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Post-market safety profile of cefiderocol: a real-world pharmacovigilance exploratory analysis based on U.S. FDA adverse event reporting system (FAERS)

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Abstract

Background Cefiderocol is a new drug class, which is approved to treat Gram-negative bacteria infection. Its approval for marketing has provided clinicians with additional options for treating antimicrobial resistant gram-negative infections. The aim of our study was to assess the safety profiles of cefiderocol in real-world through data mining of the United States Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods We included adverse event (AE) reports regarding cefiderocol submitted to the FAERS from 2019 quarter 4 (2019Q4) to 2024 quarter 3 (2024Q3). Disproportionality analyses, including reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN) and Multi-item Gamma Poisson Shrinker (MGPS) techniques were performed to identify the signals of disproportionate reporting of AEs in patients receiving cefiderocol. A signal of disproportionate reporting was detected if the lower limit of the 95% confidence interval (CI) of ROR > 1, the PRR was ≥ 2(while the Chi-Square of PRR was ≥ 4), the lower limit of 95% CI of the information component (IC025) was > 0, the lower limit of 95% CI of the Empirical Bayes Geometric Mean (EBGM05) was > 2 and at least 3 AEs were reported.

Results A total of 29 significant preferred terms (PTs) were identified among the 592 cefiderocol-associated adverse events (AEs) reports collected from the FAERS database. Cefiderocol-induced adverse events involved 24 System Organ Class (SOC). 29 positive signals of disproportionate reporting are also presented, such as Pathogen resistance ($n = 16$, ROR 189.35, PRR 184.26, IC 7.52, EBGM 183.89), Systemic candida ($n = 3$, ROR 138.79, PRR 138.19, IC7.11, EBGM 137.88), Drug resistance ($n = 30$, ROR 131.96, PRR 125.33, IC6.97, EBGM 125.16), and Drug effect less than expected ($n = 6$, ROR 68.42, PRR 67.74, IC6.08, EBGM 67.69). The most frequently observed were Death, Drug resistance and Treatment failure.

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Conclusions Our findings offer significant evidence regarding the safety profile of cefiderocol in real-world settings. This information may assist clinicians and pharmacists in enhancing their vigilance and improving the overall safety of cefiderocol in clinical practice.

Keywords Cefiderocol, FDA adverse event reporting system, Real-world data analysis, Adverse drug events

Background

Gram-negative bacteria represent some of the most prevalent pathogens encountered in clinical settings, with a significant proportion producing extended-spectrum β-lactamases (ESBLs) and exhibiting resistance to cephalosporins. Carbapenems are widely regarded as the most effective agents for treating these resistant strains. However, the emergence of carbapenem-resistant Gram-negative bacteria has been closely linked to the overuse and misuse of antibiotics, resulting in an annual increase in resistance rates. In February 2017, the World Health Organization (WHO) identified carbapenem-resistant Enterobacterales, carbapenem-resistant Pseudomonas aeruginosa, and carbapenem-resistant Acinetobacter baumannii as critical pathogens requiring urgent development of new antibiotics, categorizing them at the highest risk level of "critical" [1]. Cefiderocol is a novel cephalosporin that exhibits iron-carrier properties similar to those of ceftazidime and cefepime. It employs a unique mechanism of action by mimicking the binding affinity of trivalent iron ions to iron carriers, thereby facilitating their transport into bacterial cells via specific bacterial iron transport proteins. This strategy enables cefiderocol to achieve elevated intracellular concentrations within bacterial cells, resulting in potent antibacterial activity [2]. Cefiderocol has been approved in the United States for the treatment of adults with complicated urinary tract infections, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia. However, due to its relatively recent introduction to the market and the increasing prevalence of its clinical use, there are currently limited post-marketing safety studies available. As a result, it is essential to investigate and analyze risk signals associated with adverse drug events (ADEs) related to cefiderocol to enhance our understanding of its safety profile and ensure its rational clinical use. The growing interest in drug safety has attracted the attention of researchers and clinicians alike. The US Food and Drug Administration Adverse Event Reporting System (FAERS) is a database designed to support post-marketing safety monitoring of drugs and therapeutic biologic products by the US Food and Drug Administration (FDA) and includes all information on adverse events and medication errors collected by the FDA. The data structure of the FAERS database adheres to the rapid reporting format outlined in ICH E2B [Regional Implementation Guide for Individual Safety Reporting E2B(R3) by the International Technical Coordination Committee for the Registration of Medicinal Products for Human Use]. Key variables recorded include gender, age, time of medication administration, time of occurrence, and agents associated with adverse events. Additional information encompasses quantity, causality assessments, outcomes, and other relevant content. This comprehensive database encompasses reports submitted by healthcare professionals, patients, pharmaceutical companies, and other stakeholders, detailing adverse event information related to a wide range of medications. Disproportionality analysis is a widely employed method for detecting pharmacovigilance risk signals within drug adverse event (AE) reporting system databases. The fundamental principle of disproportionality analysis involves utilizing the classical four-cell table method to assess the imbalance between the ratios of target drug-AE combinations and those of other drug-AE pairs, thereby evaluating the strength of the association between drugs and AEs. Proportion imbalance refers to a frequency of a specific drug-AE combination that surpasses the background frequency observed in the entire database or meets predetermined discriminant criteria, indicating a statistical association between the drug and AE that is unlikely to be attributed to chance. This may signify a potential risk signal for adverse drug reactions (ADRs). By calculating and quantifying these proportion imbalances among various drug-AE combinations, disproportionality analysis identifies possible risk signals. A larger signal value indicates an increased likelihood that the target drug is statistically associated with the corresponding AE. The analysis aims to promptly identify new or rare ADEs, thereby preventing large-scale drug-related harm events and improving the therapeutic management of cefiderocol. The findings hold significant importance for promoting post-marketing re-evaluation and ensuring the rational and safe use of cefiderocol in clinical practice.

Materials and methods

Study design and data source

The original data utilized in this data mining study is sourced from the FAERS database (http://www.fda.gov/), which can be downloaded from the official website of the U.S.FDA. This database has been publicly accessible since the first quarter of 2004 [3]. The data are updated and released on a quarterly basis, with two formats available for download simultaneously: ASCII data packages and XML data packages. In this research, raw ASCII packets

were obtained for subsequent data mining and statistical analysis. We extracted data from the FAERS database covering the period from Q4 2019 to Q3 2024, with a specific focus on cefiderocol, which received approval from the United States Food and Drug Administration (FDA) in November 2019. Our analysis began in the final quarter of 2019. The keywords utilized for data mining included "cefiderocol" and its brand name "Fetroja®." Adverse event names in the FAERS database were coded with the use of the current Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 27.1). Adverse event (AE) reports within the FAERS database are categorized using Preferred Terms (PTs), following MedDRA's hierarchical structure that facilitates grouping PTs into relevant System Organ Classes (SOCs), representing MedDRA's highest level of classification. In the database, each patient (one report) was associated with a unique "Primary Suspect Drug (PS)," and only the PS was taken into account when identifying target drug users in consideration of credibility in present study. If the patient's PS in the analyzed background database corresponded to the target drug of this study, that patient was included in the target drug population; otherwise, they were categorized into the other drug population.

Data processing

Since the data collected in the database were submitted spontaneously, there were instances of duplicate reports as well as reports that had been withdrawn or deleted. The official guidance document from the FDA provided corresponding rules for data deduplication and a list of reports that need to be removed. This study was conducted in strict accordance with the guidance document available on the official FDA website. The rules for data cleaning are as follows: First, following the method recommended by the FDA for removing duplicate reports, we selected the PRIMARYID, CASEID, and FDA_DT fields from the DEMO table. The records were sorted by CASEID, FDA_DT, and PRIMARYID. For reports sharing the same CASEID, only those with the largest FDA_DT value were retained; if both CASEID and FDA_DT values were identical, we kept the report with the highest PRIMARYID value. Second, since Q1 2019 onwards, each quarterly data package includes a list of deleted reports. After deduplication of data has been completed, any remaining reports are removed based on their CASEIDs listed in this deletion inventory.

Table 1 Four grid table

	Target AEs	Non-target AEs	Total
Cefiderocol	a	b	a+b
Non-cefiderocol	c	d	c+d
Total	a+c	b+d	N=a+b+c+d

Statistical analysis

The present study employed a combination of disproportionality methods, including reporting odds ratios (ROR) [4], proportional reporting ratios (PRR) [5], Bayesian Confidence Propagation Neural Network (BCPNN) [6], and Multi-item Gamma Poisson Shrinker (MGPS) [7] techniques, to simultaneously identify drug ADE signals. Data processing and analyses were performed by SAS 9.4 and Microsoft Excel 2019. The ROR is instrumental in mitigating biases associated with events that have a limited number of reports. The PRR is distinguished by its superior specificity compared to the ROR. The BCPNN excels at integrating and cross-validating data from multiple sources. Moreover, the MGPS proves particularly effective in detecting signals arising from infrequent events. This study employs a combination of ROR, PRR, BCPNN, and MGPS to leverage their respective strengths, thereby enhancing detection and validation capabilities from various angles. This integrated methodology facilitates more precise identification of safety signals while minimizing false positives through cross-validation. A positive signal of disproportionate reporting for PT in our research was determined if the lower limit of 95% CI of ROR was >1, the PRR was ≥ 2(while the Chi-Square of PRR was ≥ 4), the lower limit of 95% CI of the information component (IC025) was >0, the lower limit of 95% CI of the Empirical Bayes Geometric Mean (EBGM05) was >2 and the reported number was ≥ 3. The calculations for both types of methods can be derived from fourfold table data, as illustrated in Table 1. The thresholds for determining positive signals of disproportionate reporting for the aforementioned methods are presented in Table 2.

Result

Population characteristics

According to Fig. 1, The total number of background patients included in the analysis for the 83 quarters from Q1 2004 to Q3 2024 was 18,278,243 (with 543,36884 adverse events), of which 271 patients in the target drug population (with 592 adverse events). Patient characteristics and AE reports regarding cefiderocol are presented in Table 3. In the adverse event reports involving cefiderocol, male patients outnumbered female patients (35.42% vs. 24.72%). 18 to 65 age group reported most PTs (31.74%). From the fourth quarter of 2019 to the third quarter of 2024, adverse event reports related to cefiderocol exhibited a consistent annual increase, with the highest number of reports recorded in the first three quarters of 2024, accounting for 29.89%. Notably, more than 90% of reports came from medical professionals rather than customers. Almost one fourth of reports originated from the US, accounting for 26.94% of the total, followed by Italy (17.71%) and France (15.13%). In terms of clinical

Table 2 ROR, PRR, BCPNN, and EBGM methods, formulas, and thresholds

Method	Formula	Threshold
ROR	$ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$ $SE(\ln ROR) = \sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}$ $95\%CI = e^{\ln(ROR)\pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	a≥3 and 95% CI (lower limit)>1
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$ $SE(\ln PRR) = \sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}$ $95\%CI = e^{\ln(PRR)\pm 1.96\sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}}$	a≥3 and 95% CI (lower limit)>1
BCPNN	$\chi^2 = \frac{(ad-bc)^2(a+b+c+d)}{(a+b)(a+c)(c+d)(b+d)}$ $IC = log_2 \frac{p(x,y)}{p(x)p(y)} = log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$ $E(IC) = log_2 \frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$ $V(IC) = \frac{1}{(ln2)^2}\{[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}] + [\frac{(a+b+c+d)-(a+b)+\alpha-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}] + [\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta)}]\}$ $\gamma = \gamma 11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$ $IC\text{-}2SD = E(IC) - 2\sqrt{V(IC)}$	IC025>0
EGBM	$EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$ $95\%CI = e^{\ln(EBGM)\pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	EBGM05>2

outcomes, apart from unspecified serious adverse events, those leading to death were most frequent (54.61%). The mean onset time of AE was 10.8 days, and the median onset time was 6.5 days.

Disproportionality analysis

In this study, adverse events related to cefiderocol were analyzed through the examination of adverse event reports. The findings revealed that 24 System Organ Classes (SOCs) were involved in these events. The results indicated that the most frequently observed systems were General disorders and administration site conditions ($n = 197$, ROR 2.36, PRR 1.91, IC 0.93, EBGM 1.91), Infections and infestations ($n = 108$, ROR 4.04, PRR 3.49, IC 1.80, EBGM 3.49), Injury, poisoning and procedural complications ($n = 35$, ROR 0.55, PRR 0.57, IC -0.81, EBGM 0.57), and Renal and urinary disorders ($n = 35$, ROR 3.23, PRR 3.10, IC 1.63, EBGM 3.10). More details can be found in Table 4.

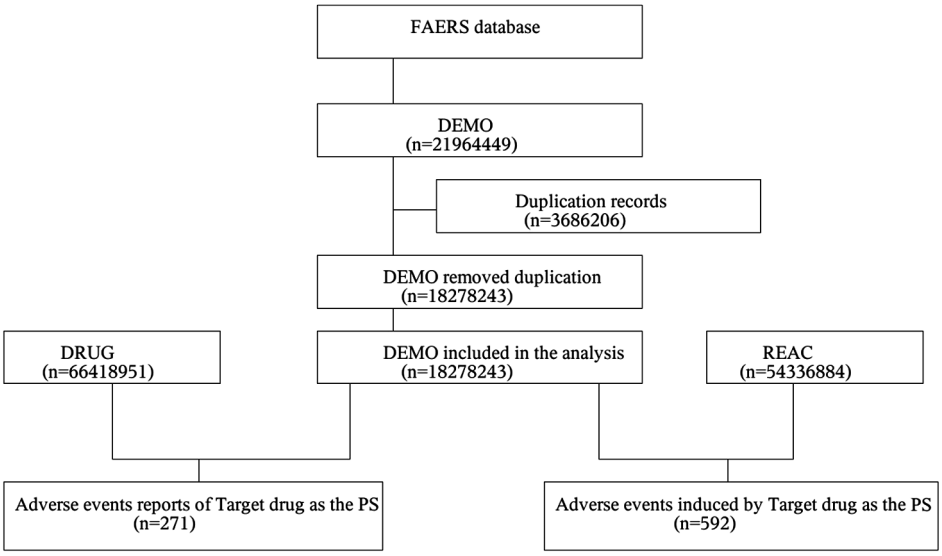

Fig. 1 The flow diagram of selecting target drug AEs in the overall population from FAERS database

On the PT level, this study employed four statistical models to analyze drug adverse events. Ranked according to the most stringent EBGM method, Table 5 presents the 29 positive signals of disproportionate reporting. The findings revealed PTs with significant signal strength, such as Pathogen resistance ($n = 16$, ROR 189.35, PRR 184.26, IC 7.52, EBGM 183.89), Systemic candida ($n = 3$, ROR 138.79, PRR 138.19, IC7.11, EBGM 137.88), Drug resistance ($n = 30$, ROR 131.96, PRR 125.33, IC6.97, EBGM 125.16), and Drug effect less than expected ($n = 6$, ROR 68.42, PRR 67.74, IC6.08, EBGM 67.69). The most frequently observed were Death, Drug resistance and treatment failure.

Discussion

Cefiderocol utilizes a "Trojan horse" mechanism by binding ferric iron, effectively linking the cephalosporin core of the drug to penicillin-binding proteins located on the bacterial cell membrane. This interaction inhibits peptidoglycan synthesis in the bacterial cell wall, thereby exerting a bactericidal effect [8]. Cefiderocol is well-tolerated and associated with a favorable trend toward improved overall survival [9]. Recent guidelines have been updated to recommend cefiderocol as an alternative treatment for patients with antimicrobial-resistant Gram-negative infections [10]. Consequently, an increasing annual trend in prescriptions is anticipated, along with growing clinical experience with cefiderocol. It is crucial to emphasize the importance of monitoring safety and conducting post-marketing surveillance for cefiderocol. Our current study provides real-world data on the safety profile of cefiderocol based on the FAERS database.

The findings of this study indicate that the median AE onset time was 6.5 days. Additionally, we identified an adverse event involving COVID-19 pneumonia that occurred on Day 82 following the initiation of cefiderocol treatment in a 69-year-old patient. It is essential to recognize that latency is influenced not only by the pharmacological properties of the drug but also by the inherent characteristics of the adverse event itself. Consequently, it remains uncertain whether the provided latency information holds significant utility, particularly considering that several reported preferred terms with a positive signal for disproportionate reporting did not correspond to clinical adverse events. Furthermore, it is important to highlight that latency data were unknown in 165 cases (60.89%), which limits the generalizability of these findings concerning latency.

Pathogen resistance, Drug resistance, Drug effect less than expected, or Treatment failure should not be defined as adverse events of drug although disproportionate analysis showed a positive result. As a matter of fact, although the approval of cefiderocol by the FDA in 2019 has established it as a last-resort treatment for severe antimicrobial-resistant gram-negative infections, its efficacy remains controversial. Among patients with carbapenem-resistant nosocomial pneumonia and bloodstream infections, all-cause mortality was found to be higher in the cefiderocol group compared to those receiving the best available treatment [11, 12]. Therefore, further clinical studies are necessary to evaluate the effectiveness of cefiderocol in managing severe infections. Additionally, despite its capacity to overcome typical enzyme-producing resistance mechanisms and address drug-resistant gram-negative bacterial infections, clinically isolated strains resistant to cefiderocol have been identified; however, their resistance mechanisms remain unclear. Previous research has indicated that alterations

Table 3 Demographics and characteristics of population

Factors	Number of events(%)
Gender	
Female (%)	67(24.72)
Male (%)	96(35.42)
Not Specified (%)	108(39.85)
Age	
<18(%)	1(0. 37)
18–44(%)	33(12.18)
45–64(%)	53(19.56)
≥65(%)	56(20.66)
Not Specified (%)	128(47.23)
Report year	
2020(%)	17(6.27)
2021(%)	26(9.59)
2022(%)	70(25.83)
2023(%)	77(28.41)
2024Q1-Q3(%)	81(29.89)
Reporter	
Consumer (%)	15(5.54)
Not Specified (%)	1(0.37)
Pharmacist (%)	139(51.29)
Physician (%)	116(42.80)
Reported countries	
United States of America (%)	73(26.94)
Italy (%)	48(17.71)
France (%)	41(15.13)
Japan (%)	26(9.59)
Germany (%)	24(8.86)
Serious criteria	
Serious reports of events	250(92.25)
Non-serous reports of events	21(7.75)
Serious outcome	
Life-Threatening (%)	22(8.12)
Hospitalization - Initial or Prolonged (%)	44(16.24)
Disability (%)	4(1.48)
Death (%)	148(54.61)
Congenital Anomaly (%)	0(0.00)
Required Intervention to Prevent Permanent Impairment/Damage (%)	1(0.37)
Other (%)	79(29.15)
Adverse event occurrence time - medication date (days)	
0–30(%)	100(36.90)
31–60(%)	5(1.85)
61–90(%)	1(0.37)
>90(%)	0(0.00)
Not Specified (%)	165(60.89)
Adverse event occurrence time - medication date (days)	
N(missing)	
Mean (SD)	10.80(12.41)
Median (Q1, Q3)	6.50(2.00,15.00)
Min, Max	0.00,82.00
Body weight (Kg)	
N(Missing)	42(229)
Mean (SD)	77.88(27.27)
Median (Q1, Q3)	72.90(61.00,90.00)
Min, Max	32.40,170.00

Table 4 Signal strength of ADEs at the system organ class (SOC) level in FAERS database

System organ class (SOC)	SOC Code	Case reports	ROR (95% CI)	PRR (95% CI)	Chi_Square	IC(IC025)	EBGM(EBGM05)
General disorders and administration site conditions	10,018,065	197	2.36(1.99,2.80)	1.91(1.70,2.14)	103.15	0.93(0.69)	1.91(1.61)
Infections and infestations	10,021,881	108	4.04(3.28,4.98)	3.49(2.94,4.13)	202.00	1.80(1.47)	3.49(2.83)
Injury, poisoning and procedural complications	10,022,117	35	0.55(0.39,0.77)	0.57(0.41,0.79)	12.48	-0.81(-1.29)	0.57(0.41)
Renal and urinary disorders	10,038,359	35	3.23(2.30,4.54)	3.10(2.25,4.27)	50.69	1.63(1.05)	3.10(2.20)
Nervous system disorders	10,029,205	31	0.59(0.41,0.85)	0.62(0.44,0.87)	8.13	-0.70(-1.21)	0.62(0.43)
Investigations	10,022,891	26	0.70(0.47,1.04)	0.71(0.49,1.04)	3.17	-0.49(-1.04)	0.71(0.48)
Hepatobiliary disorders	10,019,805	25	4.76(3.19,7.11)	4.60(3.14,6.76)	71.18	2.20(1.44)	4.60(3.08)
Respiratory, thoracic and mediastinal disorders	10,038,738	21	0.74(0.48,1.15)	0.75(0.50,1.15)	1.77	-0.41(-1.02)	0.75(0.49)
Blood and lymphatic system disorders	10,005,329	20	2.04(1.31,3.19)	2.00(1.30,3.08)	10.24	1.00(0.29)	2.00(1.28)
Skin and subcutaneous tissue disorders	10,040,785	18	0.55(0.35,0.88)	0.57(0.36,0.89)	6.36	-0.82(-1.46)	0.57(0.35)
Gastrointestinal disorders	10,017,947	15	0.28(0.17,0.47)	0.30(0.18,0.49)	27.14	-1.75(-2.42)	0.30(0.18)
Metabolism and nutrition disorders	10,027,433	14	1.09(0.64,1.85)	1.09(0.65,1.83)	0.11	0.12(-0.64)	1.09(0.64)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10,029,104	9	0.57(0.30,1.10)	0.58(0.30,1.10)	2.87	-0.79(-1.65)	0.58(0.30)
Cardiac disorders	10,007,541	9	0.57(0.29,1.10)	0.58(0.30,1.10)	2.89	-0.80(-1.66)	0.58(0.30)
Immune system disorders	10,021,428	7	1.08(0.51,2.27)	1.08(0.52,2.25)	0.04	0.11(-0.94)	1.08(0.51)
Musculoskeletal and connective tissue disorders	10,028,395	5	0.16(0.06,0.38)	0.16(0.07,0.39)	22.65	-2.62(-3.59)	0.16(0.07)
Surgical and medical procedures	10,042,613	4	0.50(0.19,1.34)	0.50(0.19,1.34)	1.99	-0.99(-2.14)	0.50(0.19)
Psychiatric disorders	10,037,175	4	0.11(0.04,0.30)	0.12(0.05,0.32)	27.50	-3.06(-4.08)	0.12(0.04)
Vascular disorders	10,047,065	4	0.31(0.12,0.83)	0.32(0.12,0.84)	6.04	-1.66(-2.75)	0.32(0.12)
Product issues	10,077,536	1	0.10(0.01,0.73)	0.10(0.01,0.74)	7.78	-3.25(-4.44)	0.10(0.01)
Ear and labyrinth disorders	10,013,993	1	0.39(0.05,2.76)	0.39(0.05,2.75)	0.97	-1.36(-2.88)	0.39(0.05)
Congenital, familial and genetic disorders	10,010,331	1	0.56(0.08,3.97)	0.56(0.08,3.96)	0.35	-0.84(-2.53)	0.56(0.08)
Social circumstances	10,041,244	1	0.36(0.05,2.58)	0.36(0.05,2.58)	1.12	-1.46(-2.95)	0.36(0.05)
Eye disorders	10,015,919	1	0.08(0.01,0.59)	0.08(0.01,0.60)	10.07	-3.56(-4.72)	0.08(0.01)

SOC: system organ class; PT: preferred terms; ROR: reporting odds ratios; PRR: proportional reporting ratios; IC: information component; EBGM: Empirical Bayes Geometric Mean

in the structure of AmpC β-lactamase, deletion of iron transporters, and co-expression of β-lactamases may play a role in this phenomenon [13–15].

Cefiderocol exhibits a linear kinetic profile and is primarily excreted via the kidneys, with no significant hepatic metabolism observed. Dose adjustments are necessary for patients with renal impairment; however, such adjustments are not required for those with hepatic impairment. Although the concept of PT Hepatic cytolysis is not explicitly mentioned in the US Prescribing Information (USPI) for this product, it is important to acknowledge that similar terms indicative of cytolysis have already been included. These terms refer to elevations in liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), blood alkaline phosphatase, and other increases in hepatic enzymes. It is widely accepted that drug-induced liver injury associated with cephalosporins predominantly manifests as hepatocellular injury or a mixed type, primarily driven by an immune response [16, 17].

Our study found that cefiderocol may be associated with certain kidney-related adverse events, including tubulointerstitial nephritis and acute kidney injury. In 2021, Australia reported a case of a patient who experienced acute elevation in creatinine levels and an increased peripheral blood eosinophil count following treatment for a spinal infection caused by pan-sensitive Pseudomonas aeruginosa and pan-drug-resistant Acinetobacter baumannii with cefiderocol. Interstitial nephritis was considered after consultation with nephrologists, and the patient's creatinine levels returned to normal upon discontinuation of the drug [18]. Previous studies have suggested that the nephrotoxicity of cephalosporins may be related to factors such as the area under the curve (AUC) in renal cortex exposure, disruption of mitochondrial respiratory enzymes within cortical renal tubular cells, and direct effects of the lactam ring [19, 20]. The structure of cefiderocol is similar to that of ceftazidime and cefepime; therefore, we hypothesize that its mechanism for inducing renal injury may also resemble those observed with ceftazidime and cefepime. However,

Table 5 Signal strength of adverse events at the preferred term (PT) level ranked by EBGM

System organ class (SOC)	Preferred term (PT)	Case reports	ROR (95% CI)	PRR (95% CI)	Chi Square	IC (IC025)	EBGM (EBGM05)
Infections and infestations	Pathogen resistance	16	189.35 (115.16,311.33)	184.26 (113.58,298.92)	2910.82	7.52 (3.26)	183.89 (111.84)
Infections and infestations	Systemic candida	3	138.79 (44.59,431.94)	138.09 (44.63,427.31)	407.70	7.11 (0.52)	137.88 (44.30)
General disorders and administration site conditions	Drug resistance	30	131.96 (91.38,190.57)	125.33 (88.41,177.65)	3696.46	6.97 (4.11)	125.16 (86.67)
General disorders and administration site conditions	Drug effect less than expected	6	68.42 (30.60,152.97)	67.74 (30.55,150.21)	394.28	6.08 (1.59)	67.69 (30.28)
Hepatobiliary disorders	Hepatic cytolysis	7	60.22 (28.58,126.92)	59.52 (28.49,124.34)	402.60	5.89 (1.81)	59.48 (28.23)
General disorders and administration site conditions	Treatment failure	27	38.47 (26.15,56.60)	36.76 (25.43,53.14)	940.05	5.20 (3.45)	36.75 (24.97)
Infections and infestations	Bacteraemia	4	36.99 (13.84,98.92)	36.75 (13.84,97.61)	139.08	5.20 (0.88)	36.74 (13.74)
Infections and infestations	COVID-19 pneumonia	4	35.54 (13.29,95.02)	35.31 (13.29,93.78)	133.31	5.14 (0.87)	35.29 (13.20)
Immune system disorders	Haemophagocytic lymphohistiocytosis	3	34.40 (11.06,107.01)	34.24 (11.07,105.87)	96.77	5.10 (0.43)	34.22 (11.00)
General disorders and administration site conditions	Multiple organ dysfunction syndrome	14	33.23 (19.55,56.46)	32.46 (19.34,54.48)	427.07	5.02 (2.63)	32.45 (19.10)
Blood and lymphatic system disorders	Disseminated intravascular coagulation	4	28.72 (10.74,76.80)	28.54 (10.74,75.80)	106.28	4.83 (0.84)	28.53 (10.67)
Nervous system disorders	Status epilepticus	3	28.23 (9.08,87.79)	28.09 (9.08,86.86)	78.36	4.81 (0.41)	28.08 (9.03)
Hepatobiliary disorders	Cholestasis	5	27.83 (11.54,67.12)	27.60 (11.53,66.08)	128.20	4.79 (1.16)	27.60 (11.44)
Renal and urinary disorders	Chromaturia	6	26.67 (11.93,59.61)	26.41 (11.91,58.55)	146.68	4.72 (1.41)	26.40 (11.81)
Nervous system disorders	Encephalopathy	6	25.90 (11.59,57.90)	25.65 (11.57,56.87)	142.15	4.68 (1.41)	25.64 (11.47)
Renal and urinary disorders	Tubulointerstitial nephritis	4	21.09 (7.89,56.39)	20.95 (7.89,55.65)	76.01	4.39 (0.77)	20.95 (7.84)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	3	20.35 (6.54,63.28)	20.25 (6.55,62.61)	54.89	4.34 (0.35)	20.24 (6.51)
Infections and infestations	Septic shock	8	20.09 (10.00,40.36)	19.83 (9.96,39.47)	143.12	4.31 (1.71)	19.83 (9.87)
Injury, poisoning and procedural complications	Prescribed overdose	3	16.67 (5.36,51.83)	16.59 (5.36,51.29)	43.95	4.05 (0.31)	16.58 (5.33)
Nervous system disorders	Epilepsy	4	14.18 (5.30,37.91)	14.09 (5.31,37.42)	48.67	3.82 (0.66)	14.09 (5.27)
Injury, poisoning and procedural complications	Incorrect product administration duration	6	12.29 (5.50,27.47)	12.18 (5.49,27.00)	61.60	3.61 (1.13)	12.18 (5.45)
Infections and infestations	Infection	13	9.93 (5.73,17.21)	9.74 (5.69,16.67)	102.15	3.28 (1.80)	9.74 (5.62)
General disorders and administration site conditions	Death	71	9.72 (7.58,12.45)	8.67 (6.97,10.79)	488.73	3.12 (2.61)	8.67 (6.77)
Hepatobiliary disorders	Hepatic function abnormal	3	8.72 (2.81,27.13)	8.68 (2.81,26.85)	20.41	3.12 (0.12)	8.68 (2.79)
Infections and infestations	Sepsis	9	8.46 (4.38,16.35)	8.35 (4.37,15.97)	58.34	3.06 (1.35)	8.35 (4.32)
Renal and urinary disorders	Acute kidney injury	14	7.55 (4.45,12.83)	7.40 (4.41,12.41)	77.71	2.89 (1.62)	7.40 (4.35)
Respiratory, thoracic and mediastinal disorders	Respiratory failure	4	5.66 (2.12,15.12)	5.63 (2.12,14.94)	15.23	2.49 (0.25)	5.63 (2.10)

Table 5 (continued)

System organ class (SOC)	Preferred term (PT)	Case reports	ROR (95% CI)	PRR (95% CI)	Chi Square	IC (IC025)	EBGM (EBGM05)
General disorders and administration site conditions	Condition aggravated	13	4.86 (2.80,8.42)	4.77 (2.79,8.17)	38.96	2.26 (1.13)	4.77 (2.76)
General disorders and administration site conditions	No adverse event	7	4.47 (2.12,9.42)	4.43 (2.12,9.25)	18.63	2.15 (0.60)	4.43 (2.10)

ROR: reporting odds ratios; PRR: proportional reporting ratios; IC: information component; EBGM: Empirical Bayes Geometric Mean

Signals are detected when all the following criteria are met: case reports ≥ 3, PRR ≥ 2 and Chi-Square ≥ 4, lower limit of 95% CI of ROR > 1, IC025 > 0, EBGM05 > 2

different classes of cephalosporins exhibit varying thresholds for nephrotoxicity based on their ionic charge as well as their direct effects on renal tubules [21]. Since a renal biopsy was not performed in this reported case, we cannot definitively ascertain the role played by immune-precipitates or lymphoblastic interstitial infiltration. We recommend close monitoring of renal function parameters in patients at risk for potential long-term exposure to this antibiotic, as symptoms indicative of acute interstitial nephritis can manifest insidiously during the early stages of illness.

In the past, cephalosporins were believed to antagonize the binding of γ-aminobutyric acid (GABA) to its receptor, inhibit the synthesis and transport of central neurotransmitter amino acids, and impede Na+-K+-ATPase activity in central nerve cells [22]. These mechanisms were thought to reduce the resting membrane potential, ultimately contributing to central toxic events. Common manifestations of these events included abnormal movements such as myoclonus, tremors, and encephalitis. Data from the French Pharmacovigilance system revealed that among 511 patients treated with cephalosporins for central nervous system (CNS) issues, the incidence of adverse drug events (ADEs) associated with ceftazidime was 19.6%. The most prevalent symptoms were encephalopathy, mental confusion, and convulsions [23]. The findings of this study indicated that the neurological abnormalities caused by cefiderocol were similar to those induced by ceftazidime, primarily including encephalopathy and epilepsy. Some case reports have suggested that cefiderocol may be effective in treating drug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii infections within the central nervous system [24–27]. Researchers further discovered that the trough concentration of cefiderocol in cerebrospinal fluid (CSF) is approximately 4–8.5% of its plasma concentration at corresponding times. Additional clinical studies are warranted to explore both the therapeutic application of cefiderocol in treating CNS infections and its associated adverse events in this context.

A number of previous case reports have suggested that patients may experience chromaturia following the administration of cefiderocol. Earlier researchers proposed that this phenomenon might be associated with elevated iron levels in the body, which could result from intravenous iron supplementation or high-dose enteral iron supplementation during episodes of gastrointestinal bleeding [28, 29]. However, a recent report detailing brown urine in a patient with osteomyelitis who was treated with cefiderocol indicated no significant abnormalities in routine urinalysis or renal function tests. Notably, the urine color returned to normal after discontinuation of the drug, and the patient did not receive any intravenous or enteral iron supplementation [30]. This observation suggests that alternative mechanisms may be involved in this process. The researchers speculate that the observed chromaturia could be attributed to iron precipitation resulting from interactions between iron ions and hydroxide ions. Although limited clinical data imply that cefiderocol-induced urine discoloration may be reversible, further studies are warranted to elucidate its implications for patient health.

It is important to consider that patients undergoing cefiderocol treatment frequently present with complex and severe medical conditions, which render them susceptible to secondary infections caused by other pathogens, including fungi and viruses. Regarding COVID-19 pneumonia and systemic candida, it is essential to recognize that these conditions may represent underlying issues rather than direct complications associated with the drug.

The FAERS database cannot establish a causal relationship between drugs and adverse drug events (ADEs). FAERS relies on voluntary and spontaneous reporting, allowing not only healthcare professionals but also non-medical individuals, such as consumers and manufacturers, to submit reports. In this study, 5.9% of the reports were submitted by non-medical professionals, and the information provided in these reports has not been verified by healthcare practitioners. As a result, the data may be subject to significant bias. Furthermore, the database contains gaps in patient-related information; for instance, 47.23% of cases lacked age data for the reported patients, and 39.85% were missing gender information. Such incomplete reporting can substantially affect the findings of this study. Additionally, the association between drugs and ADRs may be influenced by comorbidities and concomitant medications; therefore, any causal relationships require further verification through prospective studies.

Conclusion

Overall, our study delineated the clinical characteristics of patients experiencing ADRs associated with cefiderocol across various systems and conducted relevant signal of disproportionate reporting for mining and data analysis based on real-world data from the FAERS database. These adverse clinical outcomes warrant attention in clinical practice to inform safe medication practices or to avoid use in high-risk populations. It is important to note that this investigation is solely based on data analysis; factors such as dosage, treatment duration, and comorbidities have not been fully elucidated regarding their effects on these results. While the findings from signal mining indicate a statistical association, the existence of a causal relationship necessitates further evaluation and research in future studies.

Abbreviations

FAERS	Food and Drug Administration Adverse Event Reporting System
ADE	Adverse drug events
PTs	Preferred terms
SOC	System Organ Class
ROR	Reporting odds ratios
PRR	Proportional reporting ratios
BCPNN	Bayesian Confidence Propagation Neural Network
MGPS	Multi-item Gamma Poisson Shrinker
IC025	The lower limit of 95% CI of the information component
EBGM05	The lower limit of 95% CI of the Empirical Bayes Geometric Mean

Supplementary Information

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Supplementary Material 1

Author contributions

Conceptualization, Mohan Ju and Jindong Hu.; methodology, Hao Lin and Chen Zhu.; sofware, Hao Lin and Chen Zhu; formal analysis, Hao Lin and Mohan Ju.; data curation, Shuang Liu and Yingmin Bi; writing—original draf preparation, Hao Lin, Chen Zhu and Jindong Hu; writing— review and editing, Mohan Ju; funding acquisition, Shuang Liu and Yingmin Bi. All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

Not applicable.

Consent to participate

The requirement for obtaining individual patient consent was waived as the study did not have an impact on clinical care and all protected health information was de-identified.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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