# CEFEPIME E NEUROTOSSICITÀ: UNA COMPLICANZA SOTTOVALUTATA NELLA POPOLAZIONE GERIATRICA

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## Riassunto

Il cefepime è una cefalosporina di quarta generazione ampiamente utilizzata per il trattamento delle infezioni nosocomiali anche se è nota una potenziale neurotossicità in particolare nei pazienti anziani e fragili. Questa condizione, caratterizzata da alterazioni cognitive e stato confusionale, si manifesta più frequentemente in presenza di insufficienza renale e/o dosaggi non ottimizzati. Questo lavoro presenta due casi di pazienti geriatrici che hanno sviluppato neurotossicità associata al cefepime.

## Introduction

Cefepime, a fourth-generation cephalosporin, acts by inactivating penicillin-binding proteins on bacterial cell walls. Cefepime is recommended as a first-line drug for nosocomial lower respiratory tract infections. However, it has been known that cefepime can cause encephalopathy secondary to neurotoxicity, with an estimated incidence ranging from 1% to 15% (1). The mechanism of cefepime's neurotoxicity is related to antagonism towards the GABA (A) receptor at the blood-brain barrier in a concentration-dependent manner (2). Normally, only 10% of the drug crosses the blood-brain barrier, but in patients with chronic kidney disease, the reduction of membrane proteins and the accumulation of organic acids can increase this percentage up to 45% (3). Despite these effects being well-documented, cases of cefepime-induced encephalopathy continue to be observed and reported in clinical practice, particularly in patients with an estimated glomerular filtration rate (eGFR) ≤ 30 mL/min. Serum cefepime concentrations >20 mcg/mL are frequently associated with an increased risk of neurotoxicity, with a fivefold higher risk of neurological events (4). Symptoms, including encephalopathy, confusion, seizures with electroencephalogram (EEG) abnormalities, aphasia, and hallucinations, typically appear around the fourth day of therapy (5). In this arti-

**Fig. 1:** Electroencephalogram (EEG)
The EEG tracing shows a diffuse slowing of the baseline activity with frequent large triphasic waves of diffuse expression. These types of alterations are often associated with moderate-grade diffuse encephalopathy, for example of metabolic origin, compatible with neurotoxicity from cefepime.

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cle, we describe two clinical cases of cefepime-induced neurotoxicity observed in the Geriatrics Department of the Regional Hospital of Mendrisio.

**Patient 1**
A 91-year-old man with a history of metastatic prostate adenocarcinoma was admitted after two episodes of falls at home, with an inability to get up independently. Radiological examinations ruled out intracranial haemorrhages.

A per protocl for patients admitted under the complex early geriatric rehabilitation program, a neuropsychological screening is performed upon admission which identified deficit of memory, working memory, praxis impairments, fronto-executive dysfunctions, visuospatial difficulties and perceptual deficits that defined a minor neurocognitive disorder.
During hospitalization he developed nosocomial pneumonia and he was treated with intravenous cefepime (2 g 3x/d). The dosage was prescribed based on an estimated glomerular filtration rate (eGFR) of 66 mL/min (CKD-EPI) but renal function adjusted for age and weight or body surface area (BSA) calculated according to the Cockcroft-Gault formula (40 mL/min e 36 mL/min adjusted for BSA) was not taken into account, thereby resulting in a prescribing error.

On the fourth day of therapy, a deterioration in ideomotor function was observed, along with episodes of agitation and confusion, with slowed thinking and drowsiness (the patient is easily awakened but repeats the questions asked without responding). A few days after the onset of the condition, a native brain CT was performed to assess any subacute ischemic lesions, which resulted negative. Given the persistence of the altered state of consciousness, in order to better clarify its origin, an electroencephalogram (EEG) was indicated. The exam revealed background activity with theta and theta-delta waves associated with widespread, non-periodic triphasic waves (**Figure 1**). The electroencephalographic findings are suggestive of a toxic-metabolic cause. After excluding the presence of concurrent metabolic alterations, and considering the recent introduction of Cefepime, the hypothesis of toxicity related to the antibiotic is raised. Discontinuation of the antibiotic led to a gradual clinical improvement and recovery of consciousness.

**Patient 2**
A 77-year-old woman with a known history of arterial hypertension but with no anamnestic evidence of cognitive impairment, she was admitted due to disorientation. The laboratory tests revealed an elevated C-reactive protein level (158 mg/L) and cytolytic and cholestatic hepatopathy. An ultrasound showed a gallstone in the gallbladder without biliary tract dilation. During hospitalization, the patient developed fever (max temperature 38.3°C). An abdominal CT scan

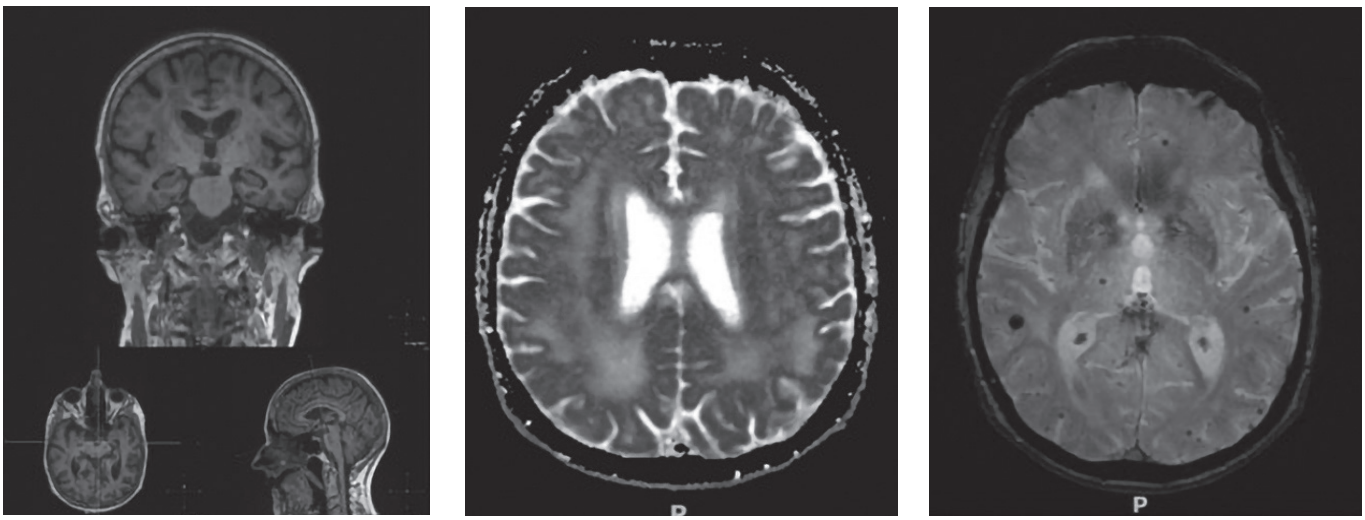


**Fig. 2:** Magnetic Resonance Imaging (MRI) of the brain
1) In the coronal, axial e sagittal slices a reduction in hippocampal volumes is evident in the sections used to calculate the medial temporal atrophy (MTA score 2).
2) This image shows diffuse confluent chronic vascular leukoencephalopathy (Fazekas 3)
3) The axial slices, diffuse lesions consistent with hemosiderin deposits are observed, suggestive of probable cerebral amyloid angiopathy
fepime.

documented a perforated calculous cholecystitis complicated by multiple hypodense hepatic collections. The patient was treated with intravenous cefepime (2 g 3x/d) and metronidazole (500 mg 3x/d), given her normal renal function (93 mL/min/1.73m²). Forty-eight hours after initiating antibiotic therapy, the patient exhibited a slowed speech, anomia, paraphasias, and severe visuospatial and praxic difficulties (Mini Mental State Examination (MMSE) 19/30, cut-off 24; Clock test 3/9). A neuropsychological assessment confirmed significant apraxia, visuospatial and perceptual difficulties. A brain MRI revealed chronic vascular leukoencephalopathy (Fazekas 3), bilateral cortical-subcortical hemosiderin deposits, and areas of mesiotemporal atrophy (MTA score 2) bilaterally (Atrophy is suggestive of Alzheimer's disease AD; however, a CSF analysis was not performed as the cerebrospinal fluid results would not be reliable in this acute phase) (**Figure 2**). Discontinuation of cefepime and substitution with ceftriaxone led to a progressive improvement in cognitive, visuospatial, and perceptual difficulties within 48 hours. A subsequent neuropsychological evaluation showed near-complete recovery, with only mild persistent praxic difficulties (MMSE 28/30; Clock test 7/9).

## Discussion

The presented cases demonstrate that cefepime can cause neurotoxicity in elderly patients even in the absence of preexisting neurocognitive disorders, chronic kidney disease, or prolonged therapy. Cefepime-induced neurotoxicity has been observed within 4–5 days from the start of therapy, although it can occur up to 15 days after its initiation (6). In elderly patients, age-related pharmacokinetic and pharmacodynamic changes increase the risk of toxicity. Therefore, it is crucial to calculate drug dosage based on renal function. Current Recommendations for antibiotic dosing (Swiss monograph, Sanford Guide, UpToDate) according to renal function rely on the Cockcroft-Gault formula, which has been used in the vast majority of drug efficacy and safety studies. Serum cefepime concentrations above 20 mcg/mL have been associated with a high risk of neurotoxicity, considering that the normal therapeutic range is between 5 and 10 mcg/mL (7). A 2017 systematic review showed that 25% of cefepime-induced neurotoxicity cases occurred even in patients who received appropriate dosing (1).

In patients with impaired renal function and those with normal renal function, the initial loading dose of cefepime remains the same. However, maintenance doses should be adjusted based on actual renal function, as described in **Table 3** (8). Elderly patients may exhibit increased sensitivity to drug effects due to receptor and cellular signaling alterations, leading to more pronounced or prolonged responses. These changes require special attention when selecting and dosing medications, as well as regular monitoring to promptly identify signs of toxicity or therapeutic inefficacy.

EEG can aid in assessing neurotoxicity, particularly in settings where therapeutic drug monitoring is not readily available. In toxic-metabolic encephalopathies, EEG is a sensitive but nonspecific tool, typically revealing generalized periodic discharges with triphasic wave morphology (9).

In the first case, calculating clearance using the Cockcroft-Gault formula adjusted for BSA would have indicated an estimated glomerular filtration rate (eGFR) of 36 mL/min/1.73m2, making the administered cefepime dosage excessive. The use of the CKD-EPI value provided by the laboratory led to an error.

In the second case, despite appropriate dosing, neurotoxicity still occurred possibly related to severe vascular encephalopathy with signs of amyloid angiopathy and likely focal impairment of the blood-brain barri-

| eGFR* / Infection | >60 | 30-60 | 11-29 | <11 | CAPD | Dialysis |
|---|---|---|---|---|---|---|
| MILD (UTI) | 500mg/12h | 500 mg/24h | 500 mg/24h | 250 mg/24h | 500 mg/48h | 1g on D1, then 500 mg/24h |
| MODERATE (Pneumonia) | 1 gr/12h | 1 gr/24h | 500 mg/24h | 250 mg/24h | 1 g/48h | 1g on D1, then 500 mg/24h |
| SEVERE (Intra-abdominal, complicated UTI or pneumonia) | 2 gr/12h | 2 gr/24h | 1 gr/24h | 500 mg/24h | 2 gr/48h | 1g on D1, then 500 mg/24h |
| FEBRILE NEUTROPENIA | 2 gr/8h | 2 gr/12h | 2 gr/24h | 1gr/24h | 2 gr/48h | 1 gr/ 24h |

**Tab. 3:** Adjustment of Cefepime dosage according to renal function
(*eGFR as calculated by the Cockroft-Gault equation)
The table indicates Cefepime dosages adjusted according to renal function for infections of varying severity. Adapted from: Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. Pharmacotherapy. 2006;26(8):1169-74.

er possibly though a toxicodynamic mechanism.

The underlying pre-existing cognitive condition, as described by neuropsychological assessment and brain imaging, likely played a role in the development of neurotoxicity, identifying this patient population as vulnerable.

A major limitation in these cases is the lack of TDM (Therapeutic Drug Monitoring) results, which makes it unclear whether the toxicity was due to pharmacokinetic variability (e.g., increased drug concentration) or to toxicodynamic susceptibility (neurotoxicity at therapeutic levels).
Given pharmacokinetic variability and the narrow therapeutic window with potential for toxicity, cefepime TDM can be a valuable tool, particularly for vulnerable patient populations such as geriatric and pediatric patients, those with chronic kidney disease (CKD), ICU patients, and those on ECMO. Indeed, the currently recommended dosing regimens may lead to overexposure in geriatric patients.

## Conclusions

Cefepime-induced neurotoxicity is a significant complication in elderly patients. It is crucial to closely monitor renal function, adjust drug dosage accordingly (starting from the first dose) and consider alternative therapies in frail or malnourished patients. The use of TDM can play a crucial role in assessing the appropriate cefepime dosage in these patients. Awareness of these complications allows for the optimization of antibiotic therapy safety and efficacy, reducing the risk of adverse events in a vulnerable population such as the geriatric one. Personalizing pharmacological therapy is essential to maximize benefits and minimize risks, taking into account the specific clinical needs and comorbidities of elderly patients.

## Cefepime and Neurotoxicity An Underestimated Complication in the Geriatric Population

## Abstract

Cefepime is a widely used fourth-generation cephalosporin for the treatment of nosocomial infections but is known for its potential neurotoxicity, particularly in elderly and frail patients. This condition, characterized by cognitive impairment and confusion, occurs more frequently in the presence of renal insufficiency and/or suboptimal dosing. This paper presents two cases of geriatric patients, who developed cefepime-associated neurotoxicity.

**Keywords:** cefepime, neurotoxicity, adverse effect, older patient, geriatrics

### Bibliography

1. Appa AA, Jain R, Rakita RM, Hakimian S, Pottinger PS. Characterizing cefepime neurotoxicity: a systematic review. Open Forum Infect Dis. 2017;4:ofx170.
2. Payne LE, Gagnon GJ, Riker RR, Seder DB, Glisic EK, Morris JC, Fraser GL. Cefepime-induced neurotoxicity: a systematic review. Crit Care. 2017;21:276.
3. Durand-Maugard C, Lemaire-Hurtel AS, Gras-Champel V, Hary L, Maizel J, Prud'homme-Bernardy A, Andréjak C, Andréjak M. Blood and CSF monitoring of cefepime-induced neurotoxicity: nine case reports. J Antimicrob Chemother. 2012;67:1297-9.
4. Huwyler T, Lenggenhager L, Abbas M, Ing Lorenzini K, Hughes S, Huttner B, Karmime A, Uçkay I, von Dach E, Lescuyer P, Harbarth S, Huttner A. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. Clin Microbiol Infect. 2017;23:454-9.
5. Deshayes S, Coquerel A, Verdon R. Neurological adverse effects attributable to β-lactam antibiotics: a literature review. Drug Saf. 2017;40:1171-98.
6. Alagha Z, Crow S, Abdeen AMZ, Alastal M, Alastal A. Cefepime neurotoxicity in patients with normal renal function: an overlooked cause of encephalopathy in the intensive care unit. J Investig Med High Impact Case Rep. 2024:12:23247096241259534.
7. Keerty D, Shareef NA, Ramsakal A, Haynes E, Syed M. Cefepime-induced encephalopathy. Cureus. 2021;13:e13125.
8. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. Pharmacotherapy. 2006;26:1169-74.
9. Bausch S, Araschmid LJ, Hardmeier M, Osthoff M. Cefepime-induced neurotoxicity in the setting of acute kidney injury: a case series and discussion of preventive measures. Cureus. 2022;14:e26392.

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**Declarations**

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