scientific reports

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A disproportionality analysis of adverse events associated with ertapenem using the FAERS database from 2004 to 2024

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Through an in-depth analysis of ertapenem-associated adverse events (AEs) in the FDA Adverse Event Reporting System (FAERS) database, this study provides a reference for monitoring and safety management of ertapenem. Data from the FAERS database from Q1 2004 to Q1 2024 were analyzed via four nonproportional analysis techniques, including the reporting odds ratio (ROR). Gender, age, and sensitivity analyses were conducted for a more detailed assessment of ertapenem-associated signals. A total of 2,931 reports with ertapenem as the primary suspected drug were collected, covering 27 system organ classes (SOCs). The two SOCs with the strongest signals were nervous system disorders and psychiatric disorders, with overall stronger signals in individuals aged ≥ 65 years. The most frequently reported AEs were confusional state (*n* = 265) and convulsions (*n* = 214). Among the strongest signals were oropharyngeal edema (ROR = 191.05, 95% CI: 60.76–601.35) and granulomatous dermatitis (ROR = 150.49, 95% CI: 55.9–405.15). Eleven AEs not listed on the FDA label were identified. The top 20 AEs were predominantly associated with nervous system and psychiatric disorders, with a median time to onset ranging from 3.5 to 8.5 days. This study highlights the neuropsychiatric risks of ertapenem, providing strong evidence for its safety assessment and emphasizing the need for monitoring and individualized management in high-risk patients. Ertapenem, FAERS, Adverse events, Drug safety, Disproportionality analysis.

Ertapenem is a first-generation carbapenem antibiotic that exerts its antibacterial effect by binding to penicillin-binding proteins, thereby interfering with the synthesis of the bacterial cell wall[1]. The drug was approved in the United States in November 2001 and received approval in Europe in April 2002[2]. In both the United States and the European Union, ertapenem is indicated for community-acquired pneumonia (CAP), complicated intra-abdominal infections (cIAIs), and acute pelvic infections caused by susceptible strains. Additionally, other indications approved in the United States include complicated skin and skin structure infections (cSSSIs) and complicated urinary tract infections[3].

Ertapenem has a high protein binding rate of up to 85–95%, resulting in a prolonged elimination half-life, which allows for once-daily dosing advantages. Despite the significant increase in resistance to carbapenem antibiotics among gram-negative bacteria[4], several studies have demonstrated the success of double-carbapenem therapy based on ertapenem in treating infections caused by carbapenemase-producing *Klebsiella pneumoniae*[5–7]. Therefore, ertapenem remains an important option for the treatment of various bacterial infections.

As the clinical use of ertapenem has increased, reports of drug-associated adverse events (AEs) have also increased. Common AEs include gastrointestinal reactions (such as nausea and vomiting)[8], neurotoxicity (such as seizures, altered consciousness, and hallucinations)[9], and liver function abnormalities[10], among others. Additionally, isolated case reports have documented rare but severe AEs, such as acute generalized exanthematous pustulosis[11]. However, existing AE reports mainly consist of case reports or small-scale studies, and lack large-scale systematic analyses, which limit a comprehensive understanding of the potential effects of ertapenem.

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The U.S. food and drug administration (FDA) adverse event reporting system (FAERS) database, one of the most influential drug safety monitoring systems globally, provides a wealth of spontaneous reporting data on drug safety. By analyzing the FAERS database, we can better assess the safety of ertapenem in a broad population, particularly in identifying rare or severe AEs. This study aims to provide a reference for drug monitoring and management of ertapenem through an in-depth analysis of its AEs in the FAERS database.

Materials and methods

This study was conducted in accordance with the reporting of a disproportionality analysis for drug safety signal detection via individual case safety reports in pharmacovigilance (READUS-PV) guidelines[12,13].

Data sources and extraction

The FAERS database, updated quarterly by the FDA, is a key drug surveillance system. It contains seven files: DEMO (patient demographics), DRUG (drug/biologic information), REAC (all terms coded for events), OUTC (patient outcomes), RPSR (report source), THER (start and end dates of drug therapy), and INDI (all terms coded for indications). FAERS collects spontaneous AE reports from healthcare professionals, manufacturers, and patients worldwide and is widely used for drug safety information.

Following the FDA's recommended method for removing duplicate reports, the report with the highest FDA_DT value was retained for identical case IDs, and for those with the same case ID and FDA_DT, the report with the highest primary ID was retained. This study focused on reports in which ertapenem was the primary suspect (PS) drug. Data on AE report sources, patient gender, age, and clinical outcomes were extracted for descriptive analysis. AE reports were standardized and classified using preferred terms (PTs) and system organ classes (SOCs) per MedDRA 26.0.

This study extracted ertapenem data from FAERS (Q1 2004–Q1 2024), cleaned and analyzed using R (v4.3.2) and Excel 2016. The data processing workflow is shown in Fig. 1.

AE signal detection

The FAERS database contains many drugs similar to ertapenem in population and indications, providing sufficient reports for signal detection. This study used all drugs except ertapenem as controls for disproportionality analysis to reduce bias and improve comprehensiveness. Various disproportionality analysis techniques were utilized for the comprehensive detection of drug safety signals, including the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma-Poisson shrinker (MGPS), to uncover AE signals. The two-by-two table for understanding these methods is provided in Supplementary Table S1, and the formulas and thresholds are provided in Supplementary Table S2.

The ROR offers high sensitivity for rapid detection of potential signals, while the PRR provides greater specificity. The BCPNN and MGPS remain reliable for rare AEs. To reduce false negatives, statistical shrinkage

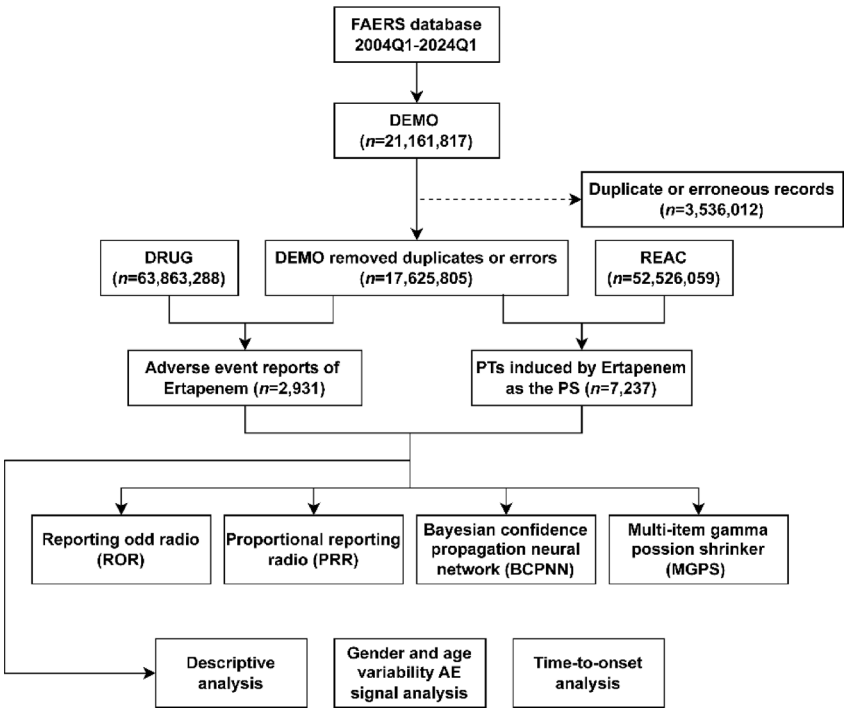


Fig. 1. A flowchart of the whole study. AE, adverse event; DEMO, demographics; DRUG, drug; FAERS, the FDA Adverse Event Reporting System; PS, primary suspect, preferred term; REAC, reaction; PT, preferred term.

was applied to the BCPNN. To minimize false positives and improve detection accuracy, PTs with ≥3 reports were selected, excluding non-AEs and indication-related events of ertapenem. Bonferroni correction was also employed to further reduce false positives.

We quantified and compared AE signal strengths using ROR values, where higher values indicate stronger signals. Multiple algorithms improved result reliability, supporting clinical drug safety and further research.

Sensitivity analysis

Concomitant drug use is common in clinical practice and may influence ertapenem-associated AEs, affecting signal detection. To enhance analytical robustness and minimize confounding bias, we first applied the Random Forest algorithm to impute missing data for gender, age, primary disease, top 10 concomitant drugs, reporting region, and reporter. Subsequently, we conducted a sensitivity analysis using multivariable logistic regression to adjust the ROR, thereby improving the reliability of AE signal detection.

Gender differences and age analysis

To explore the potential impact of gender and age on ertapenem- associated AEs, we performed a differential analysis and used the Random Forest algorithm to impute missing data, reducing potential bias.

Time to onset (TTO) analysis

TTO refers to the time between AE onset and drug initiation. After excluding reports with missing or inaccurate dates and those where AE onset preceded drug initiation, we assessed TTO using median, quartile, and Weibull shape parameter analyses[14]. Weibull shape parameter analysis is used to determine the proportional changes in AEs, indicating whether the signal increases or decreases over time.

The Weibull shape parameter has two main parameters: the scale (α) and the shape (β). This study primarily focuses on the significance of the β value: if $\beta < 1$ and the 95% confidence interval (CI) < 1, the signal of AEs decreases over time, referred to as the early failure type; if β is approximately equal to 1 and the 95% CI includes 1, the signal does not change over time, known as the random failure type; if the shape parameter $\beta > 1$ and the 95% CI does not include 1, the signal increases over time, referred to as the wear-out failure type[15,16].

Results

General characteristics

After removing duplicates, we collected 2,931 AEs associated with ertapenem from the FAERS database, spanning from Q1 2013 to Q1 2024.

The general characteristics of the relevant AEs are shown in Table 1. Among 2,601 with reported gender, 1,160 were female (39.58%), and 1,441 were male (49.16%). 70.62% of reports lacked weight information. Among the 2,203 reports with age data, 57 (1.94%) were ≥17 years, 866 (29.55%) were 18–64 years, 971 (33.13%) were 65–84 years, and 309 (10.54%) were ≥85 years. Most reports were submitted by healthcare professionals ($n = 2,421$, 82.77%), supporting data reliability. The most common clinical outcome was other serious illnesses ($n = 1,280$, 43.67%), followed by hospitalization ($n = 1,207$, 41.18%), life-threatening events ($n = 232$, 7.92%), and death ($n = 176$, 6.00%). The United States reported the most cases ($n = 1,445$, 49.30%), followed by France ($n = 270$, 9.21%), Spain ($n = 204$, 6.96%), and China ($n = 145$, 4.95%). Figure 2A showed the annual AE reporting trends, with the lowest in 2005 ($n = 55$, 1.88%) and a peak in 2023 ($n = 229$, 7.81%).

Signal detection at the SOC level

The number of reports and signal strength for ertapenem at the SOC level are detailed in Supplementary Table S3. The relevant AEs involved 27 SOCs, with the top five by report count being nervous system disorders ($n = 1,534$, 21.20%), psychiatric disorders ($n = 1,056$, 14.59%), general disorders and administration site conditions ($n = 870$, 12.02%), injury, poisoning and procedural complications ($n = 743$, 10.27%), and skin and subcutaneous tissue disorders ($n = 474$, 6.55%).

Among the four disproportionality analysis methods, five SOCs presented at least one positive signal: nervous system disorders ($n = 1,534$, 21.20%), psychiatric disorders ($n = 1,056$, 14.59%), skin and subcutaneous tissue disorders ($n = 474$, 6.55%), blood and lymphatic system disorders ($n = 211$, 2.92%), and hepatobiliary disorders ($n = 113$, 1.56%), as shown in Supplementary Table S3. The first two SOCs met the criteria of all four methods and had the highest ROR values, while the latter three SOCs satisfied the ROR and BCPNN methods. Figure 2B displays the forest plot of the ROR values and their 95% confidence intervals (CIs) for the SOC signals related to ertapenem. The Bonferroni-corrected P-values for all five SOCs were < 0.001 (Supplementary Table S3).

Signal detection at the PT level

A total of 104 PTs associated with ertapenem showed positive signals across all four algorithms. Except for hepatitis cholestatic and eye movement disorder, all had Bonferroni-corrected P-values below 0.05 (Supplementary Table S4). These PTs were grouped by SOC and ranked by ROR values. Figure 3 illustrates the ROR results, with log-transformed values. The five AEs with the highest ROR values were oropharyngeal edema (ROR = 191.05, 95% CI: 60.7–601.35), granulomatous dermatitis (ROR = 150.49, 95% CI: 55.9–405.15), toxic encephalopathy (ROR = 80.55, 95% CI: 59.59–108.88), decreased convulsive threshold (ROR = 80.23, 95% CI: 29.94–214.99), and mental disorders due to a general medical condition (ROR = 78.91, 95% CI: 25.29–246.24).

The PTs that exceeded 50 included confusional state ($n = 265$), convulsions ($n = 214$), hallucination ($n = 181$), seizure ($n = 144$), epilepsy ($n = 107$), delirium ($n = 100$), encephalopathy ($n = 81$), mental status changes ($n = 61$), visual hallucination ($n = 61$), agitation ($n = 58$), disorientation ($n = 55$), and neurotoxicity ($n = 53$). These findings aligned with FDA drug label warnings. Notably, we found several AEs not listed in the FDA warnings, including leukocytosis ($n = 9$), apnoea ($n = 7$), purpura ($n = 6$), decubitus ulcer ($n = 6$), decreased anticonvulsant drug level

Categories	Case number	Case proportion (%)
All report	2931	100.00
Sex		
Female	1160	39.58
Male	1441	49.16
Missing	330	11.26
Weight		
< 50 kg	80	2.73
50–100 kg	600	20.47
> 100 kg	181	6.18
Missing	2070	70.62
Age		
≤ 17	57	1.94
18–64	866	29.55
65–84	971	33.13
≥ 85	309	10.54
Missing	728	24.84
Reporter		
Consumer	450	15.35
Health-professional	418	14.26
Physician	925	31.56
Other health-professional	469	16.00
Pharmacist	614	20.95
Missing	55	1.88
Outcomes [a]		
Death	176	6.00
Life-threatening	232	7.92
Disability	122	4.16
Hospitalization	1207	41.18
Required Intervention	40	1.36
Other serious illness	1280	43.67
Missing	685	23.37
Reported countries (show top five)		
United States	1445	49.30
France	270	9.21
Spanish	204	6.96
China	145	4.95
United Kingdom	102	3.48
Other	556	18.97
Missing	209	7.13
Report year		
2004	114	3.89
2005	55	1.88
2006	87	2.97
2007	93	3.17
2008	104	3.55
2009	78	2.66
2010	73	2.49
2011	84	2.87
2012	95	3.24
2013	194	6.62
2014	162	5.53
2015	200	6.82
2016	144	4.91
2017	147	5.02
2018	172	5.87
2019	215	7.34
Continued		

Categories	Case number	Case proportion (%)
2020	201	6.86
2021	190	6.48
2022	203	6.93
2023	229	7.81
2024 Q1	91	3.10

Table 1. Cases characteristics on AEs related to ertapenem. [a] Since a case may experience different clinical outcomes during drug therapy, it is reasonable that the sum percentage of the outcome under this item may exceed 100%.

($n=6$), enterococcal infection ($n=6$), sleep talking ($n=5$), hepatic cytolysis ($n=5$), Acinetobacter infection ($n=4$), cerebellar syndrome ($n=4$), cerebral atrophy ($n=4$), and acquired haemophilia ($n=3$).

Sensitivity analysis

To enhance the reliability of our findings, we first applied the Random Forest algorithm to impute missing data for gender, age, primary disease, the top 10 concomitant drugs, reporting region, and reporter, followed by multivariable logistic regression to adjust the ROR. Cases in which ertapenem was the PS drug were examined, and the top 10 concomitant drugs were identified. Acetaminophen, vancomycin, and furosemide were the most frequently used. Based on FDA label information, we determined whether these concomitant drugs had warnings for corresponding systemic toxicity (Supplementary Table S5).

Sensitivity analysis of the five SOCs with at least one positive signal in the disproportionality analysis showed that the signals remained robust after adjusting for six variables (adjusted ROR > 1, $P<0.05$; Table 2). Additionally, sensitivity analysis of the 12 AEs not listed in the FDA warnings showed that after adjusting for six variables, all maintained significant signals except for apnoea (adjusted ROR > 1, $P<0.05$; Table 3).

Gender differences and age analysis

We conducted a gender-differential analysis using the ROR method, with results in Supplementary Table S6 and the forest plot in Fig. 4A. AEs with stronger signals in females included hypotension, acute renal failure, agitation, confusional state, dysarthria, clostridium difficile colitis, and drug interactions. In males, somnolence, dizziness, muscular weakness, arthralgia, urinary tract infection, pain, abasia, general physical deterioration, nausea, dysphagia, diarrhea, and swollen tongue showed stronger signals.

We similarly performed an age-differential analysis using the ROR method for age groups (≥ 65 years vs. 18–64 years), excluding those ≤ 17 years due to insufficient reports. Results are presented in Supplementary Table S7 with the forest plot shown in Fig. 4B. Except for hypoesthesia and convulsions, signals for psychiatric and nervous system disorders were stronger in patients aged ≥ 65 years, with disorientation (ROR = 6.61, 95% CI: 2.643–16.6) showing the strongest signal. Additionally, muscular weakness, falls, asthenia, and death also exhibited stronger signals in this group. In contrast, hypoesthesia, septic shock, drug resistance, drug inefficacy, and drug interactions showed stronger signals in the 18–64 age group.

TTO analysis

We selected the top 20 PTs based on report count. Except for muscular weakness, pathogen resistance, and neutropenia, the remaining 17 PTs belonged to psychiatric disorders or nervous system disorders. After excluding reports with inaccurate or missing dates and those where AE onset preceded drug initiation, we sorted them in descending order and conducted a TTO assessment (Table 4).

The results showed that due to the lack of available reports for convulsions and grand mal convulsions, the median onset time for the 18 PTs was relatively short. The shortest onset times were observed for epilepsy (IQR: 2.5–5.5) and muscular weakness (IQR: 0.5–7.0), both at 3.5 days, while the longest onset time was for dysarthria (IQR: 2.5–12.5), at 8.5 days. Seventeen PTs were eligible for Weibull shape parameter analysis. Confusional state, hallucination, epilepsy, encephalopathy, and status epilepticus were categorized as early failure types, while agitation and disorientation were wear-out failure types. Seizure, delirium, mental status changes, visual hallucination, neurotoxicity, myoclonus, toxic encephalopathy, neutropenia, muscular weakness, and dysarthria were classified as random failure types.

Discussion

We analyzed FAERS data from Q1 2004 to Q1 2024 to assess ertapenem-associated AEs using a large database.

Our study indicated that ertapenem-associated AEs primarily occurred in the elderly individuals (≥ 65 years), with higher reporting rates in males, likely due to the drug's common indications (e.g., CAP, cIAI, cSSSI) in older men[17–19]. Most reports lacked weight data, limiting weight-associated analysis. The reports were predominantly from the United States, reflecting regional differences. Hospitalizations and other serious illnesses constituted the majority of AEs, highlighting the need for close monitoring. Since 2013, reporting has remained high, potentially linked to increased ertapenem use. This distribution no longer aligns with the Weber effect (i.e., AE reports peak in the second year postlaunch, and then decline). Hoffman et al. analyzed AE reports for 62 new drugs (2006–2010), suggesting that modern FAERS data no longer follow the Weber effect trend[20].

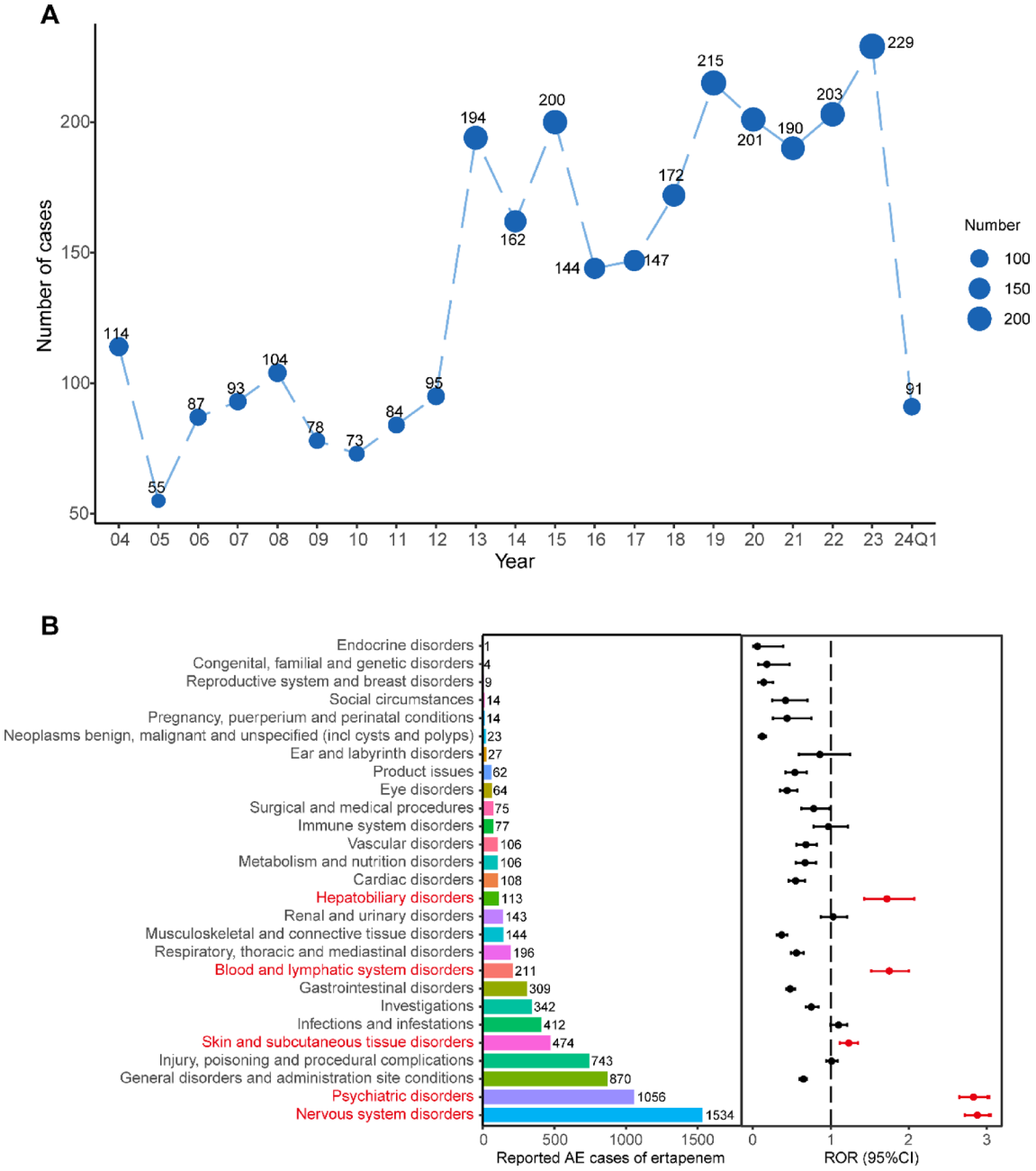


Fig. 2. Signal detection at the SOC level. (**A**) Distribution of AEs of ertapenem from 2004 to the first quarter of 2024 (2024Q1). (**B**) The bar chart displays the reported cases of AEs at each SOC level. The ROR values and their 95% confidence intervals (95% CI) displays the disproportionate signal values. We label the SOCs with positive signal values to make a distinction. FAERS, FDA Adverse Event Reporting System; AEs, adverse events; SOC, System Organ Class; ROR, reporting odds ratio.

On the basis of the disproportionate analysis results of this study, the following section discusses the important AEs associated with ertapenem:

AEs associated with psychiatric disorders and nervous system disorders

This study revealed that nervous system disorders and psychiatric disorders had the highest number of reports and strongest signals among ertapenem-associated AEs. All AEs reported in numbers exceeding 50 were linked to these two SOCs, with the top five AEs being confusional state, convulsion, hallucination, seizure, and epilepsy. These findings underscore the association between ertapenem and neuropsychiatric disorders. Danés et al. reported 10 cases, while Hayato Mitaka et al. analyzed 125 suspected neurotoxicity cases related to ertapenem, both highlighting the need to address this issue[21,22]. Our study also found a substantial number of neurotoxicity reports, further supporting this concern.

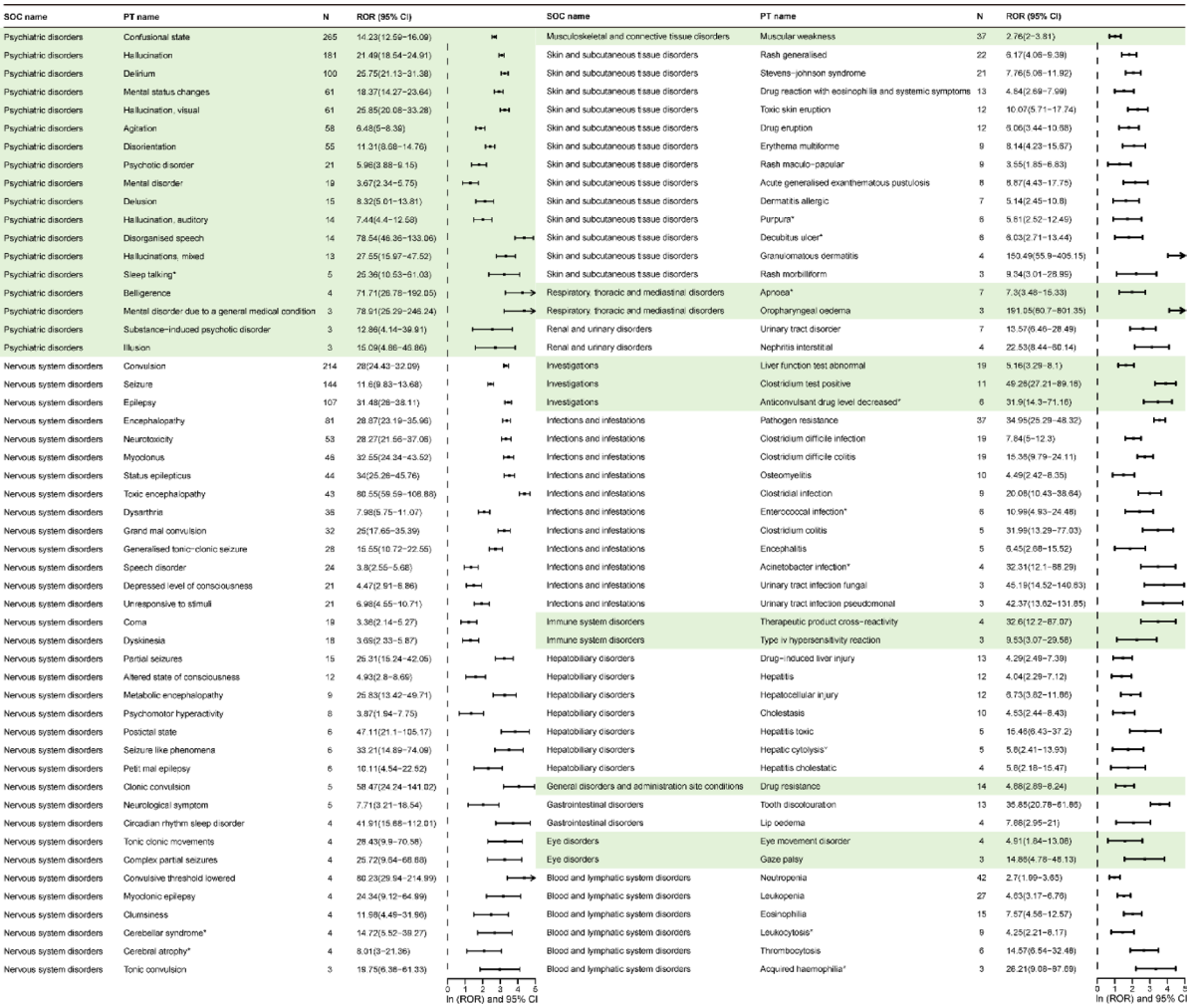


Fig. 3. Signal detection at the PT level. All PTs met four signal-positive criteria, and the forest plot was used to display the ROR and corresponding 95% CI. *, FDA label instructions for Ertapenem do not warn of this adverse event. SOC, System Organ Class; PT, preferred term; ROR, reporting odds ratio; 95% CI, 95% confidence intervals.

SOC names	Estimate	Standard error	Z value	aROR (95%CI) [a]	*P* value
Nervous system disorders	0.946	0.028	33.786	2.58 (2.44–2.72)	< 0.001
Psychiatric disorders	0.826	0.035	23.601	2.28 (2.13–2.45)	< 0.001
Skin and subcutaneous tissue disorders	0.128	0.050	2.559	1.14 (1.03–1.25)	0.010
Blood and lymphatic system disorders	0.352	0.075	4.693	1.42 (1.23–1.65)	< 0.001
Hepatobiliary disorders	0.344	0.097	3.546	1.41 (1.17–1.71)	< 0.001

Table 2. Sensitivity analysis of SOC level with at least one of the four Methods of disproportionality analysis Met the criteria. [a] The aROR represents the adjusted reporting odds ratio. The aROR is adjusted for sex, age, primary disease, concomitant drugs, reporting region, and reporter.

We believe that ertapenem-induced neuropsychiatric disorders are multifactorial. β-lactam antibiotics, including ertapenem, may cause neurotoxicity by antagonizing γ-aminobutyric acid type A (GABAA) receptors, particularly in patients with renal insufficiency, advanced age, or a compromised blood-brain barrier[22–24]. Approximately 80% of ertapenem is excreted in urine, with its half-life increasing as renal function declines. Even in uremic patients undergoing hemodialysis, ertapenem's half-life remains significantly prolonged[25,26]. Drug accumulation in renal insufficiency patients may increase free active ertapenem levels, heightening neuropsychiatric risk[27,28]. The European Medicines Agency does not recommend ertapenem for patients with severe renal impairment[29]. Additionally, its high protein-binding rate means that hypoalbuminemia increases unbound drug levels, enhancing cerebrospinal fluid penetration and potentially triggering neuropsychiatric

PT	Estimate	Standard error	Z value	aROR (95% Cl) [a]	*P* value
Psychiatric disorders					
Sleep talking	2.749	0.459	5.989	15.63 (6.36–38.420)	< 0.001
Nervous system disorders					
Cerebellar syndrome	1.983	0.512	3.873	7.26 (2.66–19.82)	< 0.001
Cerebral atrophy	1.123	0.506	2.219	3.07 (1.14–8.29)	0.027
Skin and subcutaneous tissue disorders					
Purpura	1.328	0.417	3.185	3.77 (1.37–8.54)	0.002
Decubitus ulcer	1.394	0.410	3.397	6.03 (2.71–13.44)	< 0.001
Respiratory, thoracic and mediastinal disorders					
Apnoea	0.729	0.384	1.898	2.07 (0.98–4.40)	0.058
Investigations					
Anticonvulsant drug level decreased	2.238	0.426	5.235	9.37 (4.07–21.61)	< 0.001
Infections and infestations					
Enterococcal infection	2.129	0.415	5.130	8.41 (3.73–18.96)	< 0.001
Acinetobacter infection	3.024	0.521	5.803	20.57 (7.41–57.12)	< 0.001
Hepatobiliary disorders					
Hepatic cytolysis	1.029	0.462	2.227	2.80 (1.13–6.92)	0.026
Blood and lymphatic system disorders					
Leukocytosis	0.827	0.349	2.369	2.29 (1.15–4.53)	0.018
Acquired haemophilia	1.877	0.598	3.139	6.53 (2.02–21.10)	0.002

Table 3. Sensitivity analysis of adverse events not listed in FDA label. [a] The aROR represents the adjusted reporting odds ratio. The aROR is adjusted for sex, age, primary disease, concomitant drugs, reporting region, and reporter.

disorders[21,28]. These factors may contribute to toxic or metabolic encephalopathy, both of which showed signals in this study. The signal for toxic encephalopathy was significantly elevated (ROR = 80.55, 95% CI: 59.59-108.88), and convulsive threshold lowering also had a strong signal (ROR = 80.23, 95% CI: 29.94-214.99). Additionally, ertapenem was associated with decreased anticonvulsant drug levels, this PT not mentioned in FDA warnings. This may reduce anticonvulsant efficacy, increasing seizure. A retrospective study found that ertapenem lowered valproate levels, further predisposing patients to seizures[30]. By diminishing anticonvulsant effectiveness, ertapenem may be one of the potential mechanisms leading to neuropsychiatric disorders, warranting further investigation.

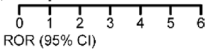
This study revealed gender differences in neuropsychiatric disorders induced by ertapenem. Stronger signals for neuropsychiatric AEs in females were observed for agitation, confusional state, and dysarthria, while in males, somnolence and dizziness showed stronger signals. Supporting this, an analysis of 125 suspected neurotoxicity cases associated with ertapenem by Hayato Mitaka et al. found that 64% of the patients were male[22]. While hypoaesthesia and convulsions showed stronger signals in the 17–64 year age group, other neuropsychiatric disorders had stronger signals in the elderly (≥ 65 years). Among these, disorientation exhibited the highest signal, followed by elevated signals for unresponsive to stimuli, encephalopathy, insomnia, and status epilepticus. These findings may be linked to the higher signals for encephalopathy and neurotoxicity observed in older patients. After ertapenem was used, the plasma concentration in older adults was relatively greater than that in younger individuals[2], and an analysis by Wang et al.[28] also indicated that older age was a risk factor for ertapenem-associated neuropsychiatric disorders. These findings underscore the importance of considering the impact of gender and age on ertapenem- associated AEs in clinical practice.

In this study, the median TTO for neuropsychiatric AEs among the top 20 AEs ranged from 3.5 to 8.5 days, similar to the 4-day median TTO (IQR: 3–9) reported by Hayato Mitaka et al.[22]. Lee et al.[9] reported TTO for seizures of 3.3 ± 2.6 days, while our results showed a median of 5.5 days (IQR: 2.5–8.5), with a minimal difference between the two findings. These findings suggest that the neuropsychiatric disorders induced by ertapenem occurred relatively quickly, typically within a few days after administration. The median TTO in our study was consistent with that reported in previous studies, further validating the rapid onset characteristics of these AEs. Weibull shape parameter analysis showed that signals for certain AEs such as confusional state, hallucination, epilepsy, encephalopathy, and status epilepticus decreased over time, while signals for agitation and disorientation increased. This indicates that monitoring priorities should be adjusted on based on signal changes: early focus on the former, and continued monitoring of the latter. AEs such as seizure, delirium, mental status changes, visual hallucinations, neurotoxicity, myoclonus, toxic encephalopathy, and dysarthria, which present as random failure types, can occur at any time throughout the treatment course, highlighting the need for ongoing monitoring of these AEs.

Future cohort or case-control studies are needed to further explore the factors influencing neuropsychiatric disorders associated with ertapenem, focusing on how patient characteristics (e.g., underlying conditions and drug regimens) impact the signal of neuropsychiatric disorders.

A

SOC name	PT name	Female/Male	ROR (95% CI)
Vascular disorders	Hypotension	7 / 21	0.41(0.17–0.96)
Renal and urinary disorders	Renal Failure Acute	3 / 14	0.26(0.08–0.91)
Psychiatric disorders	Agitation	14 / 44	0.39(0.21–0.71)
Psychiatric disorders	Confusional State	99 / 166	0.72(0.56–0.93)
Nervous system disorders	Somnolence	26 / 15	2.14(1.13–4.04)
Nervous system disorders	Dizziness	27 / 18	1.85(1.02–3.36)
Nervous system disorders	Dysarthria	8 / 28	0.35(0.16–0.77)
Musculoskeletal and connective tissue disorders	Muscular Weakness	23 / 14	2.02(1.04–3.94)
Musculoskeletal and connective tissue disorders	Arthralgia	8 / 2	4.92(1.04–23.17)
Infections and infestations	Urinary Tract Infection	16 / 6	3.28(1.28–8.4)
Infections and infestations	Clostridium Difficile Colitis	4 / 15	0.33(0.11–0.98)
General disorders and administration site conditions	Pain	18 / 5	4.44(1.64–11.96)
General disorders and administration site conditions	Abasia	8 / 1	9.84(1.23–78.68)
General disorders and administration site conditions	General Physical Health Deterioration	8 / 2	4.92(1.04–23.17)
General disorders and administration site conditions	Drug Interaction	9 / 25	0.44(0.21–0.94)
Gastrointestinal disorders	Nausea	36 / 17	2.62(1.47–4.67)
Gastrointestinal disorders	Dysphagia	8 / 1	9.84(1.23–78.68)
Gastrointestinal disorders	Diarrhoea	35 / 22	1.96(1.15–3.35)
Gastrointestinal disorders	Swollen Tongue	8 / 2	4.92(1.04–23.17)



B

SOC name	PT name	≥65/18–64	ROR (95% CI)
Psychiatric disorders	Disorientation	50 / 5	6.61(2.63–16.6)
Psychiatric disorders	Confusional State	211 / 52	2.74(2.02–3.73)
Psychiatric disorders	Delirium	73 / 27	1.78(1.14–2.78)
Psychiatric disorders	Hallucination	127 / 54	1.56(1.13–2.15)
Psychiatric disorders	Insomnia	17 / 3	3.72(1.09–12.71)
Psychiatric disorders	Hallucination, Visual	45 / 16	1.85(1.04–3.28)
Psychiatric disorders	Mental Disorder	16 / 3	3.5(1.02–12.02)
Product issues	Product Quality Issue	6 / 17	0.23(0.09–0.58)
Nervous system disorders	Encephalopathy	68 / 12	3.75(2.03–6.95)
Nervous system disorders	Status Epilepticus	36 / 7	3.39(1.5–7.62)
Nervous system disorders	Somnolence	33 / 8	2.71(1.25–5.88)
Nervous system disorders	Epilepsy	78 / 27	1.91(1.23–2.96)
Nervous system disorders	Neurotoxicity	41 / 12	2.25(1.18–4.29)
Nervous system disorders	Unresponsive To Stimuli	18 / 3	3.94(1.16–13.39)
Nervous system disorders	Speech Disorder	20 / 4	3.28(1.12–9.62)
Nervous system disorders	Seizure	98 / 41	1.58(1.09–2.28)
Nervous system disorders	Hypoaesthesia	1 / 7	0.09(0.01–0.76)
Nervous system disorders	Convulsion	105 / 107	0.63(0.48–0.83)
Musculoskeletal and connective tissue disorders	Muscular Weakness	28 / 8	2.3(1.05–5.05)
Investigations	Aspartate Aminotransferase Increased	4 / 10	0.26(0.08–0.83)
Investigations	Alanine Aminotransferase Increased	5 / 10	0.33(0.11–0.96)
Injury, poisoning and procedural complications	Fall	47 / 7	4.43(2–9.82)
Injury, poisoning and procedural complications	Off Label Use	32 / 59	0.35(0.23–0.54)
Injury, poisoning and procedural complications	Drug Dose Omission	3 / 12	0.16(0.05–0.58)
Injury, poisoning and procedural complications	Product Use In Unapproved Indication	88 / 120	0.47(0.35–0.62)
Injury, poisoning and procedural complications	Inappropriate Schedule Of Drug Administration	4 / 9	0.29(0.09–0.94)
Infections and infestations	Pathogen Resistance	15 / 22	0.44(0.23–0.86)
Infections and infestations	Septic Shock	2 / 7	0.19(0.04–0.9)
Immune system disorders	Anaphylactic Reaction	2 / 11	0.12(0.03–0.54)
Immune system disorders	Hypersensitivity	6 / 12	0.33(0.12–0.87)
General disorders and administration site conditions	Asthenia	51 / 12	2.8(1.49–5.27)
General disorders and administration site conditions	Death	41 / 12	2.25(1.18–4.29)
General disorders and administration site conditions	Drug Resistance	3 / 11	0.18(0.05–0.64)
General disorders and administration site conditions	Drug Ineffective	48 / 65	0.48(0.33–0.7)
General disorders and administration site conditions	Drug Interaction	12 / 22	0.36(0.18–0.72)

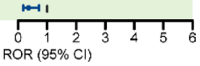


Fig. 4. Analysis of gender- and age-differentiated signals in ertapenem. (**A**) Reporting odds ratios with 95% CI for all positive gender-associated AEs. (**B**) Reporting odds ratios with 95% CI for all positive age-associated AEs. AEs, adverse events; CI, confidence interval. SOC, System Organ Class; PT, preferred term; ROR, reporting odds ratio; 95% CI, 95% confidence intervals.

PT name	N	Available N	Median (IQR)	WSP analysis		Failure type
				α (95% CI)	β (95% CI)	
Dysarthria	36	27	8.5 (2.5–12.5)	9.38 (5.48–13.19)	0.96 (0.66–1.25)	Random failure
Hallucination, visual	61	43	7.5 (4.5–12.0)	10.44 (7.37–13.52)	1.08 (0.85–1.30)	Random failure
Confusional state	265	181	6.5 (3.5–10.5)	10.01 (8.03–11.98)	0.78 (0.71–0.85)	Early failure
Delirium	100	54	6.5 (3.0–11.5)	8.49 (6.31–10.67)	1.09 (0.87–1.32)	Random failure
Hallucination	181	107	6.5 (4.0–12.5)	10.42 (7.96–12.88)	0.85 (0.74–0.95)	Early failure
Mental status changes	61	47	6.5 (2.5–14.0)	9.53 (6.40–12.66)	0.92 (0.72–1.12)	Random failure
Agitation	58	38	6.5 (4.0–12.0)	8.27 (6.37–10.17)	1.45 (1.08–1.83)	Wear-out failure
Disorientation	55	35	6.5 (4.0–10.0)	7.69 (5.72–9.67)	1.42 (1.02–0.81)	Wear-out failure
Neutropenia	42	24	6.5 (3.5–16.0)	11.92 (6.65–17.19)	0.96 (0.67–1.25)	Random failure
Encephalopathy	81	60	6.0 (4.5–10.5)	11.63 (7.16–16.11)	0.70 (0.59–0.81)	Early failure
Myoclonus	46	27	5.5 (2.5–13.0)	8.13 (5.20–11.07)	1.10 (0.78–1.43)	Random failure
Seizure	144	87	5.5 (2.5–8.5)	7.69 (5.92–9.46)	0.97 (0.82–1.11)	Random failure
Status epilepticus	44	34	5.5 (3.5–7.5)	8.89 (4.81–12.97)	0.78 (0.62–0.94)	Early failure
Neurotoxicity	53	15	4.5 (2.0–8.5)	5.92 (2.88–8.97)	1.04 (0.62–1.46)	Random failure
Toxic encephalopathy	43	22	4.0 (2.5–8.5)	7.33 (4.54–10.11)	1.17 (0.80–1.53)	Random failure
Epilepsy	107	81	3.5 (2.5–5.5)	5.29 (3.84–6.74)	0.84 (0.73–0.95)	Early failure
Muscular weakness	37	20	3.5 (0.5–7.0)	5.12 (2.12–8.13)	0.79 (0.53–1.05)	Random failure
Pathogen resistance	37	1	1.5 (1.5–1.5)	--	--	--
Convulsion	214	0	--	--	--	--
Grand mal convulsion	32	0	--	--	--	--

Table 4. Weibull shape parameter AEs positive signals in the top 20 ertapenem reports. α, scale parameter, represents the scale of the distribution function as the quantile in which 63.2% of AEs occur. β, shape parameter, could be used to confirm the distribution type: early failure type (β < 1), random failure type (95% CI of β include 1), and wear-out type (β > 1). --, cannot calculate. 95% CI, 95% confidence interval; IQR, interquartile range; WSP, Weibull shape parameter; PT, preferred term.

AEs based on gender and age differences (beyond neuropsychiatric disorders)

Females exhibited stronger signals for hypotension, acute renal failure, Clostridium difficile colitis, and drug interactions, while males showed stronger signals for muscular weakness, arthralgia, urinary tract infection, pain, abasia, general physical deterioration, nausea, dysphagia, diarrhea, and a swollen tongue. These differences may be attributed to biological factors, but gender-specific social influences also play a role. For instance, males often underestimate illness, whereas females are more proactive in health management, potentially affecting reporting patterns[31]. It should also be noted that the missing gender-associated data may have influenced the results. Therefore, gender-specific drug monitoring and individualized management are recommended in clinical practice.

In terms of age, ertapenem was associated with a greater signal of muscular weakness, falls, and asthenia in patients aged 65 years and older, possibly associated with the decline in muscle strength among the elderly[32], deterioration of renal function leading to drug accumulation, and other comorbidities. Additionally, ertapenem might increase the signal of these AEs by affecting the nervous system. Apart from these three AEs and those associated with neuropsychiatric disorders, other AEs, including hypoaesthesia, septic shock, drug resistance, drug inefficacy, and drug interactions, had a greater signal in patients aged 18–64 years. These AEs aligned with warnings in FDA drug labeling, indicating the importance of targeted drug monitoring across different age groups.

Other important AEs

According to our study results, the two AEs with the strongest signals associated with ertapenem were oropharyngeal oedema (ROR = 191.05, 95% CI: 60.7–601.35) and granulomatous dermatitis (ROR = 150.49, 95% CI: 55.9–405.15). Oropharyngeal oedema can lead to difficulties in speech, swallowing, and breathing, requiring emergency medical intervention, such as intubation, in severe cases. Drug-induced granulomatous dermatitis typically manifests as interstitial granulomatous drug eruption[33], with symptoms generally improving after discontinuation of the drug, although severe cases might require further management. While FDA drug safety alerts mentioned oedema and dermatitis, our study provided more specific signals, indicating a close relationship with ertapenem and highlighting the need for heightened clinical awareness regarding these signals.

Eleven AEs not mentioned on FDA label were identified, involving hepatocellular injury, infections, hematologic abnormalities, and neurological effects. Regarding infection-related AEs, ertapenem exhibits weak activity against certain bacteria, such as Enterococcus and Acinetobacter baumannii[34,35], which may disrupt microbial balance and increase the risk of opportunistic infections. Hematologic abnormalities, including leukocytosis, purpura, and acquired hemophilia, may be associated with immune or coagulation system dysfunction, highlighting the need for monitoring relevant hematologic parameters during ertapenem use.

Cerebellar syndrome, somniloquy, and brain atrophy may be linked to the neurotoxicity of ertapenem. Although the number of these new AEs is small, they warrant attention, and if future studies further validate these findings, they should be included in FDA adverse drug event reports.

The limitations of this study include several points. First, the FAERS database relies on voluntary reporting, which may introduce bias and result in an incomplete representation of adverse events. Data heterogeneity and reporting delays may also affect accuracy, leading to overestimation or underestimation of certain signals. Second, missing data (e.g., incomplete age and gender information) may introduce bias, and the lack of detailed patient background limits in-depth analysis of adverse event signals in specific populations. Third, the AEs not mentioned on the FDA label suggest a potential association with ertapenem but lack sufficient literature support, future large-scale controlled studies are needed for further validation. Finally, as an observational study, causal relationships cannot be established, and caution should be taken when interpreting the results. Future research should expand the sample size, improve data collection, and use randomized controlled trials or prospective cohort studies to validate these findings and improve adverse event monitoring.

Conclusion

In summary, our comprehensive analysis of FAERS data highlighted the signals of nervous system disorders and psychiatric disorders associated with ertapenem, particularly in patients aged ≥ 65 years, emphasizing the need for focused monitoring. This study provides strong scientific evidence for the safety assessment of ertapenem and stresses the importance of drug safety monitoring and implementing individualized management. We anticipate further experimental and clinical research to clarify the associated mechanisms and management strategies.

Data availability

The data that support the findings of this study are publicly available in the FAERS quarterly data at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Received: 20 November 2024; Accepted: 13 May 2025
Published online: 19 May 2025

References

1. Congeni, B. L. *Ertapenem Expert Opin. Pharmacother* ; **11**(4):669–672. doi: https://doi.org/10.1517/14656561003631397 (2010).
2. Nix, D. E., Majumdar, A. K. & DiNubile, M. J. Pharmacokinetics and pharmacodynamics of ertapenem: an overview for clinicians. *J. Antimicrob. Chemother.* **53** (Suppl 2), ii23–ii28. https://doi.org/10.1093/jac/dkh205 (2004).
3. Keating, G. M. & Perry, C. M. Ertapenem: a review of its use in the treatment of bacterial infections. *Drugs* **65** (15), 2151–2178. https://doi.org/10.2165/00003495-200565150-00013 (2005).
4. Global burden of bacterial antimicrobial. Resistance 1990–2021: a systematic analysis with forecasts to 2050. *Lancet* **404** (10459), 1199–1226. https://doi.org/10.1016/S0140-6736(24)01867-1 (2024).
5. Oliva, A. et al. Bactericidal and synergistic activity of double-carbapenem regimen for infections caused by carbapenemase-producing *Klebsiella pneumoniae*. *Clin. Microbiol. Infect.* **22** (2), 147–153. https://doi.org/10.1016/j.cmi.2015.09.014 (2016).
6. Giamarellou, H. et al. Effectiveness of a double-carbapenem regimen for infections in humans due to carbapenemase-producing pandrug-resistant *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **57** (5), 2388–2390. https://doi.org/10.1128/AAC.02399-12 (2013).
7. De Pascale, G. et al. Double carbapenem as a rescue strategy for the treatment of severe carbapenemase-producing *Klebsiella pneumoniae* infections: a two-center, matched case–control study. *Crit. Care.* **21** (1), 173. https://doi.org/10.1186/s13054-017-1769-z (2017).
8. Solomkin, J. S. et al. Phase 2, randomized, double-blind study of the efficacy and safety of two dose regimens of Eravacycline versus ertapenem for adult community-acquired complicated intra-abdominal infections. *Antimicrob. Agents Chemother.* **58** (4), 1847–1854. https://doi.org/10.1128/AAC.01614-13 (2014).
9. Lee, Y-C. et al. Risk factors associated with the development of seizures among adult patients treated with ertapenem: A matched case–control study. *PLoS One.* **12** (7), e0182046. https://doi.org/10.1371/journal.pone.0182046 (2017).
10. Teppler, H. et al. Safety and tolerability of ertapenem. *J. Antimicrob. Chemother.* ii75–ii81. https://doi.org/10.1093/jac/dkh209 (2004). 53 Suppl 2.
11. Fernando, S. L. Ertapenem-induced acute generalized exanthematous pustulosis with cross-reactivity to other beta-lactam antibiotics on patch testing. *Ann. Allergy Asthma Immunol.* **111** (2), 139–140. https://doi.org/10.1016/j.anai.2013.05.015 (2013).
12. Fusaroli, M. et al. The reporting of a disproportionality analysis for drug safety signal detection using individual case safety reports in pharmacovigilance (READUS-PV): development and statement. *Drug Saf.* **47** (6), 575–584. https://doi.org/10.1007/s40264-024-01421-9 (2024).
13. Fusaroli, M. et al. The reporting of A disproportionality analysis for drug safety signal detection using individual case safety reports in pharmacovigilance (READUS-PV): explanation and elaboration. *Drug Saf.* **47** (6), 585–599. https://doi.org/10.1007/s40264-024-01423-7 (2024).
14. Cornelius, V. R., Sauzet, O. & Evans, S. J. W. A signal detection method to detect adverse drug reactions using a parametric time-to-event model in simulated cohort data. *Drug Saf.* **35** (7), 599–610. https://doi.org/10.2165/11599740-000000000-00000 (2012).
15. Sauzet, O. et al. Cornelius VR illustration of the Weibull shape parameter signal detection tool using electronic healthcare record data. *Drug Saf.* **36** (10). https://doi.org/10.1007/s40264-013-0061-7 (2013).
16. Zou, F. et al. Adverse drug events associated with linezolid administration: a real-world pharmacovigilance study from 2004 to 2023 using the FAERS database. Front Pharmacol. ; **15**:1338902. (2024). https://doi.org/10.3389/fphar.2024.1338902
17. Corica, B. et al. Cangemi R sex and gender differences in community-acquired pneumonia. *Intern. Emerg. Med.* **17** (6), 1575–1588. https://doi.org/10.1007/s11739-022-02999-7 (2022).
18. Blot, S., Antonelli, M., Arvaniti, K., ESICM Trials Group Project. & et al Epidemiology of intra-abdominal infection and sepsis in critically ill patients: AbSeS, a multinational observational cohort study and. *Intensive Care Med.* **45** (12), 1703–1717. https://doi.org/10.1007/s00134-019-05819-3 (2019).
19. Cho, Y. K. et al. The clinical and economic burden of community-onset complicated skin and skin structure infections in Korea. *Korean J. Intern. Med.* **35** (6), 1497–1506. https://doi.org/10.3904/kjim.2018.374 (2020).
20. Hoffman, K. B. et al. The Weber effect and the united States food and drug administration's adverse event reporting system (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. *Drug Saf.* **37** (4), 283–294. https://doi.org/10.1007/s40264-014-0150-2 (2014).

21. Danés, I. et al. A case series of confusional States and other neurotoxic effects caused by ertapenem. *Br. J. Clin. Pharmacol.* **87** (4), 2140–2145. https://doi.org/10.1111/bcp.14582 (2021).
22. Mitaka, H. et al. Characterizing ertapenem neurotoxicity: A systematic review and experience at a tertiary medical center. Open forum infect dis. ; **11**(5):ofae214. (2024). https://doi.org/10.1093/ofid/ofae214
23. Roger, C. & Louart, B. Beta-Lactams toxicity in the intensive care unit: an underestimated collateral damage?? Microorganisms. ; **9**(7). (2021). https://doi.org/10.3390/microorganisms9071505
24. Campany-Herrero, D. et al. Ertapenem blood concentration: A retrospective cohort study to analyze risk of neurotoxicity. *Br. J. Clin. Pharmacol.* **89** (9), 2843–2850. https://doi.org/10.1111/bcp.15782 (2023).
25. Hsaiky, L. M. et al. Pharmacokinetics and investigation of optimal dose ertapenem in intermittent Hemodialysis patients. *Nephrol. Dial Transpl.* **34** (10), 1766–1772. https://doi.org/10.1093/ndt/gfy166 (2019).
26. Mistry, G. C. et al. Pharmacokinetics of ertapenem in patients with varying degrees of renal insufficiency and in patients on Hemodialysis. *J. Clin. Pharmacol.* **46** (10), 1128–1138. https://doi.org/10.1177/0091270006291839 (2006).
27. Wen, M-J. et al. Acute prolonged neurotoxicity associated with recommended doses of ertapenem in 2 patients with advanced renal failure. *Clin. Nephrol.* **80** (6), 474–478. https://doi.org/10.5414/CN107247 (2013).
28. Wang, C. et al. Ertapenem-Induced neurotoxicity: A literature review of clinical characteristics and treatment outcomes. *Infect. Drug Resist.* **16**, 3649–3658. https://doi.org/10.2147/IDR.S406852 (2023).
29. European Medicines Agency. INVANZ-INN Ertapenem. Product information. (2024). https://www.ema.europa.eu/en/documents/product-information/invanz-epar-product-information_en.pdf. Accessed October 12.
30. Wu, C-C. et al. The effect of different carbapenem antibiotics (Ertapenem, Imipenem/Cilastatin, and Meropenem) on serum valproic acid concentrations. Ther drug monit. ; **38**(5):587–592. (2016). https://doi.org/10.1097/FTD.0000000000000316
31. Lee, K. M. N. et al. A gender hypothesis of sex disparities in adverse drug events. *Soc. Sci. Med.* **339**, 116385. https://doi.org/10.1016/j.socscimed.2023.116385 (2023).
32. Cruz-Jentoft, A. J. & Sayer, A. A. *Sarcopenia Lancet* ; **393**(10191):2636–2646. doi: https://doi.org/10.1016/S0140-6736(19)31138-9 (2019).
33. Bangalore Kumar, A. et al. Reactive granulomatous dermatitis as a clinically relevant and unifying term: a retrospective review of clinical features, associated systemic diseases, histopathology and treatment for a series of 65 patients at Mayo clinic. *J. Eur. Acad. Dermatol. Venereol.* **36** (12), 2443–2450. https://doi.org/10.1111/jdv.18203 (2022).
34. Qiu, Z. et al. Cross-talk of MLST and transcriptome unveiling antibiotic resistance mechanism of carbapenem resistance *Acinetobacter baumannii* clinical strains isolated in Guiyang. *China Front. Microbiol.* **15**, 1394775. https://doi.org/10.3389/fmicb.2024.1394775 (2024).
35. Livermore, D. M., Sefton, A. M. & Scott, G. M. Properties and potential of ertapenem. *J. Antimicrob. Chemother.* **52** (3), 331–344. https://doi.org/10.1093/jac/dkg375 (2003).

Author contributions

FT: Conceptualization, methodology, data curation, formal analysis, writing-original draft. YH: Investigation, Resources, Validation, Writing-Original Draft. WO: Visualization, Writing-Review&Editing, Project administration. NY: Methodology, data curation, visualization, Writing-Review&Editing. XB: Writing-Review&Editing, Supervision.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-02359-3.

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