Prolonged Cefepime-Induced Neurotoxicity in a Patient with End-Stage Renal Disease

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Financial support: None declared
Conflict of interest: None declared

Patient: Female, 86-year-old
Final Diagnosis: Drug reaction
Symptoms: Encephalopathy • seizure
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Unusual clinical course
Background: Cefepime, a fourth-generation cephalosporin, has a known adverse effect of neurotoxicity. It occurs notably in patients with end-stage renal disease, but symptom resolution typically occurs within a median of 2 days following drug discontinuation.

Case Report: We present a patient with end-stage renal disease on hemodialysis (TWThSat) who developed prolonged neurotoxicity lasting longer than 1 week complicated by nonconvulsive status epilepticus 2 days after cefepime discontinuation. She presented initially with a right upper-extremity arteriovenous graft infection from extended-spectrum beta-lactamase Escherichia coli, and was treated with cefepime. She eventually developed acute encephalopathy, and cefepime was discontinued. However, 2 days later, she developed seizures with worsened mental status. She was stabilized on levetiracetam and lorazepam, but developed hypotension in the Neurological Intensive Care Unit (Neuro-ICU), delaying hemodialysis. Hemodialysis was performed 6 days after cefepime discontinuation once she was stabilized, and her mental status improved 1 to 2 days after, with full improvement 20 days after admission. She was discharged on levetiracetam and meropenem. In addition, we review risk factors and symptomology of cefepime-induced neurotoxicity and discuss important management issues.

Conclusions: Careful attention should be paid when administering cefepime to patients with end-stage renal disease. Patients showing signs of encephalopathy should not be on cefepime any longer, and more aggressive measures may be taken, such as prompt hemodialysis, assessment of cefepime blood levels, and electroencephalogram (EEG) to monitor for signs of seizures. Prolonging hemodialysis in patients with signs of cefepime neurotoxicity can pose a danger for more serious sequelae, such as status epilepticus. Close monitoring of patients at high risk of developing adverse events from cefepime administration can ensure patient safety and well-being.

Keywords: Brain Diseases • Cefepime • Renal Insufficiency, Chronic • Seizures

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/934083
Background

Cefepime is a commonly used fourth-generation cephalosporin. Its most notable adverse effect, neurotoxicity, occurs mostly in patients with impaired renal function [1]. Symptom resolution typically occurs within a median of 2 days after drug discontinuation [2]. We discuss a case occurring outside this time window, an 86-year-old woman with end-stage renal disease on hemodialysis, presenting with right upper-extremity arteriovenous graft infection, who later had complications of encephalopathy and nonconvulsive status epilepticus following 2 days of cefepime discontinuation.

Case Report

An 86-year-old woman with a history of end-stage renal disease (ESRD) on hemodialysis sessions 4 times a week was admitted to the hospital for a right upper-extremity arteriovenous (AV) graft infection. Cultures from the wound grew extended-spectrum beta-lactamase (ESBL) Escherichia coli (E. coli). Sensitivities of ESBL E. coli are documented in Table 1. Given the sensitivities, she was started on cefepime 2 g i.v. every 48 h renally dosed for 1 day, then switched to meropenem 500 mg every 24 h for 3 days. The patient was noted to have confusion reported 2 days after cefepime initiation, but there were no other reported incidents thereafter. For her AV graft infection, she underwent resection and ligation of the AV graft, washout, debridement, and wound closure, and opted for placement of a tunneled dialysis catheter for hemodialysis access. Ultimately, she was placed back on cefepime 1 g i.v. every 24 h renally dosed while an inpatient, which she was scheduled to take for 6 weeks after washout. She was discharged to a skilled nursing facility on cefepime 2 g i.v. renally dosed after hemodialysis sessions 3 times a week, and her home medications acetaminophen 650 mg every 4 h as needed, carvedilol 3.125 mg twice a day, senna glycoside 17.2 mg twice a day, ipratropium bromide and albuterol sulfate every 6 h as needed.

She was readmitted for acute encephalopathy 21 days after cefepime reintiation. Her family reported her mental status had been altered since the beginning of her first hospitalization, the day after she began cefepime. Laboratory values at the time of this admission are summarized in Table 2. Due to the temporal relationship of her symptoms with cefepime administration, and the unclear picture of whether her cefepime was given correctly after her hemodialysis sessions, her condition was attributed to cefepime toxicity (Naranjo algorithm – ADR probability score of 9, definite) and the antimicrobial was discontinued. She was switched to piperacillin/tazobactam for her ESBL E. coli. Encephalopathy work-up, including basic laboratory tests, broad infectious work-up, endocrinopathies, toxin-mediated encephalopathy, and CT head were unremarkable. Two days after cefepime discontinuation, near the end of dialysis, she had bilateral upper-extremity tonic-clonic seizures with upgaze lasting 30 s to 1 min, followed by worsening mental status (A&amp;Ox0) and subsequent bleeding from her mouth. She was nonresponsive to pain and verbal stimuli, which was highly concerning for nonconvulsive status epilepticus. Lorazepam and levetiracetam loads were administered, after which she began responding to pain but was still verbally nonresponsive.

Electroencephalogram (EEG) showed high-voltage, generalized, anterior predominant 2.5-3 Hz sharp wave discharges. After lorazepam and levetiracetam administration, there were no spontaneous evolving electrographic seizures.

Laboratory findings on the day after are summarized in Table 2. She continued maintenance levetiracetam 500 mg twice a day with 500 mg after hemodialysis. That same day, she was admitted to the Neurological Intensive Care Unit (Neuro-ICU) for close neurological monitoring. In the Neuro-ICU, the etiology of her seizures was considered to be cefepime neurotoxicity vs meningitis or encephalitis, and she was administered acyclovir 350 mg every 24 h and vancomycin 1 g i.v. once for

| Antibiotic                  | VITEK MIC (mcg/mL) | Susceptibility |
|-----------------------------|--------------------|----------------|
| Amikacin                    | 4                  | Susceptible    |
| Ampicillin                  | ≥32                | Resistant      |
| Ampicillin/Sulbactam        | ≥32                | Resistant      |
| Cefazolin                   | ≥8                 | Resistant      |
| Cefepime                    | 2                  | Susceptible    |
| Ceftriaxone                 | ≥64                | Resistant      |
| Cefuroxime                  | ≥64                | Resistant      |
| Ciprofloxacin               | ≥4                 | Resistant      |
| Gentamicin                  | ≥16                | Resistant      |
| Levofloxacin                | ≥8                 | Resistant      |
| Piperacillin/Tazobactam     | 16                 | Susceptible    |
| Tobramycin                  | ≥16                | Resistant      |
| Trimethoprim/Sulfamethoxazole | ≤20               | Susceptible    |

MIC = minimum inhibitory concentration.
| Time           | Clinical event                      | Associated laboratory values                  | Pharmacologic intervention | Notes                                                                 |
|---------------|-------------------------------------|-----------------------------------------------|----------------------------|----------------------------------------------------------------------|
| Admission #1  | RUE AV graft infection              | WBC 13.3×10^9 cells/L Na 135 mEq/L K 6.1 mEq/L CO2 22 mg/dL Cr 8.6 mg/dL BUN 56 mg/dL Glu 117 mg/dL Ca 8.2 mEq/L | Cefepime                  | Noted to have some confusion after                                   |
| Day #1 after admission | WBC 7.6×10^9 cells/L Na 139 mEq/L K 3.7 mEq/L CO2 29 mg/dL Cr 5.1 mg/dL BUN 30 mg/dL Glu 131 mg/dL Ca 8.1 mEq/L | Cefepime switched to Meropenem | Status post resection and ligation of RUE AV graft, washout, and partial closure, hemodialysis. Patient responded to Meropenem for prior infections, change made |
| Day #15 after admission | Discharge                          | WBC 8.7×10^9 cells/L Na 139 mEq/L K 4.2 mEq/L CO2 29 mg/dL Cr 3.6 mg/dL BUN 36 mg/dL Glu 88 mg/dL Ca 8.8 mEq/L | Cefepime                  | Per Infectious Diseases consult, patient back on Cefepime. Discharged on Cefepime |
| Admission #2  | Encephalopathy                      | WBC 8.2×10^9 cells/L Na 141 mEq/L K 4.7 mEq/L CO2 26 mg/dL Cr 5.7 mg/dL BUN 20 mg/dL Glu 95 mg/dL Ca 9.4 mEq/L | Cefepime switched to Piperacillin/Tazobactam | Patient’s condition attributed to Cefepime neurotoxicity             |
| Day #2 after admission | Seizures                           | WBC 6.6×10^9 cells/L Na 142 mEq/L K 4.4 mEq/L CO2 26 mg/dL Cr 8.3 mg/dL BUN 43 mg/dL Glu 93 mg/dL Ca 8.2 mEq/L | Levetiracetam, Lorazepam. Piperacillin/Tazobactam switched to Meropenem | Meropenem was to cover for empiric meningitis and patient’s continued antibiotic course for her prior infection |
| Day #2 after admission | Entered Neuro ICU, where patient was hypotensive, suspicion for meningoecephalitis |                                    | Acyclovir, Vancomycin | Later discontinued with lower suspicion for meningoecephalitis    |
| Day #6 after admission | Hemodialysis                       |                                    |                            |                                                                      |
empiric meningitis treatment. Piperacillin/tazobactam was also switched to meropenem, and meropenem was dosed for meningitis treatment. Three days after her seizures and 6 days after admission, she underwent hemodialysis, which had been delayed due to hypotension in the Neuro-ICU. That same day, she had atrial flutter with RVR, for which she received metoprolol tartrate. Her mental status improved 1 day later (7 days after admission), and she was alert and oriented to person, place, and time, with some waxing and waning. She improved even further on the next day, and was alert and oriented to person, place, and time with some waning and waning. She underwent MRI following her atrial flutter, and she was diagnosed with an asymptomatic subacute cerebrovascular accident (CVA) due to small-vessel disease. However, due to the small size of the CVA, it was unlikely to be the cause of her acute encephalopathy. A lumbar puncture was attempted but was not successful. As there was a lack of inflammation on MRI, fever, and leukocytosis, meningitis was also an unlikely cause, so acyclovir and vancomycin were discontinued 7 days after initiation.

The patient became conversant and remained seizure-free and alert and oriented to person, place, and time. Given her improved mental status, she was discharged 20 days after admission with home health on levetiracetam 500 mg twice a day and 500 mg after hemodialysis, meropenem 500 mg every 24 h until 5 days after discharge, aspirin 81 mg every day, metoprolol tartrate 12.5 mg twice a day, midodrine 10 mg twice a day, pravastatin 20 mg every night at bedtime, and sevelamer carbonate 800 mg 3 times a day. She remained seizure-free and her encephalopathy was improved (alert and oriented to person, place, and time) after discharge. These events are summarized in Table 2.

### Table 2. Summary and timeline of major clinical events, with associated laboratory values and pharmacologic interventions.

| Time                  | Clinical event                     | Associated laboratory values     | Pharmacologic intervention | Notes                                              |
|-----------------------|------------------------------------|----------------------------------|---------------------------|----------------------------------------------------|
| Day #7-8 after admission | Improvement in mental status       | WBC 4.4×10⁹ cells/L Na 139 mEq/L K 4.0 mEq/L CO2 24 mEq/L Cr 5.0 mg/dL BUN 20 mg/dL Glu 84 mg/dL Ca 8.4 mEq/L |                           |                                                    |
| Day #7 after admission | CVA on MRI                         |                                 | Aspirin                   | Thought less likely cause of encephalopathy       |
| Day #20 after admission | Discharge                          | WBC 6.3×10⁹ cells/L Na 136 mEq/L K 4.0 mEq/L CO2 26 mEq/L Cr 3.9 mg/dL BUN 17 mg/dL Glu 88 mg/dL Ca 8.1 mEq/L |                           | Patient completed course of Meropenem outpatient, remained seizure-free and showed no signs of encephalopathy |

### Discussion

Cefepime is a broad-spectrum cephalosporin commonly used in hospital and community settings. It has many associated adverse effects: encephalitic signs (associated with 94% of patients with neurological signs after cefepime), confusion (50%), seizures (15%), aphasia (10%), and hallucinations (2%) [2]. Myoclonus was associated with 45.5% of cases. Its most notable adverse effect, neurotoxicity, is believed to be linked to antagonism of concentration-dependent GABA receptors [3].

Risk factors include renal failure (associated with 89% of cases) and underlying brain disease (18%), which includes CVA, Korsakoff’s syndrome, small-vessel disease, Alzheimer disease, benign brain tumor, malignancy, and previous seizures. Renal failure was the most widely studied, as the half-life of cefepime increases as renal function declines [4]. Impaired renal function can increase available unbound cefepime, which can reach the CNS via increased CSF cefepime concentrations and decreased CSF to blood elimination [1]. Studies show cefepime-induced encephalopathy can occur in ESRD patients regardless of dosing, with these as low as 0.5 g/day of cefepime [5].
In regards to symptomatology, these occur within a median of 4 days, with increased dosages linked to increased occurrence of neurologic symptoms [2]. Discontinuation leads to resolution within 2-7 days (median 2 days), and decreasing the dosage also often leads to symptom resolution. Cefepime reinitiation leads to quicker recurrence. Our patient began to improve 7 days after cefepime discontinuation, but still had waxing and waning of symptoms. She improved even further by days 8 and 9, with improvement in her waxing and waning, and was fully improved at discharge, 20 days after discontinuation.

Hemodialysis contributes to faster symptom resolution by facilitating a rapid decrease in serum cefepime concentration. For this reason, current data supports early hemodialysis, as it can decrease cerebral exposure to cefepime levels [6]. Unfortunately, her episode of status epilepticus and hypertension had delayed her hemodialysis. If conditions had been safe for the patient to undergo hemodialysis, she likely would have avoided the complications of her cefepime neurotoxicity.

Switching antibiotics to piperacillin or carbapenems often resolves symptoms, but in a few cases, the switches to meropenem and piperacillin were suspected to have extended the recovery phase [2]. Our patient was switched to piperacillin and later meropenem, and although her prolonged recovery was more likely due to her prolonged interval between hemodialysis sessions, this possibility cannot be denied.

Common electroencephalogram findings include diffuse and symmetrical slow activity, diffuse delta rhythm, and paroxysmal abnormalities, like sharp waves, spike waves, slow-wave complexes, triphasic waves predominating in anterior regions, at a frequency of 2-3 Hz. EEG abnormalities often disappear with benzodiazepine administration [2]. Indeed, this was the pattern initially displayed on EEG monitoring of our patient – high-voltage, generalized, anterior predominant 2.5-3Hz spike and wave discharges. This abated with the administration of lorazepam.

Our patient’s ESRD on dialysis increased her risk for cefepime-induced neurotoxicity, and the course of her symptomatology – confusion, encephalitis, seizures, EEG findings, and seizure resolution – were typical of symptoms described in the literature. However, given the information above, our patient was an atypical case. Instead of symptom resolution 2 days after cefepime discontinuation, we saw prolonged encephalopathy lasting more than 7 days and nonconvulsive status epilepticus occurring 2 days later. Several factors may have contributed to this progression. Following cefepime discontinuation, our patient had not been able to complete dialysis prior to her seizure. Discontinuing the drug alone may have been insufficient to prevent further adverse events caused by cefepime. Given that she improved quickly after hemodialysis, and had she been hemodynamically and neurologically stable enough to undergo the procedure, she may have recovered sooner. Patients with ESRD displaying signs of cefepime neurotoxicity may benefit from more aggressive dialysis soon after discontinuing the drug.

Furthermore, our patient did initially show signs of encephalopathy on cefepime at her first admission prior to switching to meropenem. She was later restarted on the medication and again showed signs of encephalopathy. In such cases where a patient displays signs thought to be related to cefepime, care should be taken to refrain from further use and not to restart them on the drug after discontinuation. Early recognition of signs, early hemodialysis, and monitoring of blood levels are key to the safety of patients on cefepime.

Our patient may have also been in nonconvulsive status epilepticus prior to her witnessed event and would have benefited from earlier EEG monitoring. Furthermore, our patient had a CVA around the time of her seizures. As CVA and small-vessel disease are risk factors for cefepime-induced neurotoxicity, perhaps her small-vessel disease contributed to her prolonged encephalopathy and delayed recovery. Her ESRD was also a risk factor for CVA, which can pose a risk for seizures as well, in addition to her cefepime neurotoxicity. These are factors to consider when assessing the risk of a patient with ESRD for neurologic adverse effects before starting the patient on cefepime.

**Conclusions**

Our case depicts the neurologic sequelae that can occur when starting a patient with ESRD on cefepime, and portrays the need to adhere to scheduled hemodialysis when they begin to show signs of neurotoxicity. Careful attention should be paid when administering cefepime to patients with impaired renal function, as renal disease poses a risk for CVAs, which compounds the risk for encephalopathy and seizures. If a patient begins to display signs of encephalopathy on cefepime, this should be seen as an early sign and the drug should be quickly discontinued. Afterward, more aggressive interventions should be completed to prevent serious adverse events and delayed recovery, such as completing prompt hemodialysis and performing an early EEG. Delaying hemodialysis can prolong encephalopathy and increases patients’ risk for more serious sequelae such as status epilepticus. Cefepime blood levels should be monitored in these patients. Proper identification of risk factors and care of patients suspected of cefepime-induced neurotoxicity during and after administration are essential to their well-being and full recovery.
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