***Case report***

**Ertapenem-Induced Encephalopathy: A Case Report Highlighting Carbapenem-Associated Neurotoxicity**

**Abstract**

**Background:** Ertapenem is a once-daily carbapenem antibiotic commonly used in the treatment of complicated infections. Although traditionally associated with a lower risk of central nervous system (CNS) toxicity compared to imipenem, emerging reports highlight the potential for ertapenem-induced neurotoxicity, especially in patients with renal impairment and hypoalbuminemia. Early recognition is crucial, as symptoms are often reversible with drug discontinuation.

**Case Presentations**: We report a case of a 46-year-old woman with type 2 diabetes, advanced chronic kidney disease, developmental delay, and hypoalbuminemia who developed acute encephalopathy with visual hallucinations approximately three weeks into outpatient ertapenem therapy for suspected diabetic foot osteomyelitis. Despite stable vitals and supportive care for acute kidney injury, she exhibited a sudden decline in mental status. Extensive investigations excluded metabolic, structural, and infectious causes. Ertapenem was discontinued, and the patient was treated with intravenous albumin and supportive measures, resulting in rapid and complete neurologic recovery within 48 hours. A Naranjo score of 7 supported a probable adverse drug reaction.

**Conclusions:** This case highlights ertapenem-induced encephalopathy as a reversible yet underrecognized complication in vulnerable populations. Risk factors such as renal dysfunction and hypoalbuminemia should prompt close monitoring and dose adjustment. Albumin infusion may represent a promising adjunctive therapy in select cases.

**Keywords:** Ertapenem, neurotoxicity, encephalopathy, carbapenem, hypoalbuminemia, chronic kidney disease, adverse drug reaction.

Introduction:

Ertapenem is a long-acting, once-daily carbapenem antibiotic widely used for the treatment of complicated intra-abdominal infections, urinary tract infections, diabetic foot infections, and osteomyelitis. ¹ While its pharmacokinetic profile makes it suitable for outpatient parenteral antibiotic therapy, emerging literature has highlighted its potential to induce central nervous system adverse effects, including encephalopathy, particularly among high-risk patient populations. ²

Carbapenem-induced neurotoxicity is believed to be mediated through antagonism of gamma-aminobutyric acid type A (GABA-A) receptors. ¹ This effect disrupts inhibitory neurotransmission in the CNS, leading to a spectrum of neurologic manifestations that include altered mental status, delirium, agitation, hallucinations, myoclonus, seizures, and encephalopathy. ³ In patients with renal impairment, the risk is significantly heightened due to reduced clearance and consequent drug accumulation. Additionally, hypoalbuminemia, which results in increased free (unbound) drug levels, further exacerbates neurotoxic risk. ³ ⁴ The lipophilic nature of ertapenem enhances its CNS penetration, and its relatively long half-life may sustain neurotoxic concentrations even after drug discontinuation (*see Appendix: Diagram 1)*. ⁵

Although imipenem has historically been associated with a higher incidence of CNS toxicity, case reports over the past decade have drawn attention to similar effects with ertapenem, particularly in those with compromised renal function. ⁵ Despite the growing recognition of this phenomenon, ertapenem-induced encephalopathy remains underdiagnosed, in part due to the nonspecific nature of symptoms and a lack of awareness among clinicians. The diagnosis is often one of exclusion, made after ruling out structural, metabolic, or infectious causes of encephalopathy. Timely identification is crucial, as discontinuation of the offending agent typically results in rapid and complete resolution of symptoms. Supportive measures, including hydration, optimization of renal function, and in some cases administration of albumin or antipsychotics, may accelerate recovery. ⁶

In this report, we present the case of a 46-year-old woman with multiple risk factors—including advanced chronic kidney disease, developmental delay, and hypoalbuminemia—who developed a profound encephalopathy with hallucinations within 10 days of starting ertapenem for suspected diabetic foot osteomyelitis. Her case illustrates the need for vigilance when prescribing carbapenems in vulnerable populations, and the importance of early recognition and intervention to reverse a potentially serious adverse drug event.

Case Presentation:

46-year-old woman presented to the emergency department with a 3-day history of generalized weakness, dizziness, nausea, vomiting, and non-bloody diarrhea. Her past medical history was notable for Type II diabetes (T2DM), chronic kidney disease (CKD), developmental delay, hypertension, asthma, and dyslipidemia. She resided at home and had been treated for a diabetic foot infection of the left great toe. Two weeks prior to admission, she had been prescribed ertapenem 1 g IV daily following an outpatient infectious diseases consultation for suspected osteomyelitis.

At presentation in the emergency department, she appeared volume depleted with dry mucous membranes and poor oral intake. Laboratory investigations revealed an acute-on-chronic kidney injury with a serum creatinine of 303 µmol/L (baseline ~160 µmol/L), a non-anion gap metabolic acidosis with a pH of 7.29 and serum bicarbonate of 16–17 mmol/L, hypoalbuminemia with an albumin of 22 g/L (36-47 g/L) and evidence of mild electrolyte imbalances *(see full lab panel in Appendix: Table 1).* Imaging with CT abdomen and pelvis demonstrated non-obstructive nephrolithiasis and bilateral hydroureteronephrosis, but no evidence of bowel obstruction, mass, or fluid collections. Stool and nasopharyngeal swabs were negative for Clostridioides difficile, influenza, RSV, and SARS-CoV-2. Cardiology was initially consulted for concerning ST elevations noted on ECG; however, these were deemed non-ischemic and consistent with demand ischemia in the setting of uremia and systemic illness. Over the first 11 days of admission, she remained hemodynamically stable but required IV sodium bicarbonate infusion for her metabolic acidosis with ongoing antibiotic therapy ertapenem continued as per infectious diseases. She also received three doses of IV iron replacement therapy for her ongoing anemia.

On hospital day 12, she experienced a sudden and significant decline in her mental status, including visual hallucinations and increased somnolence. Given her known renal impairment, longstanding developmental delay, and hypoalbuminemia, a diagnosis of ertapenem-induced encephalopathy was strongly considered. Other potential causes of delirium—including intracranial pathology, metabolic disturbances, and active infection—were excluded via unremarkable CT imaging, laboratory studies, and negative infectious screening. Her medication list was also reviewed in detail and revealed no newly introduced neuroactive drugs.

A rapid response was initiated due to concern for declining level of consciousness. The patient was assessed by internal medicine and infectious disease teams, who concurred with the diagnosis of probable ertapenem neurotoxicity. Ertapenem was immediately discontinued and replaced with ceftriaxone to continue antimicrobial therapy for osteomyelitis. In parallel, two infusions of 25% albumin (100 mL each) were administered over 48 hours in an effort to bind residual free ertapenem and facilitate clearance. She also received haloperidol as needed to manage agitation. Over the following 48 hours, the patient demonstrated marked neurological improvement, with resolution of hallucinations and progressive normalization of her mental status, strongly supporting the diagnosis of ertapenem-induced encephalopathy.

Investigations:

On admission day 12, approximately three weeks after initiating ertapenem, the patient developed new and profound alterations in mental status. Nursing staff reported increased confusion and episodes of vivid visual hallucinations, including agitation and periods of unresponsiveness. An urgent CT head was performed and showed no acute intracranial pathology—no hemorrhage, mass effect, or ischemia. Serum glucose and electrolyte panel were within normal limits, and liver function testing was unremarkable. No hypoglycemia or hyponatremia was identified. Urine culture from her admission remained negative, and a repeat culture sent one week later was also negative. There was no evidence of systemic infection, and blood cultures remained sterile.

Other initial investigations completed in the emergency department including CT abdomen and pelvis demonstrated non-obstructive nephrolithiasis and bilateral hydroureteronephrosis, but no evidence of bowel obstruction, mass, or fluid collections. Stool and nasopharyngeal swabs were negative for Clostridioides difficile, influenza, RSV, and SARS-CoV-2.

Treatment:

Upon her admission for AKI and systemic symptoms, she continued receiving ertapenem, which was endorsed by both internal medicine and infectious diseases teams with an anticipated total duration of six weeks. Her acute kidney injury, thought to be multifactorial but predominantly pre-renal in origin, was managed with intravenous fluids and sodium bicarbonate infusion. Renal function showed slow but gradual improvement. She was also treated with intravenous iron sucrose receiving three doses in total to address significant microcytic anemia. Cardiology ruled out acute coronary syndrome, attributing ECG changes to uremic demand ischemia.

After developing altered mental status and hallucinations three weeks after starting the agent, ertapenem was promptly discontinued given high suspicion for drug-induced neurotoxicity. The patient was started on haloperidol 1 mg BID as needed to control agitation. Albumin 25% in 100 mL was administered daily for 48 hours in an attempt to enhance protein binding and clearance of circulating free ertapenem, based on its pharmacokinetic properties. This intervention was considered especially important in the context of her low serum albumin and impaired renal clearance.

Infectious diseases recommended switching her therapy to ceftriaxone 2 g IV daily to complete the remainder of her antibiotic course. This agent was selected for its comparable spectrum for skin/soft tissue and bone infections, and more favorable CNS side effect profile. The patient remained on ceftriaxone for a total of 6 weeks of antibiotic therapies, at which point her PICC line was removed, and no further antimicrobial follow-up was required unless symptoms recurred.

Discussion:

This case highlights a clinically significant but often under recognized adverse effect of ertapenem—drug-induced encephalopathy—in a high-risk patient. While imipenem is traditionally considered the carbapenem with the highest neurotoxicity risk, a growing body of literature now implicates ertapenem in similar central nervous system complications, particularly among patients with compromised renal function. ³ ⁷ The patient's constellation of risk factors—advanced chronic kidney disease and hypoalbuminemia—likely synergistically increased her susceptibility to neurotoxic effects. ³ These conditions contribute to impaired clearance, higher unbound drug concentrations, and enhanced CNS penetration of ertapenem, all of which facilitate neurologic side effects.

Mechanistically, carbapenem-induced neurotoxicity is attributed to the competitive inhibition of GABA-A receptors, resulting in impaired inhibitory neurotransmission and heightened CNS excitability. ⁸ This explains the wide spectrum of neurologic manifestations ranging from confusion and agitation to hallucinations and seizures. ⁹ In this case, the patient experienced vivid visual hallucinations and profound encephalopathy, with symptom onset approximately two weeks into therapy. Importantly, her presentation occurred in the absence of other metabolic, structural, or infectious causes, strengthening the causal association with ertapenem.

The diagnosis of ertapenem-induced neurotoxicity remains challenging, as symptoms are often nonspecific and may be misattributed to delirium, underlying dementia, or uremia. As such, recognition often requires a high index of suspicion and a structured process of exclusion. In our case, early identification and discontinuation of ertapenem were pivotal in reversing symptoms. Notably, the patient experienced rapid neurologic improvement within 48 hours of stopping ertapenem and initiating supportive measures, including albumin infusion and symptom-directed pharmacologic therapy. This time course aligns with prior case reports and reinforces the reversibility of symptoms with prompt intervention.

The use of intravenous 25% albumin to accelerate clearance of free ertapenem represents a novel and rational approach in this setting. ¹⁰ Ertapenem is highly protein-bound (85–95%), primarily to albumin, and hypoalbuminemia has been shown to significantly increase the free, pharmacologically active fraction of the drug, thus raising neurotoxicity risk. ¹¹ Studies in critically ill patients have demonstrated that hypoalbuminemia not only affects drug pharmacokinetics but also correlates with higher rates of adverse drug events, including neurotoxicity. ¹²

Albumin administration in hypoalbuminemic patients has been explored as a strategy to restore protein binding and reduce free drug concentrations, thereby mitigating toxicity. Although direct evidence in ertapenem neurotoxicity is limited, analogous clinical experience with other highly protein-bound drugs supports this approach. ¹³ An experimental pharmacokinetic study in sheep demonstrated that albumin replacement significantly altered the pharmacokinetics of highly protein-bound beta-lactams, including ceftriaxone and ertapenem, by reducing the apparent volume of distribution of total drug concentration. ¹⁰ However, published case reports involving albumin infusion in carbapenem-related neurotoxicity in humans are sparse, and further research is needed before this approach can be routinely recommended in clinical practice.

An important limitation in the evaluation of this case is the lack of therapeutic drug monitoring (TDM) for ertapenem. While TDM is increasingly used for beta-lactams in critically ill patients, no routine assays are currently available for ertapenem in most clinical settings. Although we did not obtain an ertapenem level in this patient, a recent study suggested that mean ertapenem trough concentrations may be significantly higher in patients with renal impairment, potentially exceeding pharmacodynamic targets.¹⁶ However, this small pharmacokinetic study did not correlate trough levels with neurotoxicity risk, and larger, prospective studies are needed to establish clinically relevant exposure thresholds. As such, the inability to quantify ertapenem levels in real time remains a barrier to early detection and mitigation of carbapenem-associated neurotoxicity.

To further evaluate the likelihood of a causal relationship between ertapenem and the patient's neurotoxicity, we applied the Naranjo Adverse Drug Reaction Probability Scale. The patient received a score of 7, indicating a probable adverse drug reaction. This was based on the temporal association of symptom onset with ertapenem therapy, lack of alternative explanations, improvement following drug discontinuation, and previous reports of similar reactions. No rechallenge was performed due to ethical concerns. While central nervous system infections were initially considered in the differential diagnosis, cerebrospinal fluid analysis, neuroimaging, and the absence of fever or leukocytosis made an infectious etiology highly unlikely. The structured application of the Naranjo tool supports ertapenem as the most plausible causative agent in this case.

This report is subject to several limitations. First, as a single case report, the findings may not be generalizable to broader patient populations. Second, the retrospective nature of the chart review introduces the possibility of incomplete documentation, particularly regarding the patient’s neurologic baseline and timeline of symptom onset. Third, while causality is strongly supported by the clinical course and resolution after drug discontinuation, rechallenge was not performed for ethical reasons, and serum ertapenem levels were not measured. Additionally, the use of albumin as an adjunctive therapy, while biologically plausible, lacks randomized data and cannot be definitively linked to the patient’s improvement. Finally, confounding variables such as uremia and polypharmacy, though carefully evaluated and deemed unlikely contributors, cannot be entirely excluded.

This case also underscores the need for careful antibiotic selection in patients with multiple medical comorbidities, particularly when initiating long-term intravenous therapy in outpatient settings. Risk stratification for neurotoxicity should include assessment of renal function, albumin levels, and pre-existing neurologic vulnerability. Dose adjustments, close therapeutic monitoring, and early follow-up should be considered standard practice for carbapenems in these populations.

Conclusion:

Ertapenem-induced encephalopathy is an important and potentially serious complication of antimicrobial therapy, particularly in patients with renal dysfunction and low albumin levels. Clinicians must maintain a high index of suspicion in patients who develop new neuropsychiatric symptoms while on carbapenems, particularly in the absence of clear metabolic, structural, or infectious causes. Prompt discontinuation of the offending agent and supportive measures can result in full neurologic recovery. Consideration should be given to adjunctive therapies such as albumin infusion to enhance clearance in hypoalbuminemic patients. This case underscores the importance of vigilant monitoring, individualized pharmacotherapy, and interdisciplinary collaboration in managing complex hospitalized patients.

**Declarations**

**Ethical Approval:** Ethical approval for the publication of this case report was obtained in accordance with the hospital’s guidelines for ethical conduct in case reporting.

**Consent for Publication:** Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Availability of Supporting Data:** Data supporting the findings of this study are available from the corresponding author upon reasonable request.

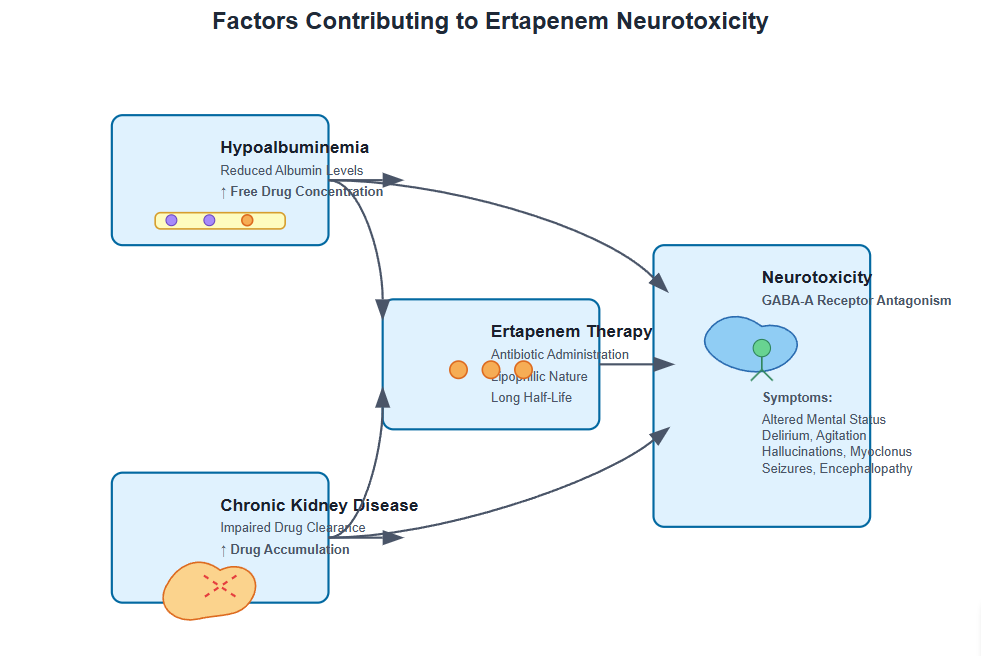
**Competing Interests:** The authors declare that they have no competing interests.

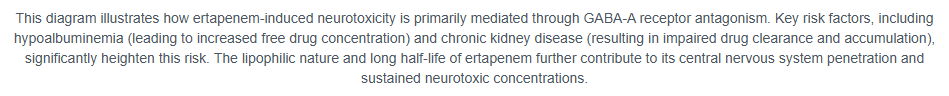
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*Appendix:*

**Diagram 1: Factors in Ertapenem-Induced Neurotoxicity**





**Table 1: Admission Day 1 Blood work in Emergency Department:**

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