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# PRACTICAL TEACHING CASE

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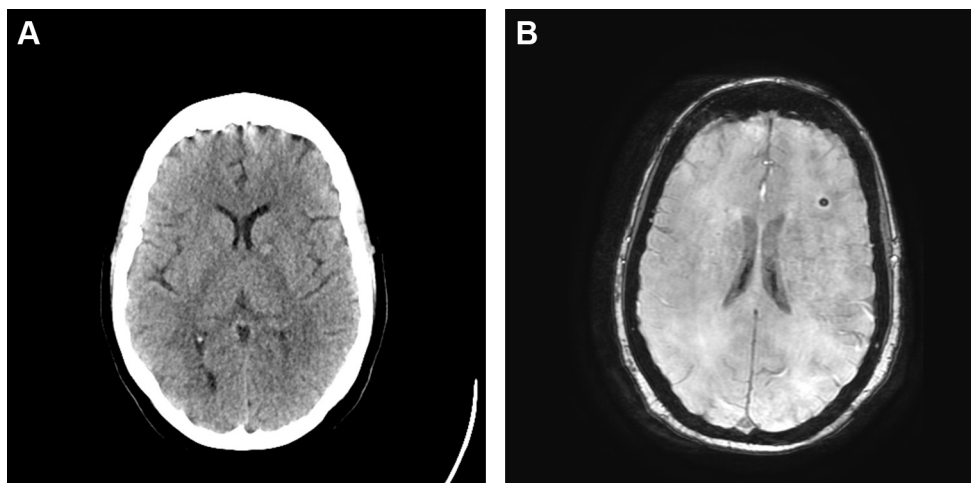
## A Curious Case of Confusion in a Patient With Cirrhosis



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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e14. Learning Objective: Upon completion of this practical teaching case, successful learners will be able to identify cefepime-induced neurotoxicity.



**Question:** A 40-year-old woman presented with dyspnea and bilateral lower extremity edema. She had a past history of decompensated alcohol-related cirrhosis complicated by small esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy on lactulose and rifaximin, and small volume ascites on furosemide and spironolactone. She had severe alcohol use disorder but had been abstinent for 6 months and was recently listed for liver transplantation.

On admission, the patient had a new 2L oxygen requirement. Physical examination was notable for a non-tender, nondistended abdomen, crackles in bilateral lung bases, and 2+ lower extremity edema. Laboratory work-up (reference range in parenthesis) showed baseline hemoglobin of 7.1 g/dL (11.6-15), leukocytes  $9.3 \times 10^9/L$  (3.4-9.6), platelets  $62 \times 10^9/L$  (157-371), INR 3.9 (0.9-1.1), sodium 132 mmol/L (135-145), creatinine 1.54 mg/dL (0.59-1.04) [baseline 1.2], ALT 41 U/L (7-45), AST 99 U/L (8-43), alkaline phosphatase 91 U/L (35-104), total bilirubin 28 mg/dL ( $\leq 1.2$ ) with direct 13.3 mg/dL (0-0.3). The MELD-Na score was 39. Chest x-ray demonstrated diffuse consolidative airspace opacities and small bilateral pleural effusions. Blood cultures, SARS Coronavirus-2 testing, and diagnostic paracentesis were unremarkable.

Shortly after admission, the patient developed worsening hypoxia requiring intensive care transfer and ultimately mechanical ventilation secondary to hypoxemic respiratory failure. She was started on broad spectrum antibiotics including vancomycin, cefepime, and metronidazole. Lactulose and rifaximin were continued. Bronchoscopy with bronchoalveolar lavage and bacterial cultures was unremarkable. The patient was initiated on continuous renal replacement therapy for volume overload non-responsive to diuretics.

While her respiratory condition improved, she remained intubated for altered mental status over the next 8 days. She remained minimally responsive despite discontinuation of sedation. For further work-up of the altered mental status, CT head (Figure A) and MRI brain (Figures B) were obtained.

What is the most likely cause of the patient's mental status?

- A. Acute ischemic stroke
- B. Infective endocarditis with septic emboli
- C. Refractory hepatic encephalopathy
- D. Cefepime-induced neurotoxicity

Look on page 2038 for the answer and see the *Gastroenterology* web site ([www.gastrojournal.org](http://www.gastrojournal.org)) for more information on submitting your favorite image(s) to Practical Teaching Cases.

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**Conflicts of interest**

The authors disclose no conflicts.

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## Answer (Page 2036): Cefepime-induced neurotoxicity

The correct answer is D. CT head demonstrated a new hyperattenuating focus in the genu of the left internal capsule compatible with small lacunar infarct with microhemorrhage. MRI brain showed multifocal susceptibility foci throughout the cerebral hemispheres, primarily located at the gray-white junction, raising the possibility of early septic emboli versus bland emboli with associated microhemorrhages. EEG showed moderate diffuse cerebral dysfunction with no epileptogenic activity. Neurology was consulted and felt that the brain imaging findings were discordant with patient's mental status changes. Transesophageal echocardiogram was negative for valvular vegetations. Refractory hepatic encephalopathy was less likely given the patient's high stool output (>1L daily) with lactulose and rifaximin. Antimicrobials were discontinued after extensive negative infectious work up. Within 24 hours of discontinuing cefepime, the patient had remarkable recovery of mental status. She was alert and oriented to name, age, year, and president and was able to follow simple commands. Her mental status continued to improve throughout her stay.

Cefepime is a fourth-generation cephalosporin antibiotic that is commonly used as first-line treatment for severe infections. Cefepime-related neurotoxicity is rare and can have a variety of clinical presentations including simple encephalopathy, delirium, myoclonus, seizures, and coma.<sup>1</sup> The mean onset of symptoms from cefepime initiation is 4-5 days.<sup>2,3</sup> Risk factors for cefepime related neurotoxicity include advanced age, history of renal insufficiency or neurologic disease, and prolonged use with excessive dosing.<sup>1,2</sup> In one study, patients had a median age of 69 years with 80% having renal dysfunction and 81% requiring intensive care. The proposed mechanism for neurotoxicity include gamma-aminobutyric acid (GABA) inhibition and the ability of the antibiotic to cross the blood-brain barrier.<sup>1,2</sup> Additionally, an acute or chronic decrease in the glomerular filtration rate can lead to reduced renal clearance of cefepime and increased serum and cerebrospinal levels of the antibiotic.<sup>3</sup> The mainstay of treatment involves withdrawal of the drug. Resolution of symptoms typically occurs about 2 days after cefepime discontinuation, antiepileptic administration, or hemodialysis.<sup>2</sup>

**Keywords:** Alcohol-related Cirrhosis, Cefepime Neurotoxicity, Hepatic Encephalopathy.

### References

1. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: Clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographs monitoring. *Ann Pharmacother* 2008;42:1843–1850.
2. Payne LE, Gagnon DJ, Riker RR, et al. Cefepime-induced neurotoxicity: A systematic review. *Crit Care* 2017;21:276.
3. Appa AA, Jain R, Rakita RM, et al. Characterizing Cefepime Neurotoxicity: A Systematic Review. *Open forum Infect Dis* 2017;4:ofx170.