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Case report

Probable Reversible Encephalopathy with Ceftazidime/Avibactam and Aztreonam: A Case Report

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ABSTRACT
A combination of ceftazidime-avibactam (CZA) and aztreonam (ATM) is a critical therapeutic option for infections caused by Metallo-β-lactamase (MBL) producing, multidrug-resistant Gram-negative bacteria. While neurotoxicity is a known adverse effect of β-lactam antibiotics, reports of encephalopathy associated with the CZA+ATM regimen are rare. Here, we present the case of a 30-year-old female renal transplant recipient, admitted for DJ stent replacement, who developed CRE & XDR *Klebsiella pneumoniae* bacteremia and received ceftazidime–avibactam 2.5g BD plus aztreonam 1g BD following inadequate response to prior antibiotics. No appropriate dose adjustment was made for her severe renal impairment (CrCl 8.1 mL/min). Four days after initiation of this combination regimen, she acutely developed restlessness, irritability, myoclonus, asterixis and a progressive decline in consciousness, consistent with new-onset encephalopathy. Both antibiotics were immediately discontinued, and the patient was managed supportively with electrolyte repletion and hemodialysis. Her neurological symptoms demonstrated complete and rapid resolution within 72 hours. The temporal relationship between drug administration and symptom onset, coupled with the swift recovery upon withdrawal, implicates the CZA+ATM combination as a probable causative agent, particularly in patients with renal impairment, and underscores the need for neurological monitoring during therapy.

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1. INTRODUCTION

Ceftazidime/avibactam (CZA) is a novel β-lactam/β-lactamase inhibitor combination effective against a broad spectrum of multidrug-resistant Gram-negative bacteria, including many Carbapenem-resistant Enterobacterales (CRE) and *Pseudomonas aeruginosa*. Aztreonam (ATM), a monobactam, is stable against Metallo-β-lactamases (MBL). Their synergistic combination is recommended for serious infections caused by MBL-producing organisms (Sangiorgio et al., 2025).

While generally well tolerated, the safety profiles of individual β-lactam antibiotics are well-documented. Common adverse effects include gastrointestinal disturbances and elevated liver enzymes. However, central nervous system (CNS)

toxicity is a known, although less frequent, class effect. This neurotoxicity, which can manifest as encephalopathy, myoclonus, seizures or coma, is primarily attributed to the antagonism of gamma-aminobutyric acid (GABA) at subunit A/B receptors in the CNS, leading to increased neuronal excitation (Bhattacharyya et al., 2016). Established risk factors include advanced age, underlying CNS pathology, excessive dosing and most critically, renal impairment, which predisposes patients to drug accumulation (Payne et al., 2017; Boschung-Pasquier et al., 2020).

Neurotoxicity associated with ceftazidime alone is well-recognized (Vanneste et al., 2024). In contrast, evidence for ceftazidime-avibactam (CZA)-associated neurotoxicity is more limited but emerging (Li et al., 2026). However, to our knowledge, published reports specifically describing encephalopathy induced by the combined CZA+ATM regimen remain exceedingly sparse. We present a case of acute, reversible encephalopathy in a renal transplant recipient following the initiation of CZA+ATM therapy, emphasizing the importance of clinical recognition and management.

2. CASE PRESENTATION

A 30-year-old female with a past medical history of status post renal transplant (2021), on long-term DJ stent, presented for DJ stent replacement following the implantation of ureteric stenosis. Her immunosuppressive regimen included tacrolimus, mycophenolate mofetil and prednisolone. Therapeutic drug monitoring for tacrolimus was not performed during the admission; therefore, tacrolimus levels and their potential contribution to neurotoxicity could not be assessed. Her baseline renal function was impaired, with a serum creatinine of 2.8mg/dL.

On POD 1, she had one episode of a fever spike (102.6°F). Empiric therapy with intravenous cefepime-sulbactam 1.5g BD and hydration was initiated. Due to persistent fever, loose stools (greenish coloured), new-onset left lower quadrant abdominal tenderness, and WBC counts rising to 14000 cells/mm³ on POD 3, antibiotic therapy was escalated to Meropenem 500mg TID and urine culture and blood culture were sent. IV fluids and KCl correction were given supportively. On POD 5, both cultures came back positive for *Klebsiella pneumoniae* – CRE & extensively drug-resistant species, suggestive of sepsis. Antimicrobial susceptibility testing confirmed resistance to carbapenems, intermediate sensitivity towards colistin and susceptibility to the ceftazidime-avibactam and aztreonam combination. The isolate was confirmed to be a metallo-β-lactamase (MBL)-producing strain. Consequently, antibiotic therapy was tailored to intravenous ceftazidime-avibactam (2.5g [ceftazidime 2g / avibactam 0.5g] every 12 hours) and intravenous aztreonam (1g every 12 hours). Renal function at this time showed a serum creatinine of 6.1 mg/dL and a calculated creatinine clearance (CrCl) of 8.1 mL/min/1.73m², indicating severely impaired renal function. No appropriate dose adjustment for either drug was made based on renal function at the time of initiation.

On POD 9, after receiving four days of CZA+ATM therapy, the patient developed restlessness with irritability, shivering, myoclonus, asterixis, and altered consciousness, consistent with encephalopathy. Lab investigations revealed hypocalcemia (7.2mg/dl) and hypomagnesemia (1.1mg/dl). MRI Brain was not performed due to the patient's renal impairment and rapid clinical improvement following drug discontinuation, but this remains a limitation. Given the suspicion of antibiotic-induced neurotoxicity, CZA + ATM was discontinued, and intravenous Meropenem 500mg every 8 hours was reinitiated. Supportive care was intensified, including IV calcium gluconate 10% every 12 hours and IV magnesium sulphate 2g in 100 ml NS every 12 hours and the patient was shifted to the ICU. On POD 10, she was restless with decreased sleep and tremors, and hemodialysis was initiated. No antiseizure medications were administered. By POD 11, her sensorium had cleared completely, and tremors had resolved. A repeat blood culture on POD 12 was sterile. The patient completed a 6-day course of meropenem, and her electrolyte abnormalities were managed with oral replacement therapy (calcium carbonate 500mg BD, magnesium oxide 400mg BD). She was discharged home in a stable neurological and clinical condition on POD 13.

3. DISCUSSION

β-lactam antibiotic-induced neurotoxicity is a well-known phenomenon, historically associated with cephalosporins (e.g., cefepime), and carbapenems (Anthony et al., 2015; Payne et al., 2017). The pathophysiology of β-lactam-induced neurotoxicity is primarily linked to the inhibition of GABA A/B receptor binding. The β-lactam ring structure may interfere with GABA activity, leading to a state of neuronal hyperexcitability. As a result, the patient may experience a variety of neurological manifestations ranging from confusion, agitation and myoclonus to overt seizures (Bhattacharyya et al., 2016). Ceftazidime, a cephalosporin, has a higher propensity for CNS penetration and GABA antagonism compared to many

Table 1: Laboratory Parameters During Hospitalization

DAYS	WBC (4k-11k/mm³)	CRP (<10mg/l)	UREA (15-40mg/dl)	CREATININE (0.6-1.3mg/dl)	Na + (135-145mEq/L)	K+ (3.5-5.5mEq/L)	Ca 2+ (8.5-10.5mg/dl)	Mg 2+ (1.5-2.5mg/dl)
0	9100		59	2.8	141	3.7		
POD 3	14000	191.1	101	5.9	133	3.1		
POD 5 (CZA/ATM started)	13400	206	117	6.1				
POD 6	9500		118	5.7				
POD 9 (CZA/ATM stopped)	8700		113	5.2	139	3.9	7.2	1.1
POD 11	9500	46	89	3.8	143	3.7	7.8	1.5
POD 13	9300		73	3.2	138	3.7	7.7	1.4

other β-lactams, explaining its well-documented neurotoxic potential, especially in renal failure (Vanneste et al., 2024). Although avibactam itself is not known to be neurotoxic, its combination with ceftazidime may prolong or enhance exposure to the active antibiotic component. Risk factors include advanced age, renal impairment, excessive dosing and pre-existing brain injury (Boschung-Pasquier et al., 2020; Payne et al., 2017).

This case is particularly notable for the use of CZA in combination with ATM. Aztreonam, a monobactam, is generally considered to have a low neurotoxic potential. Both drugs are primarily eliminated by the kidneys. In patients with severe renal failure (CrCl <15 mL/min), as in our case, the half-life of both drugs is significantly prolonged, leading to accumulation and a substantially increased risk of toxicity (Sangiorgio et al., 2025). Crucially, no dose adjustment was made for either drug despite the patient's severely reduced renal function, which likely contributed to drug accumulation and the subsequent neurotoxicity. For a patient with CrCl 8.1 mL/min, FDA label-recommended doses are substantially lower (e.g., ceftazidime-avibactam 0.94g every 24 hours; aztreonam 500mg every 12 hours) (Zhang et al., 2024).

The differential diagnosis for encephalopathy in this patient was broad, including sepsis-associated encephalopathy and metabolic disturbances. However, the onset of symptoms occurred after the patient's clinical condition (fever, leukocytosis) was improving (Table 1, decreasing WBC and CRP on POD 9), making sepsis-associated encephalopathy less likely and supporting drug-induced encephalopathy. The concurrent hypocalcemia and hypomagnesemia may have further lowered the seizure threshold. While these factors alone may not fully explain the severity of symptoms, they likely acted in conjunction with drug accumulation to precipitate encephalopathy. Tacrolimus-related neurotoxicity was considered; however, no trough levels were available, and the rapid resolution after antibiotic discontinuation without a change in the immunosuppressive regimen makes tacrolimus less likely to be the primary cause.

The temporal sequence (symptom onset four days after initiating the drugs and complete resolution within 72 hours of withdrawal) supports a causal relationship. Based on established causality assessment tools such as the Naranjo Adverse Drug Reaction Probability Scale and WHO-UMC criteria, the reaction can be categorized as probable. The severity of this adverse reaction was classified as Level 5 (severe) according to the Hartwig Severity Assessment Scale, as it required an intervention (drug discontinuation, ICU transfer, and hemodialysis) and prolonged the patient's hospital stay. This underscores the clinical significance of this adverse event. Management is primarily supportive and involves immediate discontinuation of the offending agent. In severe cases or those with persistent symptoms, enhanced elimination through renal replacement therapy can be considered, although data on its efficacy for CZA/ATM removal is limited. A major limitation of this report is the absence of

therapeutic drug monitoring for CZA and ATM, which would have confirmed elevated drug levels. Additionally, no advanced neuroimaging was performed.

4. CONCLUSION

This case report describes the probable neurotoxic risk associated with the use of CZA+ATM combination, especially in patients with renal impairment and when doses are not adjusted appropriately. The reversible nature of this condition, as seen in this case, highlights the excellent prognosis with timely intervention. Future research should explore the specific risk factors and potential for therapeutic drug monitoring in high-risk populations receiving this important antibiotic combination.

List of Abbreviations

Abbreviation	Full Form
ATM	Aztreonam
CNS	Central Nervous System
CRE	Carbapenem-Resistant Enterobacterales
CRP	C – Reactive Protein
CZA	Ceftazidime-Avibactam
DJ	Double-J (stent)
GABA	Gamma-Aminobutyric Acid
ICU	Intensive Care Unit
MBL	Metallo-β-Lactamase
POD	Post-Operative Day
WBC	White Blood Cells
WHO-UMC	World Health Organization-Uppsala Monitoring Centre
XDR	Extensively Drug Resistant

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Conflict of Interest

None declared.

Ethical Statement

In accordance with international or university standards, written ethical approval has been obtained and retained by the author(s).

Declaration of Generative AI

No artificial intelligence (AI) tools were used in the preparation of this manuscript

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