g/dL and elevated platelets 541 k/uL. Urinalysis showed 3+ leukocytes. Aspartate aminotransferase (AST) was 75 U/L and alanine aminotransferase (ALT) was 90 U/L but the remainder of the liver function tests were normal. Thyroid function testing was normal, and a urine drug screen was negative. Given the presence of acute aphasia, we were concerned for a left hemispheric transient ischemic attack (TIA) or stroke. Computed tomography (CT) of the brain with angiography was normal and follow-up magnetic resonance imaging (MRI) did not show any evidence of acute stroke or abnormalities in the left frontal or temporal lobes. Lumbar puncture to evaluate for infectious encephalitis was not performed on admission due to patient's inability to follow commands and need for procedural sedation to be coordinated with anesthesia.

At this time, the presumed diagnosis was acute delirium; however, the precipitating factor was unclear. Despite the abnormal urinalysis, acute infection became less likely given that the patient was afebrile with a normal white blood cell count and was already receiving broad spectrum antibiotics. Common metabolic abnormalities such as hypoglycemia and hyponatremia were ruled out. The patient was not on any sedating medications and there was no history of toxic ingestions or trauma. Cultures of the blood and urine were obtained, the patient was placed on delirium precautions and broad-spectrum antibiotics. After 24 hours of observation, the patient had made no improvement in her condition. She had been unable to take any oral food or fluids and her serum creatinine had increased to 1.9 mg/dL despite intravenous fluids and supportive care.

After the standard workup for common metabolic and infectious etiologies of encephalopathy had been unrevealing, alternate etiologies for her condition were considered. The presentation

of persistent aphasia and delirium in a patient being treated with cefepime in the setting of an acute kidney injury prompted consideration of cefepime-induced neurotoxicity. Cefepime was discontinued and additional testing with an EEG to evaluate for nonconvulsive status epilepticus (NCSE) was performed. EEG (Figure 1) revealed a bi-frontal predominant, 1.5 to 2.5 Hz rhythmic spike and wave pattern that occurred in the absence of observable tonic, clonic, or automotor behaviors. The patient received 2 doses of 2 mg intravenous lorazepam and a 1000 mg loading dose of intravenous levetiracetam. On continuous EEG monitoring, evidence of NCSE resolved within minutes of initial lorazepam administration subsequently showing intermittent normalization of the EEG. The initial EEG finding combined with both the EEG and clinical improvement after anticonvulsant administration met the Salzburg criteria for “definite NCSE” [5]. After resolution of NCSE, the patient had a GCS score of 15. She regained verbal function, was speaking in complete sentences and following commands. Her only



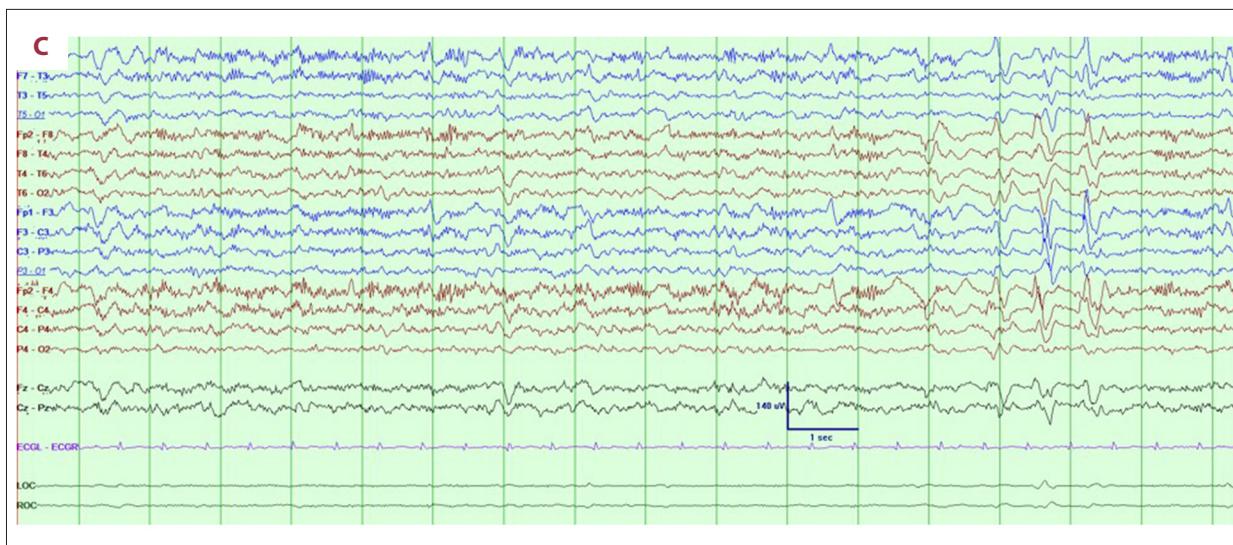


Figure 1. Electroencephalogram (EEG). Continuous EEG monitoring was performed using video monitoring. The following (A–C) are 17 second frames. Electrodes were placed using the International 10–20 system of electrode placement. Low frequency filter 1 Hz, high frequency filter 70 Hz, sensitivity 7 μ V. (A) Shows nonconvulsive status epilepticus (NCSE) characterized by 1.5–2.5 Hz rhythmic spike-wave pattern that was bifrontal predominant. (B) Continuous electroencephalogram (EEG) monitoring minutes after lorazepam showing interruption of the previous rhythmic spike-wave pattern. (C) Continuous electroencephalogram (EEG) monitoring after the second dose of lorazepam showing resolution of the epileptic discharges with now diffuse intermixed slowing.

deficit at this point was mild confusion and she was amnesic for how she presented to the hospital. Repeat EEG done the following morning showed bi-hemispheric slowing but with no further evidence of seizure. Following discontinuation of cefepime, there was no recurrence of NCSE or clinical seizures.

Discussion

Cefepime-induced neurotoxicity was first described in 1999 [6]. The most common clinical presentation is delirium (80%) but there is a spectrum of neurologic presentations with 40% presenting with myoclonus, 31% in NCSE, 11% with seizures, and 9% with aphasia [7]. Symptoms typically begin 1 to 10 days after starting cefepime [4]. The most common risk factors for development of this disorder include renal dysfunction (87%), older age, critical illness, and dosing not adjusted for renal function (50%) [6,7]. The pathophysiology is not well defined but is thought to be due to concentration dependent competitive gamma aminobutyric acid (GABA) antagonism induced by cefepime accumulation in the central nervous system (CNS) [6]. Diagnosis of cefepime-induced neurotoxicity requires either the temporal association of compatible neurologic symptoms after cefepime administration or if patients have clinical or EEG improvements after discontinuation of cefepime without another identified cause [8]. Prior reviews show that delays in diagnosis are common [9]. In our case, this was likely due

to anchoring on more commonly seen diagnoses on the general medicine service.

Nonconvulsive status epilepticus is defined as a continuous state of seizures without convulsions, or multiple nonconvulsive seizures for more than 30 minutes without interictal full recovery. NCSE can present with multiple symptoms, none of which are specific to the disorder including: altered mental status (82%), lethargy or coma (22%), speech disturbances (15%), myoclonus (13%), and hallucinations (6%) [10]. However, the rapid onset of any of these without another explanation should lead to additional testing, including an EEG. In one study of patients admitted to an acute geriatric ward, 8 patients who were initially diagnosed as having a UTI causing altered mental status and who had not returned to their prior neurologic status were found to have NCSE on EEG [11]. In critically ill patients, the etiology of nonconvulsive seizures can be broad and include traumatic brain injury, CNS infection, anoxic brain injury, subarachnoid hemorrhage, toxic-metabolic disturbances, and sepsis [10,12]. History and physical, laboratory evaluation, and imaging did not reveal any of these alternate causes of NCSE in our patient. Cefepime concentrations that result in toxicity are not well defined, but the available literature suggests avoiding trough levels greater than 20 mg/L or steady state levels greater than 35 mg/L [13]. However, there is not a set level at which toxicity is diagnosed and levels are not required to make the diagnosis and therefore were not checked in this case.

The most critical component in management is early recognition that cefepime could be contributing to progressive confusion and delirium and to promptly discontinue the drug. Cessation of the drug alone results in clinical improvement in the majority of patients after a median of 2 days [6–8]. Those presenting with NCSE are likely to need additional anticonvulsant treatment. As for generalized convulsive status epilepticus, intravenous lorazepam is the first-line treatment. Second-line agents include phenytoin, valproic acid, and levetiracetam but these are less well studied in NCSE compared to other forms of seizure and epilepsy [10]. In some instances, dialysis may be needed to reduce cefepime concentrations [7]. In one review of cefepime-induced neurotoxicity, earlier recognition and diagnosis resulted in improved prognosis and neurologic recovery [8].

Conclusions

We presented a case of a 72-year-old female with a history of pelvic osteomyelitis treated with cefepime who presented with a developing acute kidney injury and acute encephalopathy with aphasia and was ultimately found to be in NCSE attributed to cefepime. Her acute kidney injury occurring during the 4th week of therapy was likely the precipitating factor

that led to decreased renal clearance and incorrect cefepime dosing. Most literature on this topic is in critical care, infectious disease, and neurology journals. Due to the fact that this patient had chronic osteomyelitis and had a negative stroke evaluation in the Emergency Department, she was primarily being managed by the general medicine service. In many respects, this is a classic case with a rare presentation lurking amidst much more commonly seen diagnosis on general medical wards. Knowing the various and sometimes subtle manifestations of NCSE (i.e., altered mental status) combined with the common usage of cefepime, make having an understanding of this drug's neurologic complications critical for the general internist. Patients on cefepime who experience progressive delirium, myoclonus, or speech disturbances without an alternative cause should promptly be considered for discontinuation of the drug and further evaluation with EEG.

Department and Institution where work was done

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Conflict of interests

None.

References:

1. Levy MM, Evans LE, Rhodes A: The surviving sepsis campaign bundle: 2018 update. *Crit Care Med*, 2018; 46(6): 997–1000
2. Karanika S, Paudel S, Grigoras C et al: Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. *Antimicrob Agents Chemother*, 2016; 60(8): 4840–52
3. Mattappalil A, Mergenhagen KA: Neurotoxicity with antimicrobials in the elderly: A review. *Clin Ther*, 2014; 36(11): 1489–511
4. Dakdouki GK, Al-Awar GN: Cefepime-induced encephalopathy. *Int J Infect Dis*, 2004; 8(1): 59–61
5. Krogstad MH, Høgenhaven H, Beier CP, Krøigård T: Nonconvulsive status epilepticus: Validating the Salzburg criteria against an expert EEG examiner. *J Clin Neurophysiol*, 2019; 36(2): 141–45
6. Payne LE, Gagnon DJ, Riker RR et al: Cefepime-induced neurotoxicity: A systemic review. *Crit Care*, 2017; 21(1): 276
7. Appa AA, Jain R, Rakita RM, Hakimian S, Pottinger PS: Characterizing cefepime neurotoxicity: A systematic review. *Open Forum Infect Dis*, 2017; 4(4): ofx170
8. Li HT, Lee CH, Wu T et al: Clinical, electroencephalographic features and prognosis factors of cefepime-induced neurotoxicity: A retrospective study. *Neurocrit Care*, 2019; 31(2): 329–37
9. Thabet F, Al Maghrabi M, Al Barraq A, Tabarki B: Cefepime-induced non-convulsive status epilepticus: Case report and review. *Neurocrit Care*, 2009; 10(3): 347–51
10. Sutter R, Semmlack S, Kaplan PW: Nonconvulsive status epilepticus in adults – insights into the invisible. *Nat Rev Neurol*, 2016; 12(5): 281–93
11. Shavit L, Grenader T, Galperin I: Nonconvulsive status epilepticus in elderly – a possible diagnostic pitfall. *Eur J Intern Med*, 2012; 23(8): 701–4
12. Oddo M, Carrera E, Claassen J et al: Continuous electroencephalography in the Medical Intensive. *Crit Care Med*, 2009; 37(6): 2051–56
13. Huwlyer T, Lenggenhager L, Abbas M et al: Cefepime plasma concentrations and clinical toxicity: A retrospective cohort study. *Clin Microbiol Infect*, 2017; 23(7): 454–59