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Beta-lactam–induced neurotoxicity: a narrative review of clinical impact, pathophysiological mechanisms, and practical approach

Abstract

Background: Beta-lactam antibiotics are widely used and generally safe; however, they may cause neurotoxicity, particularly in hospitalized and critically ill patients. Early detection is crucial to reduce morbidity and mortality.

Objective: To synthesize current evidence on the incidence, mechanisms, risk factors, clinical presentation, diagnostic approach, and management of beta-lactam–induced neurotoxicity (BLIN).

Methods: A narrative literature review was conducted to identify relevant publications, employing a structured search strategy in the PubMed database. The search combined Medical Subject Headings (MeSH) and free-text terms to ensure comprehensive coverage, organized into three main conceptual components: beta-lactam drugs, neurotoxic events, and clinical context and risk. Information was extracted and synthesized qualitatively, with findings organized into a "problem–mechanism–solution" framework.

Results: Ten eligible studies were identified. Cefepime was the beta-lactam most frequently associated with neurotoxicity. The predominant pathophysiological mechanism is concentration-dependent antagonism of the GABA-A receptor, although glutamatergic hyperactivity, oxidative stress, mitochondrial dysfunction, and blood–brain barrier disruption also contribute. Major risk factors include renal impairment, inappropriate dosing, advanced age, neurological comorbidities, sepsis, and critical illness. BLIN typically presents with acute encephalopathy, myoclonus, seizures, and non-convulsive status epilepticus. Diagnosis is clinical and exclusionary, supported by electroencephalography, therapeutic drug monitoring, and neuroimaging. Prompt drug discontinuation generally leads to improvement, while severe cases may require hemodialysis.

Conclusions: Beta-lactam–induced neurotoxicity is a potentially severe yet reversible complication. Early recognition, individualized dosing, and close clinical monitoring are essential to reducing the risk of this preventable adverse effect.

Keywords: beta-lactam drugs, neurotoxicity, risk factors, therapeutic drug monitoring, management

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Abbreviations: BLIN, beta-lactam–induced neurotoxicity; CIN, cefepime induced neurotoxicity

Introduction

Beta-lactams are a widely used group of antibiotics in clinical practice and, although generally considered safe, they are not exempt from serious adverse reactions.[1] These antibiotics, encompassing cephalosporins, carbapenems, and combinations such as piperacillin-tazobactam, are pivotal in treating severe infections due to their broad-spectrum efficacy. However, the therapeutic benefits of beta-lactams are occasionally overshadowed by adverse effects. Among these, one of the least studied effects is neurotoxicity, whose reported incidence varies significantly across the literature—from 7% to 23%—mainly due to the absence of standardized diagnostic criteria and the frequent use of these drugs in critically ill patients, in whom the identification of drug-associated neurotoxicity is more challenging.[2–4] Early recognition of beta-lactam–induced neurotoxicity (BLIN) is essential, as it can significantly impact patient morbidity and mortality. The purpose of this review is to synthesize the available scientific evidence regarding the identification, prevention, and management of beta-lactam neurotoxicity.

Material and methods

A narrative literature review was conducted to identify relevant publications, a structured search strategy was designed and executed in the PubMed database. The search combined Medical Subject Headings (MeSH) and free-text terms (present in title and/or abstract [tiab]) to ensure comprehensive coverage.[5] The strategy was organized into three main conceptual components, combined using the AND operator.

Component 1 (Beta-lactam Drugs):

("Cephalosporins"[MeSH] OR "Carbapenems"[MeSH] OR "Piperacillin-Tazobactam Combination"[MeSH] OR "Antibiotics"[MeSH] OR "Cefepime"[tiab] OR "Piperacillin-Tazobactam"[tiab])

Component 2 (Neurotoxic Events):

("Delirium"[MeSH] OR "Encephalopathy"[MeSH] OR "Seizures"[MeSH] OR "Neurotoxicity Syndromes"[MeSH] OR "Neurotoxicity"[tiab] OR "Encephalopathy"[tiab] OR "Seizures"[tiab] OR "Myoclonus"[tiab])

Component 3 (Clinical Context and Risk):

("Risk Factors"[MeSH] OR "Kidney Diseases"[MeSH] OR "Pharmacogenetics"[MeSH] OR "Drug Monitoring"[MeSH] OR "Glasgow Coma Scale"[Pharmacological Action] OR "Pharmacovigilance"[MeSH] OR "Renal failure"[tiab] OR "Hemodialysis"[tiab] OR "Renal impairment"[tiab])

Selection criteria:

Included studies (in English or Spanish) evaluated beta-lactam–associated neurotoxicity in humans. Systematic reviews, meta-analyses, retrospective studies, and narrative reviews were included to obtain a comprehensive synthesis of epidemiology, mechanisms, and clinical management. Studies focused primarily on pediatric populations (<18 years) were excluded.

Extracted information was analyzed and synthesized qualitatively. Findings were thematically organized following a logical "problem–mechanism–solution" structure.

The literature search and initial synthesis of results were carried out between August and November 2025 by a pharmacy student (KMA) as part of an elective course in her degree program.

Results and discussion

A total of 10 articles met the predefined inclusion criteria. All publications were in English and corresponded to the period 2021–2025 (Table 1).

Table 1 Characterization of included studies related to the neurotoxicity of beta lactams and its management

Year	PMID	Title	Type of article	Purpose
2025	40558212	The Effect of Antibiotics on the Nervous System: Importance for Anesthesiology and Intensive Care	Review	To assess the neurotoxic profiles, underlying mechanisms, and clinical manifestations associated with different antibiotic classes, including beta-lactams, fluoroquinolones, macrolides, aminoglycosides, and others.
2025	40523836	Unveiling predisposing factors for cefepime-induced neurotoxicity: A systematic review and meta-analysis	Systematic review and meta-analysis	To elucidate the risk factors associated with the development of cefepime-induced neurotoxicity (CIN).
2024	38589733	Danger in plain sight: determining who is at highest risk for cefepime induced neurotoxicity and its associated morbidity and mortality	Review	To highlight risk factors for CIN, discuss the possible value of EEG, and propose a diagnostic and management approach in the evaluation and management of CIN.
2024	38305827	Ceftazidime-related neurotoxicity in a patient with renal impairment: a case report and literature review	Case report and literature review	To search PubMed for cases from which relevant information was extracted. Using the collected data a ROC analysis was performed in R to determine a neurotoxicity threshold.
2023	37503476	The Trend of Cefepime-Induced Neurotoxicity: A Systematic Review	Systematic review	To explore the trend of cefepime-induced neurotoxicity over the last 10 years
2023	36671270	Continuous Infusion of High Doses of Cefepime in Intensive Care Unit: Assessment of Steady-State Plasma Level and Incidence on Neurotoxicity	Review	To determine factors associated with cefepime overdosing and the incidence of cefepime-induced neurotoxicity in critically ill patients
2022	35067669	Prolonged Cefepime-Induced Neurotoxicity in a Patient with End-Stage Renal Disease	Case report	To present a patient with end-stage renal disease on hemodialysis who developed prolonged neurotoxicity lasting longer than 1 week complicated by nonconvulsive status epilepticus 2 days after cefepime discontinuation
2021	34946536	Antibiotics and the Nervous System-Which Face of Antibiotic Therapy Is Real, Dr. Jekyll (Neurotoxicity) or Mr. Hyde (Neuroprotection)?	Review	To describe neurological or psychiatric adverse drug reactions which are often considered to be overlooked and undervalued issues
2021	34361942	Beta-Lactams Toxicity in the Intensive Care Unit: An Underestimated Collateral Damage?	Comprehensive literature review	To describe the clinical manifestations, risk factors and beta-lactam-induced neurological and renal adverse effects in the ICU setting
2021	32618479	Ertapenem Neurotoxicity in Hemodialysis Patients-Safe and Effective Dosing Is Still Needed: A Retrospective Study and Literature Review	Retrospective Study and Literature Review	To identify the incidence of neurotoxicity in this population and the risk factors associated with this toxicity

PMID: PubMed Unique Identifier

BLIN is a clinically significant complication, especially among hospitalized and critically ill patients, with an incidence ranging from 10% to 15% in intensive care units (ICUs).[6,7] Reports in literature most frequently describe neurotoxicity associated with third- and fourth-generation cephalosporins and carbapenems.[7] Among beta-lactams, cefepime has been the most consistently implicated agent,

with increasing reports of encephalopathy, seizures, and non-convulsive status epilepticus, and a prevalence of neurotoxicity in ICUs of approximately 20–30%.[3,8,9]

Although the association between BLIN and mortality has shown heterogeneous results, recent evidence suggests that cefepime-induced neurotoxicity (CIN) may represent an independent risk factor for adverse outcomes.[3] Recent meta-analyses identify CIN as an independent predictor of mortality, with an approximate 3.5-fold increase compared with patients without neurotoxicity.[9] Comparative studies have also shown a higher incidence of neurological dysfunction—such as delirium or coma—in patients receiving cefepime compared with piperacillin–tazobactam (20.8% vs. 17.3%).[4]

From a physiopathological standpoint, the predominant mechanism of BLIN involves concentration-dependent antagonism of the GABA-A receptor, mediated by structural similarities between the beta-lactam ring and gamma-aminobutyric acid. Binding to this receptor blocks neuronal chloride influx, promoting depolarization and neuronal hyperexcitability, which explains motor manifestations and seizures.[6,9,10]

However, this mechanism alone does not fully account for encephalopathy or diminished consciousness. Additional mechanisms have been proposed, including glutamatergic hyperactivity mediated by NMDA and AMPA receptors (particularly relevant for imipenem), mitochondrial dysfunction, oxidative stress, inflammation with blood–brain barrier disruption, and metabolic encephalopathy secondary to cefepime-induced hypocarnitinemia.[6,7,9] Furthermore, systemic inflammation—particularly in sepsis and critical illness—may increase blood–brain barrier permeability, facilitating higher CNS penetration of the drug.[6,9]

Regarding risk factors, BLIN development is determined by both patient characteristics and pharmacologic variables. Impaired renal function is among the most significant risk factors, as most beta-lactams are renally excreted. Thus, reduced glomerular filtration rate, acute kidney injury, or dialysis dependence markedly increase the risk.[10–12] For cefepime, even mild decreases in renal function are associated with exponential increases in neurotoxicity risk.[9]

Other relevant factors include inappropriate dosing (although neurotoxicity has also been reported with seemingly appropriate regimens), advanced age, pre-existing neurological disease, hypoalbuminemia, sepsis, and overall critical illness.[3,4,9,13] Certain drug interactions, such as concomitant carbapenem use with valproic acid, may precipitate severe neurological events.[6,7]

Clinically, BLIN presents with a broad spectrum of acute neurological symptoms. Encephalopathy is the most common manifestation, characterized by confusion, delirium, decreased level of consciousness, and behavioral disturbances.[6,9,10] Myoclonus and asterixis are classic motor signs, while seizures and non-convulsive status epilepticus represent severe and often underdiagnosed forms. Non-convulsive status epilepticus has been reported in up to 30% monitored patients.[6,9]

Symptom onset usually occurs between 1 and 10 days after starting therapy, with variable latency depending on the drug and clinical context. For cefepime, onset typically ranges between 2 and 6 days.[6,7,8] In most cases, symptoms are resolved within 1 to 5 days after discontinuation of the antibiotic[8], although resolution may be delayed in patients with advanced renal disease.[12]

Diagnosis is mainly clinical and by exclusion, given the overlap with other common causes of encephalopathy in hospitalized patients, including septic, uremic, or metabolic encephalopathy.[3,4,10,12–14] Electroencephalography is essential to identify toxic–metabolic encephalopathy patterns or non-convulsive status epilepticus.[6] Therapeutic drug monitoring (TDM) may help correlate plasma drug levels with toxicity,[6,9,10,15,16] and neuroimaging support exclusion of alternative diagnoses as stroke.[4,12]

Management is centered on immediate discontinuation of the suspected beta-lactam, which typically leads to clinical improvement within a few days.[6,12] In the presence of seizures, treatment should prioritize agents that potentiate GABAergic neurotransmission, such as benzodiazepines and barbiturates.[6] In patients with severe renal impairment or severe neurotoxicity, hemodialysis can accelerate drug clearance and reduce CNS exposure.[12,13]

Finally, selecting an effective alternative antimicrobial therapy with lower neurotoxic potential is essential, individualized according to patient profile and pathogen susceptibility.[17]

The main limitation of this review is that using many keywords and a single database yielded a limited number of studies, all published in English and within the last five years. This may have excluded relevant studies not indexed in PubMed or not containing search terms in the title or abstract.

Conclusion

BLIN is a potentially severe yet reversible condition when promptly recognized. Identification of at-risk patients, together with close daily clinical monitoring, individualized dosing adjustments, and appropriate therapeutic drug monitoring, can significantly reduce the occurrence of these complications, particularly in critically ill patients.

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Conflicts of interest

The author declares there is no conflict of interest.

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