

# Ertapenem-Induced Neurotoxicity: A Literature Review of Clinical Characteristics and Treatment Outcomes

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**Background:** Neurotoxicity is a rare adverse event for ertapenem. Given the limited evidence, large patient data are needed to aid in the identification and management of this fatal complication. Aim of the review, we summarize the characteristics, risk factors, and treatment of ertapenem-induced neurotoxicity.

**Methods:** Pubmed, Web of Science, Embase, Cochrane library, Wanfang, CNKI, China VIP database were searched up from 31 October 2001 to 31 December 2022. All articles concerning neurotoxicity induced by ertapenem were included. The retrieved articles were screened by two experienced clinicians by reading the titles, abstracts, and full texts.

**Results:** A total of 66 patients were included, with a median age of 71.5 years (range 40–92), of whom 45 (68.2%) were male. Twelve patients (18.2%) received irrational doses (exceeding the recommended dose), and 30 patients (45.5%) had chronic renal insufficiency. The median time to symptom onset was 5 (range 1–14). Epileptiform seizures (42.4%), visual hallucinations (36.4%), altered mental status (25.8%), and confusion (22.7%) were the most common symptoms of ertapenem-induced neurotoxicity. Of the 29 patients with reported albumin levels, 25 had serum albumin <3.5 g/dl. Ertapenem was discontinued in 95.5% of patients, and 90.9% recovered completely. Median time to symptom recovery was 7 days (range 1–42) after intervention including antiepileptic administration, or hemodialysis.

**Conclusion:** Neurotoxicity is a rare adverse event for ertapenem, especially in patients with advanced age, renal insufficiency, pre-existing neurological disease, and hypoalbuminemia. This adverse reaction usually resolves with medication interruption, or anti-epileptic administration and hemodialysis.

**Keywords:** ertapenem, carbapenem, neurotoxicity, encephalopathy, seizures

## Key Points

- Case reports of ertapenem -induced neurotoxicity were collected for retrospective analysis.
- Neurotoxicity is a rare adverse event for ertapenem, especially in patients with advanced age, renal insufficiency, pre-existing neurological disease, and hypoalbuminemia.
- Epileptiform seizures (42.4%), visual hallucinations (36.4%), altered mental status (25.8%), and confusion (22.7%) were the most common symptoms of ertapenem-induced neurotoxicity.
- Drug discontinuation is the most important treatment for ertapenem-induced neurotoxicity.

## Plain Language Summary

Neurotoxicity was a rare adverse event for ertapenem. On the other hand, reports of ertapenem-induced neurotoxicity have gradually increased. This study collected clinical reports of ertapenem-induced neurotoxicity, and summarized the occurrence and development of such adverse reactions, high-risk factors and treatment measures. A total of 66 patients were included, with a median age of 71.5

years, of whom 45 were male. Epileptiform seizures (42.4%), visual hallucinations (36.4%), altered mental status (25.8%), and confusion (22.7%) were the most common symptoms of ertapenem-induced neurotoxicity. Median time to symptom recovery was 7 days after intervention including antiepileptic administration, or hemodialysis. Clinicians should be aware of ertapenem-induced neurotoxicity and avoid extensive invasive testing and administration of antipsychotics.

## Introduction

Ertapenem is a 1-beta-methyl carbapenem that is stable to dehydropeptidases and binds better to penicillin-binding proteins (PBPs) 2 and 3 with bactericidal activity that acts by inhibition of the bacterial cell wall.<sup>1</sup> Carbapenems possess greatest broad-spectrum activity against gram-positive and gram-negative aerobic and anaerobic bacteria. Ertapenem, however, lacks the coverage against *Pseudomonas aeruginosa* and *Acinetobacter baumannii*<sup>1,2</sup> and thus exerts less selection pressure for resistance to these bacteria than do other carbapenems, which are usually used as treatments for community-acquired severe infectious diseases.<sup>3</sup> Ertapenem is a parenteral carbapenem with long-acting properties that is highly protein bound with a mean half-life of 3.8 to 4.4 hours.<sup>4</sup> The standard dose of 1 g of ertapenem once a day has been highly effective monotherapy for acute pelvic infections, complicated intra-abdominal, skin and urinary tract infections, and typical community-acquired pneumonia requiring hospitalization in clinical trials.<sup>5–7</sup> For patients with renal impairment, the Federal Drug Administration (FDA) and the European Medicines Agency (EMA) approved doses are 1 g per day if the creatinine clearance (CrCl) is >30 mL/min/1.73m<sup>2</sup>; when the CrCl is lower, ertapenem is not recommended in the European labelling, and only 500 mg per day can be used according to the FDA.<sup>8,9</sup>

Ertapenem is well tolerated, and the associated adverse reactions reported were mild to moderate. The most common drug-related adverse events (AEs) were diarrhea (5%), venous complications (4%), nausea (3%), and headache (2%).<sup>10</sup> On the other hand, reports of ertapenem-induced neurotoxicity have gradually increased.<sup>11,12</sup> Neurotoxicity has been described during treatment with all carbapenems, and the risk of seizures with imipenem, meropenem, and ertapenem is well described, whereby the most important issues are the dose and patient risk factors, such as renal insufficiency and underlying central nervous system abnormalities.<sup>13</sup> Neurotoxicity from ertapenem has frequently been described in patients with endstage renal dysfunction, as decreased renal function increases plasma ertapenem levels, suggesting that some patients with renal failure could potentially be overdosed, even if the correct doses are employed according to the product labelling.<sup>14,15</sup> However, the clinical features of ertapenem-induced neurotoxicity lack systematic research data. This results in the failure of medical staff to make timely diagnosis and treatment when ertapenem-induced neurotoxicity occurs in clinical practice. This study collected clinical reports of ertapenem-induced neurotoxicity, and summarized the occurrence and development of such adverse reactions, treatment measures and high-risk factors, in order to provide reference for medical staff to use safely and rationally.

## Methods

### Retrieval Strategy

We collected case reports and clinical studies of ertapenem-induced neurotoxicity by searching Chinese and English databases including Pubmed, Web of Science, Embase, Cochrane library, Wanfang, CNKI, China VIP database from 31 October 2001 to 31 December 2022. The search terms were “ertapenem”, “carbapenems”, “antibiotics”, “encephalopathy”, “epilepsy”, “seizure” and “neurotoxicity”. The inclusion criteria were case reports and case series related to ertapenem-induced neurotoxicity published in English and Chinese. The exclusion criteria were languages other than English or Chinese, duplicate literature, reviews, observational studies, mechanistic studies and animal studies.

### Data Collection

Two researchers independently conducted a preliminary screening of the literature according to the inclusion and exclusion criteria, and then the group discussed the literature to be included in the analysis. We extracted patients' basic information, clinical symptoms, laboratory tests, impact studies, treatment and prognosis based on self-designed table. The data was collected by 2 authors independently and crosschecked.

## Correlation Evaluation

Assessing the association between ertapenem and neurotoxicity based on 10 medically relevant questions provided by the Knott's Adverse Drug Reaction Scale.<sup>16</sup>

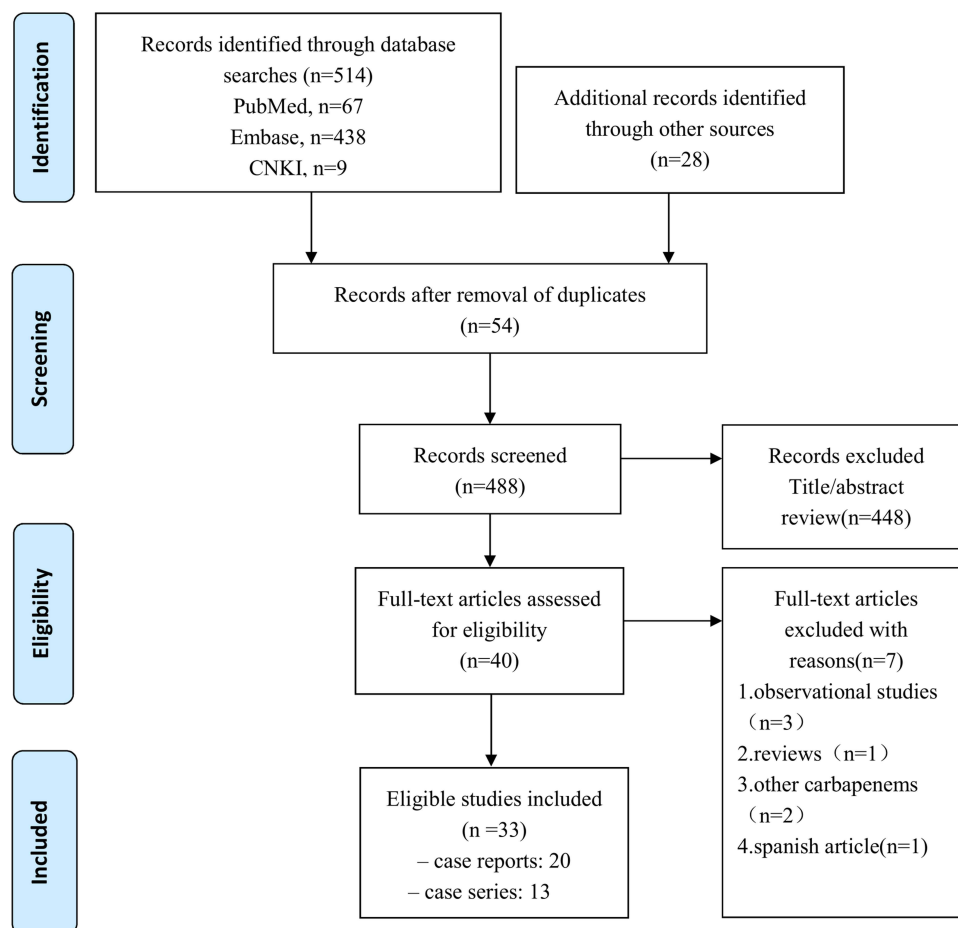
## Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM Corporation, Armonk, NY). The count data is expressed as n (%), and the measurement data is expressed as the median value (minimum, maximum).

## Results

### Basic Information

Sixty-six patients (45males and 21females) from 33 articles were identified (Figure 1), with a median age of 71.5 years (range 40–92). Table 1 summarizes the basic characteristics of the 66 patients. These patients were mainly from Asia (40.9%), Europe (28.8%) and North America (21.2%). Ertapenem was mainly used to treat urinary tract infection (36.4%), respiratory infection (19.7%) and soft tissue infection (16.7%). Thirty-seven patients (56.1%) were concomitantly using other treatments, and 62 patients (93.9%) a history of renal dysfunction, cardiovascular disease, endocrine system diseases, and other related diseases. Eight patients (12.1%) had a history of cerebral vascular accident, 2 patients (3.0%) had seizure, 1 patient (1.5%) central nervous system tumor, and 1 patient (1.5%) cortical arteriosclerotic encephalopathy.



**Figure 1** Flowchart of study selection and inclusion.

**Table I** Basic Information of 66 Patients

Parameter	Classification	Value	
Sex	Male	45 (68.2%)	
	Female	21 (31.8%)	
Age	Years	71.5 (40, 92) <sup>b</sup>	
Country	China	22 (33.3%)	
	USA	14 (21.2%)	
	Spain	14 (21.2%)	
	Singapore	3 (4.5%)	
	Chile	3 (4.5%)	
	Turkey	4 (6.1%)	
	Israel	2 (3.0%)	
	Australia	2 (3.0%)	
	Slovenia	1 (1.5%)	
	New Zealand	1 (1.5%)	
	Daily dose (61) <sup>a</sup>	0.5 g daily	18 (27.3%)
		1 g daily	41 (62.1%)
0.5 g every other day		1 (1.52%)	
0.5g daily (2 d), 1g daily		1 (1.52%)	
Dose appropriate (55) <sup>ac</sup>	Yes	43 (65.2%)	
	No	12 (18.2%)	
Time to symptoms onset (65) <sup>a</sup>	Days	5 (1.14)	
Indication (65) <sup>a</sup>	Urinary tract infection	24 (36.4%)	
	Respiratory infection	13 (19.7%)	
	Soft tissue infection	11 (16.7%)	
	Osteomyelitis	6 (9.1%)	
	Small bowel obstruction	3 (4.5%)	
	Fever	2 (3.0%)	
	Prophylactic	2 (3.0%)	
	Bacteremic	2 (3.0%)	
	Acute cholecystitis	1 (1.52%)	
	Brain abscess	1 (1.52%)	
	Bacteria (35) <sup>a</sup>	Escherichia coli	13 (19.7%)
		Klebsiella	9 (13.6%)
		Enterobacter cloacae	2 (3.0%)
		Proteus mirabilis	2 (3.0%)
Enterococcus faecalis		1 (1.52%)	
Morganella		1 (1.52%)	
Citrobacter koseri		1 (1.52%)	
Multiple mixed cultures		5 (7.6%)	
Actinomyces oris		1 (1.52%)	
Combination therapy (37) <sup>a</sup>		Cardiovascular drugs	15 (27.7%)
	Antibiotics	12 (18.2%)	
	Endocrine drugs	10 (15.2%)	
	Digestive drugs	10 (15.2%)	
	Nervous system drugs	9 (13.6%)	
	Urinary drugs	8 (12.1%)	
	Respiratory drugs	6 (9.1%)	
	Immunosuppressant	3 (4.5%)	

(Continued)

**Table 1** (Continued).

Parameter	Classification	Value
Medical history (62) <sup>a</sup>	Renal insufficiency	30 (45.5%)
	Cardiovascular disease	28 (42.4%)
	Endocrine system disease	24 (36.4%)
	Nervous system disease	19 (28.8%)
	Urinary system disease	11 (16.7%)
	Respiratory disease	8 (12.1%)
	Tumor	8 (12.1%)
History of encephalopathy (12) <sup>a</sup>	Autoimmune diseases	7 (10.6%)
	Cerebral vascular accident	8 (12.1%)
	Seizure	2 (3.0%)
	Central nervous system tumour	1 (1.5%)
	Cortical arteriosclerotic encephalopathy	1 (1.5%)

**Notes:** <sup>a</sup>Represents the number of patients out of 66 on which information regarding this particular parameter was provided. <sup>b</sup>Median (minimum-maximum). <sup>c</sup>Dose adjustment of ertapenem based on creatinine clearance (Clcr): Clcr >31 mL/min, 1 g daily; <30 mL/min, 0.5 g daily; hemodialysis, 0.5 g after each hemodialysis; continuous ambulatory peritoneal dialysis, 0.5 g daily. Appropriate dose: ertapenem dose adjustments based on calculated creatinine clearance. Irrational dose: the dose of ertapenem is not adjusted based on the calculated creatinine clearance rate and usually higher than the recommended dose.

## Ertapenem Administration

Ertapenem doses were reported in 61 patients (92.4%), of which 41 patients (62.1%) received 0.5 g daily, 1 patient (1.52%) 1 g daily, 1 patient (1.52%) 0.5 g every other day, and 5 patients (7.6%) received 0.5 g daily for the first two days, then 1 g daily. Based on the label-recommended dose, 43 patients (65.2%) received an appropriate dose and 12 patients (18.2%) received an irrational dose (exceeding the recommended dose). The median time to onset of neurotoxicity was 5 days (range 1–14).

## Clinical Symptoms

The symptoms of the 66 patients are summarized in Table 2. Epileptiform convulsions (42.4%) were the most common symptom of ertapenem-induced neurotoxicity, including myoclonus, convulsions, and epileptic seizures, followed by visual hallucinations (36.4%). The remaining common symptoms included altered mental status (25.8%), confusion (22.7%) and disorientation (16.7%). Other rare symptoms include forgetfulness (3.0%), cognitive impairment (3.0%), alert, dysarthria (3.0%), incoherent speech (3.0%), suicidal ideations (1.5%), sleepwalking (1.5%), paranoid (1.5%), miosis (1.5%), photopsia (1.5%).

## Laboratory Test

Serum albumin was described in 29 patients with a median of 2.8 g/dl (2.05, 3.8). Nine patients (31.0%) had serum albumin levels ≤ 2.5 g/dl, and 16 patients (55.2%) had serum albumin levels ranging from 2.6 to 3.5 g/dl. Twenty-eight patients (42.4%) had creatinine clearance >30 mL/min, 15 patients (22.7%) had creatinine clearance <30 mL/min, and 7 patients (10.6%) had hemodialysis, and 3 (4.5%) had peritoneal dialysis. Serum concentrations of ertapenem were monitored in 2 patients, which were 53.7 µg/mL and 150.7 µg/mL, respectively. The cerebrospinal fluid of 2 patients was examined, and the protein of cerebrospinal fluid was increased to 2.03 g/L in 1 patient.

## Imaging Examination

The imaging examinations of 65 patients are summarized in Table 2. Brain computed tomography (CT) showed normal in 23 of 27 patients (79.3%), cerebral atrophy in 3 patient (10.3%), old infarctions in 1 patient (3.4%), leukoaraiosis in 1 patient (3.4%), demyelination in 1 patient (3.4%). Brain magnetic resonance imaging (MRI) of 7 patients showed normal in 4 patients (57.1%), peripheral edema in 1 patient (14.3%), encephalomalacia in 1 patient (14.3%), and subcortical

**Table 2** Clinical Symptoms, Laboratory Tests and Imaging Examinations of 66 Patients

Parameter	Classification	Value
Symptoms	Epileptic seizures	28 (42.4%)
	Visual hallucinations	24 (36.4%)
	Altered mental status	17 (25.8%)
	Confusion	15 (22.7%)
	Disorientation	11 (16.7%)
	Numbness-weakness, gait abnormality	7 (10.6%)
	Delirium	7 (10.6%)
	Paraleresma	7 (10.6%)
	Tremors	6 (9.1%)
	Agitation	6 (9.1%)
	Insomnia	5 (7.6%)
	Disturbance of consciousness	5 (7.6%)
	Obtunded	4 (6.1%)
	Lethargic	4 (6.1%)
	Hyperexcitability	3 (4.5%)
	Forgetfulness	2 (3.0%)
	Cognitive impairment	2 (3.0%)
	Alert	2 (3.0%)
	Dysarthria	2 (3.0%)
	Incoherent speech	2 (3.0%)
Suicidal ideations	1 (1.5%)	
Sleepwalking	1 (1.5%)	
Paranoid	1 (1.5%)	
Miosis	1 (1.5%)	
Photopsia	1 (1.5%)	
Serum albumin (29) <sup>a</sup>	g/dl	2.8 (2.05, 3.8) <sup>b</sup>
	≤ 2.5	9 (31.0%)
	2.6 –3.5	16 (55.2%)
	> 3.5	4 (13.8%)
Ccr (53) <sup>a</sup>	>30	28 (42.4%)
	<30	15 (22.7%)
	Hemodialysis	7 (10.6%)
	Peritoneal dialysis	3 (4.5%)
CT (29) <sup>a</sup>	Normal	23 (79.3%)
	Cerebral atrophy	3 (10.3%)
	Leukoaraiosis	1 (3.4%)
	Demyelination	1 (3.4%)
	Old infarctions	1 (3.4%)
MRI (7) <sup>a</sup>	Normal	4 (57.1%)
	Peripheral edema	1 (14.3%)
	Encephalomalacia	1 (14.3%)
	Subcortical arteriosclerotic encephalopathy	1 (14.3%)
Electroencephalography (19) <sup>a</sup>	Normal	8 (42.1%)
	Diffuse slow wave abnormality	8 (42.1%)
	Metabolic encephalopathy	1 (5.3%)
	Widespread mild abnormalities	2 (10.5%)
Electromyography (3) <sup>a</sup>	Axonal motor Neuropathy	1 (33.3%)
	Sensorimotor polyneuropathy	2 (66.7%)

**Notes:** <sup>a</sup>Represents the number of patients out of 66 on which information regarding this particular parameter was provided. <sup>b</sup>Median (minimum-maximum).

**Abbreviations:** Ccr, Creatinine Clearance; CT, computed tomography; MRI, Magnetic Resonance Imaging.

**Table 3** Treatment and Prognosis of 66 Patients

Parameter	Classification	Value
Management	Discontinuation	63 (95.5%)
	Continue	3 (4.5%)
	Hemodialysis	8 (12.1%)
	Symptomatic treatment	19 (28.8%)
	Anticonvulsants	5 (7.6%)
	Antipsychotic	6 (9.1%)
	Antiepileptic drugs	10 (15.2%)
Outcome	Recovery	60 (90.9%)
	Death	3 (4.5%)
	Na	3 (4.5%)
Recovery (39) <sup>a</sup>	Days	7 (1, 42) <sup>b</sup>
Naranjo score	Probable	42 (63.6%)
	Possible	24 (36.4%)

**Notes:** <sup>a</sup>Represents the number of patients out of 66 on which information regarding this particular parameter was provided. <sup>b</sup>Median (minimum-maximum)

arteriosclerotic encephalopathy in 1 patient (14.3%). Electroencephalography of 19 patients showed diffuse slow wave abnormality in 8 patients (42.1%), metabolic encephalopathy 1 patients (5.3%), and widespread mild abnormalities in 2 patients (10.5%). Electromyography in 3 patients showed axonal motor neuropathy in 1 patient (33.3%) and sensorimotor polyneuropathy in 2 patients (66.7%).

## Treatment and Prognosis

The treatment and prognosis of the 65 patients are summarized in Table 3. Ertapenem was discontinued immediately in 63 patients (95.5%), and ertapenem was continued in 3 patients (4.5%). Eight patients (12.1%) received hemodialysis (HD) and 19 patients (28.8%) received antipsychotic, anticonvulsants, and antiepileptic drugs (28.8%). Ultimately, 60 patients (90.9%) recovered completely, 3 patients (4.5%) died, and 3 patients (4.5%) had no reported outcomes. The median time to recovery was 7 days (range 1–42) in 39 patients (59.1%).

## Correlation Evaluation

Using the Naranjo adverse drug reaction scale to assess the possibility of ertapenem and neurotoxicity, 42 patients (63.6%) were considered probable and 24 patients (36.4%) were possible.

## Discussion

Carbapenems are known to cause neurotoxicity by inhibiting GABA<sub>A</sub> receptors in the central nervous system, similar to other beta-lactams.<sup>17</sup> Carbapenem-induced neurotoxicity is via a side chain on the second carbon atom (C-2) in the carbapenem nucleus. Structural differences in the carbapenem C2 side chain have been shown to influence the propensity for this adverse effect.<sup>17,18</sup> Imipenem with the essential C-2 side chain increases binding to GABA<sub>A</sub>, making it more susceptible to neurotoxic adverse effects. In contrast, ertapenem has an acidic carboxyl group at the C-2 position, which binds the least to GABA<sub>A</sub> and is considered to have the lowest potential for neurotoxic activity.<sup>17</sup> The investigation results of Miller et al<sup>19</sup> seem to confirm the above theory, imipenem-cilastatin showed the highest rate of seizure rates among carbapenems (3–33%), while seizure rate caused by ertapenem, meropenem, and doripenem was rare (<1%). However, ertapenem-associated neurotoxicity is not uncommon in clinical practice. Although the value of spontaneous notification analysis is limited, a simple analysis of VigiBase®, the World Health Organization's global database for suspected adverse drug reactions (ADRs), shows different profiles for the different carbapenems: 27% of patients with suspected ADRs during ertapenem treatment exhibited neurologic or psychiatric reactions caused by or related with this drug, compared to 23% with imipenem and 6% with meropenem.<sup>20</sup> The total number of 66 cases collected in our study



also suggests that the neurotoxicity associated with ertapenem is not uncommon in clinical practice, which is enough to cause the attention of clinical physicians.

Risk factors for carbapenem neurotoxicity include advanced age, history of central nervous system disease, renal insufficiency, low body weight, and concomitant use of drugs that are nephrotoxic or that may lower the seizure threshold.<sup>21,22</sup> The median age of the patients included in this study was 71.5 years, 45.5% of the patients had previous renal insufficiency, and 28.8% of the patients had previous central nervous system diseases, similar to the above views. Firstly, the neurotoxic individuals in this study were mainly elderly, which was similar to the results of other carbapenems<sup>13</sup> and other studies related to ertapenem neurotoxicity.<sup>15,23</sup> In general, elderly patients are more likely to have chronic kidney disease and neurological disease, and are often treated with multiple drugs. In addition, several previous studies have shown that pre-existing central nervous system (CNS) disease, including prior cerebrovascular accident (thrombotic or embolic event), is a risk factor for seizures in ertapenem-treated patients.<sup>24–27</sup> A possible reason is that ertapenem may act as a mediator in lowering the seizure threshold in patients with preexisting neurological comorbidities.<sup>25</sup>

Renal dysfunction is one of the risk factors for central nervous system adverse reactions caused by ertapenem. Approximately 80% of ertapenem is excreted in the urine either unchanged or as a ring-opened metabolite.<sup>4,11,14</sup> Furthermore, The half-life of ertapenem in patients with normal renal function was reported to be around 4.4 hours, and it increases to 6.1 hours in moderate renal impairment, 10.6 hours in advanced renal impairment, and 14.1 to 19.3 hours in patients with chronic kidney disease stage 5 utilizing hemodialysis (CKD-5D).<sup>4,11,14,28</sup> In patients with renal insufficiency, free active ertapenem drug levels may be higher, and thus neurotoxicity may be increased. Wen et al<sup>29</sup> reported two patients with CKD-5 developed progressive neurotoxicity after receiving the recommended dose reduction for CKD of ertapenem (500 mg/d), they found that plasma ertapenem level measured 24 h after the last dose in Patient 2 was 53.7 mg/l, which is significantly higher than the therapeutic MIC 90 (2 mg/l) and the documented concentrations in patients with normal renal function 24 h after the administration of a single 1 g dose. On the other hand, ertapenem is highly lipophilic, but data on CNS penetration are scarce. In studies in rabbits,<sup>30</sup> the penetration of intravenous ertapenem to the cerebrospinal fluid was 7.1 and 2.4% into inflamed and uninfamed meninges, respectively. Therefore, high drug exposure in vivo may lead to increased cerebrospinal fluid concentration of ertapenem and induce neurotoxicity.

The presence of hypoalbuminemia may also be an independent risk factor for ertapenem-related seizures compared with other carbapenems.<sup>30,31</sup> The protein binding of ertapenem is 85–95%, which is inversely proportional to plasma concentration, which leads to its long elimination half-life.<sup>32</sup> In general, there is less protein-bound drug and greater volume of distribution in hypoalbuminemia. Although there were initially high concentrations of free and active drugs, they were quickly removed, resulting in a smaller reservoir of bound drugs. Faster clearance leads to shorter half-life and overall less drug exposure. However, the above situation is more in critically ill patients with normal or even increased renal clearance rate.<sup>11</sup> In patients with hypoalbuminemia and reduced renal clearance, free active ertapenem drug levels may be higher and therefore CNS toxicity may be increased.<sup>29,33,34</sup> Among patients with available serum albumin level data, 86% had hypoproteinemia. Moreover, most of the patients were elderly and about half of the patients had impaired renal function, suggesting that patients with advanced age or renal insufficiency with hypoproteinemia should be alert to ertapenem-related neurotoxicity.

Ertapenem-induced neurotoxicity favored male patients, which seems to be similar to the results of a retrospective study by El Nekidy et al<sup>15</sup> They retrospectively analyzed the occurrence of neurotoxicity in 99 dialysis patients using ertapenem. The results suggested that male (17%;  $p=0.014$ ), dementia (27%;  $p=0.012$ ) and concurrent use of  $\beta$ -lactams, aminoglycosides or fluoroquinolones (19.6%;  $p=0.042$ ) was an important predictor of seizures.

The optimal treatment regimen for ertapenem-induced neurotoxicity has not been elucidated. Drug discontinuation is the most important treatment for ertapenem-induced neurotoxicity. Symptoms may disappear within 1 day to 6 weeks after discontinuation of the drug. Patients with severe symptoms can be given symptomatic treatment such as sodium valproate. Since ertapenem can be removed by hemodialysis, the removal of ertapenem can be accelerated by hemodialysis. Symptoms recurred in three patients after re-exposure to low-dose ertapenem.<sup>26,35,36</sup> Here, we recommend that patients switch to a less neurotoxic drug rather than re-exposure to ertapenem.

Several limitations should be taken into consideration when interpreting the results of this review. First, we summarize the published case reports or series of reports. Not all patient data are complete, which affects the accuracy of the results to some extent. Secondly, an individual patient may have multiple risk factors, but due to the length of the



article, this article cannot be further analyzed. Finally, when analyzing the risk factors of ertapenem neurotoxicity, we only analyzed and described the current data, but not statistically analyzed the risk factors with significant differences. In the future, it is necessary to conduct cohort or case-control studies in the future to comprehensively analyze the risk factors of ertapenem neurotoxicity.

## Conclusion

Clinicians should be aware of the neurotoxicity of ertapenem, as it is widely used to treat multidrug-resistant bacterial infections. Patients with high risk factors (renal insufficiency, hypoalbuminemia, history of central nervous system disease, advanced age) should closely monitor the occurrence of neurotoxicity when using ertapenem. Regular reassessment of symptoms and renal function during treatment and dose adjustment may be useful, as caregivers and doctors can assess patients during visits to identify changes in mental status. Once relevant abnormalities occur, discontinuation of medication and appropriate treatment are necessary.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Disclosure

The authors report no conflicts of interest in this work.

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