Original Article

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Fosfomycin-associated adverse events: A disproportionality analysis of the FDA Adverse Event Reporting System

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SUMMARY: Fosfomycin, with its unique mechanism of action, has emerged as a promising option for clinicians to combat antimicrobial resistance and the limited availability of effective drugs, which has led to an increase in associated adverse events (AEs). This study aims to explore the AEs caused by fosfomycin through data mining of the US FDA Adverse Event Reporting System (FAERS) to inform clinical safety. As revealed by FAERS, the 796 fosfomycin-associated AEs occurred more commonly in females (61.90%), with Italy reporting the highest incidence (32.40%), and have a significant rise with peak years in 2018 and 2019. The analysis revealed that gastrointestinal disorders, injury, poisoning and procedural complications, and skin and subcutaneous tissue disorders were among the most commonly reported system organ classes (SOCs), accounting for 16.29%, 13.50%, and 11.26% of cases, respectively. The median time to onset (TTO) for fosfomycin associated AEs was 2 days, indicating an early failure type distribution. Off-label use, diarrhoea, and nausea were among the top 50 most frequent AEs, with reporting odds ratios (RORs) of 3.39, 3.87, and 1.79, respectively. These findings emphasize the need for careful monitoring of fosfomycin use, particularly among female patients and in high-reporting regions. The unique profile of fosfomycin associated AEs identified in this analysis calls for a reevaluation of existing safety profiles, as it may differ from previous studies and product labeling. Our findings offer important insights for medical and public health fields, and are essential for enhancing pharmacovigilance and refining clinical management.

Keywords: Fosfomycin, FDA Adverse Event Reporting System, characteristic, managements

1. Introduction

As the problem of antibiotic resistance is increasing alarmingly, physicians have turned to older antibiotics, such as fosfomycin. It is a phosphoenolpyruvate analogue produced by *Streptomyces* spp., discovered in 1969 and approved for treating urinary tract infections. It inhibits bacterial cell wall *via* MurA binding, enters bacteria through cAMP-dependent pathways, reduces adherence to urinary and respiratory epithelial cells, penetrates biofilms, and enhances neutrophil killing through immunomodulation (*1,2*). In addition, fosfomycin exhibits broad-spectrum activity against various Gram-positive and Gram-negative bacteria, including multi-drug-resistant strains, and is well-distributed in multiple tissues, with potential for synergistic action with other antibiotics (*3*). Owing to its unique mechanism of action and outstanding therapeutic efficacy, its clinical application has extended to respiratory, skin and soft tissue infections, and combination therapy in recent years (*1*), raising more issues that require in-depth consideration.

Fosfomycin was generally regarded as safe, with few adverse effects, including gastrointestinal symptoms, skin rashes, electrolyte disturbances, transient changes in blood markers, and abnormalities in liver function (*1,4*). However, some unexpected adverse effects have been identified recently, such as agranulocytosis (*5*) and pseudomembranous colitis (*6*), prompting the need for a systematic integration and evaluation of the fosfomycin-associated adverse events (AEs). The FDA Adverse Event Reporting System (FAERS) database is an essential tool for post-marketing surveillance and early drug safety issue detection, offering regularly updated real-world adverse event reports from various sources (*4,6*). Therefore, we conduct a comprehensively analyzed system-specific side effects of fosfomycin using this database. Our findings can help physicians and health policymakers monitor adverse drug reactions and provide recommendations for the safe clinical use of fosfomycin.

2. Methods

2.1. Ethics statement

This study utilized data from the FAERS, a publicly available and anonymized database. As no individual patient data or identifiers were involved, this analysis was exempt from formal ethics committee review by the Ethical Review Committee of The Fifth People's Hospital of Suzhou. The study conformed to the ethical principles outlined in the Declaration of Helsinki (as revised in 2013, https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki).

2.2. Data source

We performed a retrospective pharmacovigilance study from Quarter 1 (Q1) in 2004 to Q3 in 2024, utilizing the extracted data with 'fosfomycin' as the main suspect (PS), in order to examine fosfomycin-associated AEs that were recorded in the FAERS database. The FAERS data were downloaded from the FDA official website (available at *https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html*). The database included seven data files, namely patient demographic information (DEMO), drug/biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), start/end dates of drug therapy (THER) and indications for drug (INDI) (*7*). A relation was established in the FAERS database architecture to connect each data file by some special identification numbers. We managed FAERS data by Python Version 3.9 for further analysis. Statistical analysis was carried out using Microsoft Office Excel 2021. Informed consent was waived in this observational study since it used data from an international public database that had been anonymized.

2.3. Data extraction

Duplication is unavoidable because the reports are spontaneous, hence the deduplication procedure should be carried out before analysis. We carried out the deduplication in accordance with FDA guidelines. When the CASEID and PRIMARYID were the same, we manually reviewed the reports to eliminate the lower PRIMARYID. Moreover, the CASEID which listed in the deleted cases file was further eliminated. We then identified fosfomycin-associated cases in both the 'drugname' and 'prod_ai' columns using 'fosfomycin' in the 'DRUG' files. To improve accuracy, the 'role_cod' as PS was chosen in the DRUG files. All AEs in FAERS are coded by the preferred term (PT) from standardized Medical Dictionary for Regulatory Activities 26.0 (MedDRA 26.0), including five levels, system organ class (SOC), high-level group term (HLGT), high-level term (HLT), PT and lowest-level term (LLT). Accordingly, MedDRA was used to classify AEs in each report to the corresponding SOC levels in Python. All fosfomycin-associated cases extracted from the FAERS database were performed pharmacovigilance analysis according to MedDRA at both SOC and PT levels. We then retrieved and described the detailed information, including patient characteristics such as gender, age and weight, indications, reporting areas, outcomes and reporters, *etc.* The specific process of data extraction, processing and analysis is illustrated in Figure 1.

2.4. Data mining

Since we are unsure of the precise denominators, it is not possible to statistically calculate the incidence of

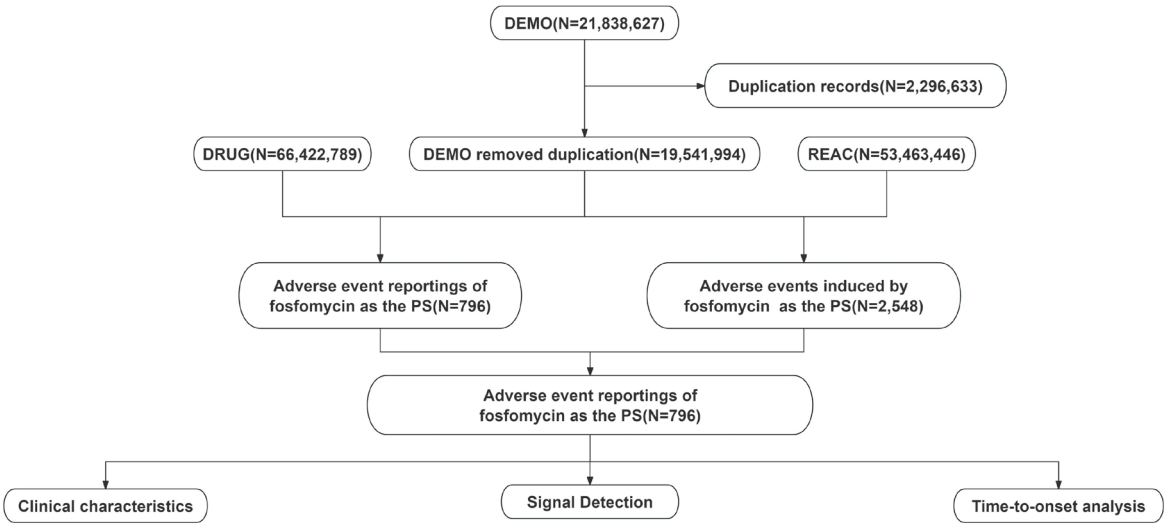

Figure 1. The flow diagram of selecting fosfomycin-related AEs from FAERS. 21,838,627 DEMO, 66,422,789 DRUG, and 53,463,446 REAC records were screened. database adverse event reporting of fosfomycin as the PS (N = 796) was subjected to clinical characteristics, signal detection, and time to onset analysis.

AEs using the FAERS information. Disproportionality analysis, an efficient technique in pharmacovigilance research, can be utilized to recognize indications of disproportionate reporting for adverse events associated with fosfomycin, nevertheless (*8*). The reporting odds ratio (ROR), proportional reporting ratio (PRR), bayesian confidence propagation neural network (BCPNN), and multiitem gamma Poisson shrinker (MGPS) were among the Bayesian and frequentist techniques used to investigate the relationship between fosfomycin and its adverse events. The calculation of the four algorithms is based on the 2 × 2 table of proportional imbalance method (Table 1). AEs were identified as signals when the four algorithms met the criteria simultaneously. The equations and criteria for the four algorithms are shown in Table 2. The higher the indicator value, the stronger the AE signal, suggesting a stronger association between the target drug fosfomycin and its AEs (*9*). PTs and SOCs were used for encoding, categorizing and localizing the signals to analyze the specific SOC involved in AE signals. PTs with reported counts ≥ 3 were selected in our study.

3. Results

3.1. Descriptive analysis

In our study, 21,838,627 AE reports were retained, among which 796 reports were associated with fosfomycin after the exclusion of duplicates. The basic characteristics of patients with fosfomycin-associated AEs were summarized in Table 3. The proportion of women in the reports was significantly higher than men (61.9% *vs.* 11.3%). The patients between 18 and 65 years accounted for the largest proportion (23.1%), while 58.3% of the AEs had missing age data. The top five countries reporting these adverse events were Italy (32.4%), the United States (20.7%), France (9.2%), Spain (4.8%), and Germany (4.4%). The annual reporting trend indicated a notable increase in reports over time, with peak reporting years in 2018 (23.0%) and 2019 (25.8%). More than half of the cases were submitted by Medicine-related workers (68.4%), while 30.3% were submitted by consumers. The reported cases shows a significant rise with peak years in 2018 and 2019, followed by a mild decline.

Table 1. Two-by-two contingency table for disproportionality analyses

	Target Aes	Other AEs	Total
Fosfomycin	A	B	a +b
Other drugs	C	D	c+d
Total	a+c	b+d	a+b+c+d

3.2. Disproportionality analysis

Fosfomycin associated AEs occurrence were distributed across 27 organ systems, the number of case reports for which are shown in Figure 2. The top five SOCs were gastrointestinal disorders (*n* = 415, 16.29%), injury, poisoning and procedural complications (*n* = 344, 13.50%), general disorders and administration site conditions (*n* = 319, 12.52%), skin and subcutaneous tissue disorders (*n* = 287, 11.26%) and nervous system disorders (*n* = 202, 7.93%). Hepatobiliary disorders (ROR = 2.81), pregnancy, puerperium and perinatal conditions (ROR = 2.64), ear and labyrinth disorders (ROR = 2.54), skin and subcutaneous tissue disorders (ROR = 2.22), gastrointestinal disorders (ROR = 2.06) and immune system disorders (ROR = 2.06) were the SOCs with the highest ROR values, indicating a stronger signal for fosfomycin associated AEs (Table 4).

The number of reporting PTs were shown in Table 5, including 35 significant PTs. The results showed that the top 10 PT signals in the reports were off label use, diarrhoea, nausea, product use issue, vomiting, pruritus, urticaria, overdose, dyspnoea and dizziness. Notably, some new and unexpected significant AEs were also found in this study, such as PTs of lip oedema and dysentery.

The analysis of fosfomycin associated AEs in Table 6

Table 2. Four major algorithms used for signal detection

Algorithms	Equation	Criteria
ROR	ROR=ad/b/c 95%CI=$e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	lower limit of 95% CI>1, N≥3
PRR	PRR=a(c+d)/c/(a+b) χ^2=[(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]	PRR≥2, χ^2≥4, N≥3
BCPNN	IC=$\log_2$a(a+b+c+d)(a+c)(a+b) 95%CI= E(IC) ± 2V(IC)^0.5	IC025>0
MGPS	EBGM=a(a+b+c+d)/(a+c)/(a+b) 95%CI=$e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	EBGM05>2

Abbreviation: a, number of reports containing both the target drug and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions. 95%CI, 95% confidence interval; N, the number of reports; χ2, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; E(IC), the IC expectations; V(IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

Table 3. Clinical characteristics of fosfomycin- associated AEs from the FAERS database (Q1 2004 - Q3 2024)

Characteristics	Case numbers	Case proportion (%)
Number of reports	796	
Gender		
Male	90	11.3%
Female	493	61.9%
Miss	213	26.8%
Age(years)		
<18	11	1.4%
18-65	184	23.1%
>65	137	17.2%
Miss	464	58.3%
Top 5 Reported Countries		
Italy	258	32.4%
United States	165	20.7%
France	73	9.2%
Spain	38	4.8%
Germany	35	4.4%
Reporter		
Consumer	241	30.3%
Health professional	45	5.7%
Physician	195	24.5%
Other health-professional	205	25.8%
Pharmacist	99	12.4%
Miss	11	1.4%
Reporting year		
2004	5	1.3%
2005	5	1.3%
2006	2	0.5%
2007	2	0.5%
2008	4	1.0%
2009	7	1.8%
2010	15	3.8%
2011	13	3.3%
2012	29	7.3%
2013	27	6.8%
2014	22	5.6%
2015	39	9.8%
2016	45	11.4%
2017	42	10.6%
2018	91	23.0%
2019	102	25.8%
2020	70	17.7%
2021	77	19.4%
2022	63	15.9%
2023	73	18.4%
2024	63	15.9%

Abbreviation: interquartile range, IQR.

demonstrates that the median time to onset (TTO) was 2 days (IQR: 1.00–6.00 days), with 75% of cases occurring within the first 6 days of treatment. Additionally, the Weibull distribution analysis revealed a shape parameter (β) of 0.59 (95% CI: 0.55–0.64), suggesting a decreasing hazard rate over time.

4. Discussion

Fosfomycin, a long-standing broad-spectrum antibiotic, re-emerges as pivotal in combating multidrug-resistant infections, and its critical role in modern antimicrobial stewardship is underscored by its prominence in managing complex infections (*1-3*). Despite decades of clinical use, the expanding indications and diverse patient populations for fosfomycin have led to a shifting adverse events. Ongoing safety monitoring across various populations is crucial, particularly for the detection and management of potential adverse reactions. The FAERS database serves as a critical platform for collecting and analyzing drug-related adverse AEs, providing essential data for pharmacovigilance and drug safety evaluation (*6*). Our study employs quantitative signal detection methods to analyze fosfomycin associated AEs within the FAERS database, providing evidence based insights to optimize its clinical use.

A systematic review of fosfomycin associated AEs was conducted through structured data mining from the FAERS, covering reports from Q1 2004 to Q3 2024, with 796 cases meeting inclusion criteria. This study noted a slightly higher incidence of AEs in females, a difference not previously reported. The observed gender disparity likely arises from intersecting biological and epidemiological factors. As fosfomycin is FDA (Food and Drug Administration)-approved for urinary tract infections, a condition with 50-fold higher incidence in women, this population inherently experiences greater drug exposure (*10,11*). Sex-specific pharmacokinetic profiles, characterized by prolonged drug elimination and elevated plasma concentrations in women, may exacerbate toxicity risks (*12,13*). Notably, fosfomycin's FDA-approved use in pregnancy introduces a vulnerable subgroup, as that serious adverse reactions are more frequently reported in pregnant women than in non-pregnant women of the same age (*14*). Additionally, female patients are more inclined to report adverse reactions (*15*). These intersecting factors collectively constitute the foundation of the observed gender differences. The analysis of age-related differences was limited to preliminary assessments due to extensive missing data. Lower AEs were observed in children, possibly related to lower drug usage and indeed higher safety in children (*16,17*).

Italy exhibited the highest proportion of fosfomycin related AEs (32.4%), which likely due to Italy's dual role as fosfomycin producer/consumer (*17,18*), combined with potential pharmacogenomic influences. CYP450 enzymes, critical mediators of drug metabolism, demonstrate ethnogeographic variability, with Italian populations displaying distinct CYP2D6 ultra-rapid metabolizer (UM) phenotypic frequencies compared to other European and global cohorts (*13*). Although no direct evidence links CYP2D6-UM status to fosfomycin toxicity, it is hypothesized that accelerated conversion to reactive metabolites or CYP-mediated alterations in renal/hepatic clearance might theoretically elevate AE risks. These genetic predispositions likely interact with regional prescribing patterns (*e.g.*, higher UTI treatment frequency in women) and surveillance biases to amplify observed disparities. Future studies must integrate population-specific CYP genotyping and AE severity

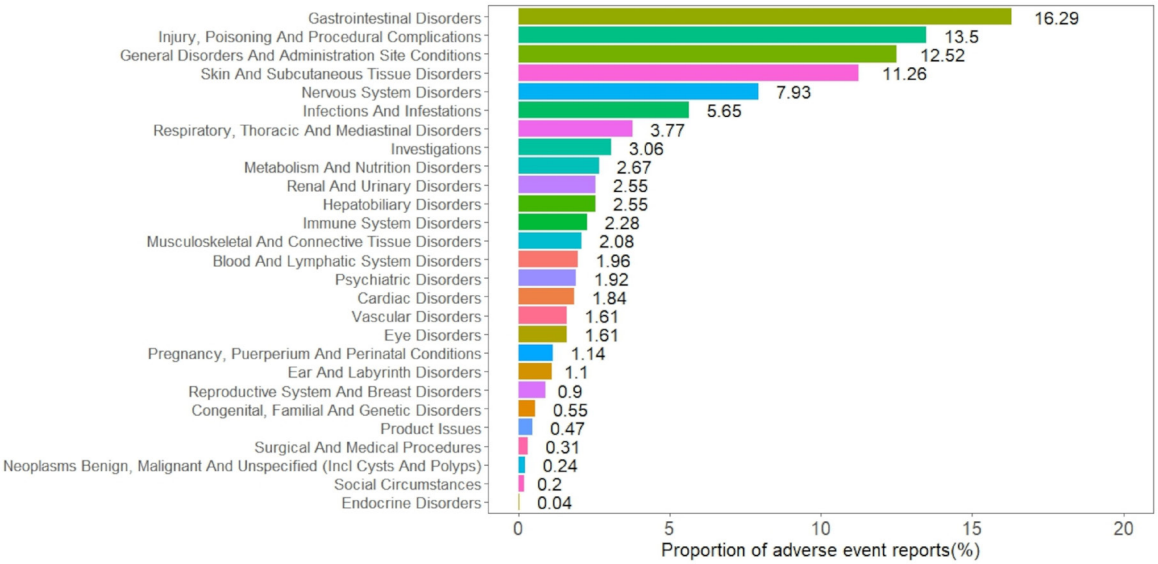

Figure 2. The reported cases of ADEs at each SOC level. The proportion of adverse event reports for each system organ class was shown. Gastrointestinal Disorders had the highest proportion (16.29%), followed by injury, poisoning and procedural complications (13.5%), general disorders and administration site conditions (12.52%), skin and subcutaneous issue disorders (7.93%), and nervous system disorders (6.65%).

Table 4. Signal strength of fosfomycin- associated AEs across system organ classes in the FAERS database

SOC	Numbers	ROR (95%CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Gastrointestinal disorders*	415	2.06 (1.86-2.29)	1.89 (190.24)	1.89 (1.73)	0.92 (0.77)
Infections and infestations	144	1.07 (0.9-1.26)	1.06 (0.59)	1.06 (0.92)	0.09 (-0.16)
Injury, poisoning and procedural complications*	344	1.5 (1.34-1.68)	1.43 (49.69)	1.43 (1.3)	0.52 (0.35)
Ear and labyrinth disorders*	28	2.54 (1.75-3.69)	2.53 (25.93)	2.53 (1.85)	1.34 (0.8)
General disorders and administration site conditions	319	0.67 (0.6-0.76)	0.71 (44.62)	0.71 (0.65)	-0.49 (-0.66)
Metabolism and nutrition disorders	68	1.24 (0.97-1.58)	1.23 (3.03)	1.23 (1.01)	0.3 (-0.05)
Investigations	78	0.47 (0.38-0.59)	0.49 (44.26)	0.49 (0.41)	-1.03 (-1.36)
Skin and subcutaneous tissue disorders*	287	2.22 (1.96-2.51)	2.08 (169.97)	2.08 (1.88)	1.06 (0.88)
Renal and urinary disorders*	65	1.38 (1.08-1.77)	1.37 (6.71)	1.37 (1.12)	0.46 (0.1)
Blood and lymphatic system disorders	50	1.15 (0.87-1.51)	1.14 (0.9)	1.14 (0.9)	0.19 (-0.22)
Respiratory, thoracic and mediastinal disorders	96	0.77 (0.63-0.95)	0.78 (6.08)	0.78 (0.66)	-0.35 (-0.65)
Musculoskeletal and connective tissue disorders	53	0.38 (0.29-0.5)	0.39 (53.21)	0.39 (0.31)	-1.36 (-1.75)
Vascular disorders	41	0.73 (0.54-1)	0.74 (3.87)	0.74 (0.57)	-0.44 (-0.89)
Immune system disorders*	58	2.06 (1.59-2.67)	2.03 (30.83)	2.03 (1.64)	1.02 (0.64)
Hepatobiliary disorders*	65	2.81 (2.2-3.6)	2.77 (74.1)	2.77 (2.25)	1.47 (1.11)
Eye disorders	41	0.79 (0.58-1.08)	0.8 (2.19)	0.8 (0.61)	-0.33 (-0.78)
Psychiatric disorders	49	0.32 (0.24-0.43)	0.33 (68.92)	0.33 (0.26)	-1.58 (-1.99)
Cardiac disorders	47	0.68 (0.51-0.91)	0.69 (6.77)	0.69 (0.54)	-0.54 (-0.96)
Nervous system disorders	202	0.92 (0.8-1.06)	0.93 (1.29)	0.93 (0.82)	-0.11 (-0.32)
Congenital, familial and genetic disorders*	14	1.79 (1.06-3.03)	1.79 (4.86)	1.79 (1.15)	0.84 (0.09)
Surgical and medical procedures	8	0.23 (0.11-0.46)	0.23 (20.85)	0.23 (0.13)	-2.12 (-3.08)
Pregnancy, puerperium and perinatal conditions*	29	2.64 (1.83-3.81)	2.62 (29.23)	2.62 (1.93)	1.39 (0.86)
Reproductive system and breast disorders	23	1.09 (0.72-1.64)	1.09 (0.17)	1.09 (0.77)	0.12 (-0.47)
Social circumstances	5	0.45 (0.19-1.08)	0.45 (3.4)	0.45 (0.22)	-1.16 (-2.34)
Endocrine disorders	1	0.15 (0.02-1.09)	0.15 (4.69)	0.15 (0.03)	-2.71 (-4.75)
Product issues	12	0.29 (0.17-0.52)	0.3 (20.17)	0.3 (0.19)	-1.75 (-2.55)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	0.09 (0.04-0.19)	0.09 (58.29)	0.09 (0.05)	-3.51 (-4.6)

Abbreviation: Asterisks (*) indicate statistically significant signals in algorithm; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% CI of EBGM; IC, information component; IC025, the lower limit of the 95% CI of the IC; CI, confidence interval; AEs, adverse events.

assessments to differentiate genetic contributions from confounding sociomedical variables.

The surge in adverse event reports during 2018-2019 likely reflects dual contributing factors. First, international guidelines (*e.g.*, German, Italian, and antimicrobial resistance consensus) issued in 2016–2017 explicitly recommended fosfomycin as first-line therapy for multidrug-resistant UTIs, particularly against ESBL-

Table 5. Top 50 most frequent adverse events for Fosfomycin at the preferred term level from FAERS

PT	Numbers	ROR (95%CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Off label use*	112	3.39 (2.8-4.09)	3.28 (180.2)	3.28 (2.8)	1.71 (1.44)
Diarrhoea*	101	3.87 (3.17-4.72)	3.75 (206.14)	3.75 (3.18)	1.91 (1.62)
Nausea*	59	1.79 (1.38-2.32)	1.77 (20.05)	1.77 (1.43)	0.82 (0.45)
Drug ineffective	57	1.02 (0.79-1.33)	1.02 (0.03)	1.02 (0.82)	0.03 (-0.35)
Product use issue*	50	6.66 (5.03-8.81)	6.55 (235.77)	6.55 (5.18)	2.71 (2.3)
Vomiting*	48	2.47 (1.86-3.29)	2.44 (41.2)	2.44 (1.92)	1.29 (0.87)
Pruritus*	43	2.92 (2.16-3.95)	2.89 (53.37)	2.89 (2.24)	1.53 (1.09)
Urticaria*	43	6.39 (4.73-8.64)	6.3 (192.12)	6.3 (4.89)	2.65 (2.22)
Overdose*	40	4.24 (3.1-5.79)	4.19 (97.3)	4.18 (3.22)	2.07 (1.61)
Dyspnoea*	38	1.59 (1.15-2.19)	1.58 (8.16)	1.58 (1.21)	0.66 (0.19)
Headache	34	1.28 (0.91-1.79)	1.27 (2)	1.27 (0.96)	0.35 (-0.14)
Dizzines*s	31	1.47 (1.03-2.09)	1.46 (4.57)	1.46 (1.09)	0.55 (0.04)
Malaise*	29	1.53 (1.06-2.21)	1.52 (5.26)	1.52 (1.12)	0.61 (0.08)
Asthenia*	28	1.76 (1.21-2.55)	1.75 (9)	1.75 (1.28)	0.8 (0.27)
Hypersensitivity*	28	3.59 (2.47-5.21)	3.56 (51.77)	3.56 (2.61)	1.83 (1.29)
Rash*	28	1.57 (1.08-2.28)	1.56 (5.75)	1.56 (1.15)	0.65 (0.11)
Fatigue	27	0.82 (0.56-1.2)	0.82 (1.04)	0.82 (0.6)	-0.28 (-0.83)
Erythema*	27	3.12 (2.13-4.56)	3.1 (38.46)	3.1 (2.25)	1.63 (1.08)
Pyrexia*	23	1.55 (1.03-2.34)	1.55 (4.5)	1.55 (1.1)	0.63 (0.04)
Urinary tract infection*	23	3.23 (2.14-4.88)	3.21 (35.16)	3.21 (2.28)	1.68 (1.09)
Abdominal pain*	21	2.15 (1.4-3.3)	2.14 (12.75)	2.14 (1.49)	1.1 (0.48)
Abdominal pain upper*	20	2.33 (1.5-3.62)	2.32 (15.11)	2.32 (1.61)	1.22 (0.58)
Product use in unapproved indication*	19	2.06 (1.31-3.23)	2.05 (10.23)	2.05 (1.4)	1.03 (0.39)
Pathogen resistance*	17	44.47 (27.58-71.68)	44.18 (715.96)	44.08 (29.57)	5.46 (4.78)
Decreased appetite	15	1.56 (0.94-2.59)	1.55 (2.98)	1.55 (1.02)	0.64 (-0.09)
Syncope*	15	3.49 (2.1-5.8)	3.48 (26.51)	3.48 (2.27)	1.8 (1.07)
Pain	14	0.52 (0.31-0.88)	0.53 (6.06)	0.53 (0.34)	-0.93 (-1.68)
Tachycardia*	13	3.46 (2.01-5.96)	3.45 (22.6)	3.45 (2.18)	1.78 (1.01)
Drug hypersensitivity	13	1.54 (0.89-2.66)	1.54 (2.45)	1.54 (0.97)	0.62 (-0.15)
Hypokalaemia*	12	6.22 (3.53-10.97)	6.2 (52.33)	6.2 (3.85)	2.63 (1.83)
Neutropenia*	12	2.1 (1.19-3.71)	2.1 (6.91)	2.1 (1.31)	1.07 (0.27)
Loss of consciousness*	12	2.19 (1.24-3.86)	2.18 (7.72)	2.18 (1.36)	1.13 (0.32)
Hypotension	11	1.29 (0.71-2.33)	1.29 (0.7)	1.29 (0.78)	0.36 (-0.47)
Condition aggravated	11	0.9 (0.5-1.63)	0.9 (0.12)	0.9 (0.55)	-0.15 (-0.99)
Exposure during pregnancy*	11	4.35 (2.41-7.87)	4.34 (28.26)	4.34 (2.64)	2.12 (1.28)
Prescribed overdose*	10	12.37 (6.65-23.02)	12.32 (104.02)	12.32 (7.32)	3.62 (2.75)
Paraesthesia	10	1.46 (0.79-2.72)	1.46 (1.46)	1.46 (0.87)	0.55 (-0.32)
Tremor	10	1.39 (0.75-2.59)	1.39 (1.11)	1.39 (0.83)	0.48 (-0.39)
Product prescribing error*	10	10.82 (5.82-20.14)	10.78 (88.76)	10.78 (6.41)	3.43 (2.56)
Lip oedema*	10	54.86 (29.46-102.16)	54.64 (525.29)	54.5 (32.39)	5.77 (4.9)
Dysentery*	9	113.39 (58.83-218.57)	113 (993.71)	112.39 (64.9)	6.81 (5.9)
Back pain	9	0.9 (0.47-1.73)	0.9 (0.1)	0.9 (0.52)	-0.15 (-1.06)
Rash erythematous*	9	4.97 (2.58-9.56)	4.95 (28.42)	4.95 (2.86)	2.31 (1.39)
Vertigo*	9	3.44 (1.79-6.61)	3.43 (15.48)	3.43 (1.98)	1.78 (0.86)
Oedema peripheral	8	1.49 (0.74-2.98)	1.49 (1.28)	1.49 (0.83)	0.57 (-0.39)
Abdominal distension	8	1.84 (0.92-3.69)	1.84 (3.09)	1.84 (1.03)	0.88 (-0.08)
Hepatocellular injury*	8	12.64 (6.31-25.31)	12.6 (85.43)	12.6 (7.05)	3.65 (2.69)
Rash maculo-papular*	8	8.71 (4.35-17.43)	8.68 (54.38)	8.68 (4.86)	3.12 (2.15)
Palpitations	8	1.61 (0.8-3.22)	1.61 (1.85)	1.61 (0.9)	0.69 (-0.28)
Dehydration	8	1.4 (0.7-2.79)	1.39 (0.9)	1.39 (0.78)	0.48 (-0.48)

Abbreviation: Asterisks (*) indicate statistically significant signals in algorithm; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% CI of EBGM; IC, information component; IC025, the lower limit of the 95% CI of the IC; CI, confidence interval; PT, preferred term.

Table 6. Time to onset of fosfomycin-associated adverse events and Weibull distribution analysis

Drug	TTO (days)		Weibull distribution		
	Case reports	Median (d)(IQR)	Scale parameter: α (95%CI)	Shape parameter: β (95%CI)	Type
Fosfomycin	225	2.00 (1.00,6.00)	6.43(4.92,7.93)	0.59 (0.55,0.64)	Early failure

Abbreviation: TTO, time to onset; CI, confidence interval; IQR, interquartile range.

producing Enterobacteriaceae and fluoroquinolone-resistant strains (*19-22*), driving increased clinical utilization. Second, enhancements in the FAERS database improved adverse event detection: the 2018 DrugCentral update standardized adverse event terminology and drug coding (*23*), while optimized data mining algorithms (*24*) and expanded consumer reporting mechanisms (*15*) elevated reporting sensitivity and accessibility. This peak likely represents combined effects of heightened drug exposure and improved surveillance efficacy. Further quantification through temporal prescription data and report source analysis would clarify their relative contributions.

Comparing with a decade-old FAERS-based study on fosfomycin associated AEs (*4*) and recent research (*5-6,10,25*), our study revealed that persistent gastrointestinal disorders and skin and subcutaneous tissue disorders, reduced blood and lymphatic system disorders, and the increase of nervous system disorders. This situation may arises from the increasing use of fosfomycin and its ability to penetrate the blood-brain barrier during meningitis (*26-28*), its role in combination therapies with interacting drugs (*29-31*), and its prolonged infusion and administration in patients with renal impairment (*31-32*) – all factors increasing nervous system disorders. Facing this new context of antibiotic use, clinicians should be encouraged to pay closer attention to neurological AEs to enhance patients' experience of care.

Among the SOCs with ROR > 2, we identified two new SOCs with high ROR, namely, pregnancy, puerperium and perinatal conditions and ear and labyrinth disorders. Although fosfomycin is generally considered safe and effective during pregnancy and lactation (*10*), its low protein binding contributes to its good diffusion into fluids and tissues, including placenta and latex (*1-2*), so it has to be considered that fosfomycin may have adverse effects throughout pregnancy. It's worth to explore the ear and labyrinth disorders, as it has been demonstrated that fosfomycin can reduce ototoxicity in combination therapy many years ago (*33,34*). While both SOCs demonstrated statistically significant associations with fosfomycin, the limited case reports in the FAERS database and absence of clinical documentation suggest their overall incidence rates may remain relatively low. Further research and ongoing monitoring are warranted to better elucidate the clinical implications of these findings.

The most frequently reported PT is off-label use, as fosfomycin, while approved for urinary tract infections, it is clinically employed for a variety of infections in multiple anatomical sites (*10,27-32*). Meanwhile, product use issue and overdose, also appeared in the top 10 PTs, which may suggest that fosfomycin's expanded therapeutic scope may increase medication-related risks, necessitating heightened vigilance in clinical practice. Among the other TOP 10 PTs, we identified two special PTs: dyspnoea and dizziness. There is currently no clear evidence based relationship between fosfomycin and dyspnoea. Considering that fosfomycin is now also used for pulmonary infections (*29-32*), it cannot be ruled out that the dyspnoea is due to the patient's underlying disease, which requires close attention in clinical practice. The dizziness is consistent with the increase of nervous system disorders mentioned in the SOC analyses, further suggesting the need for vigilance concerning the neurological AEs associated with the use of fosfomycin.

There are two off-label PTs worth further exploration: lip edema and dysentery. Lip oedema may be classified as one of the skin and subcutaneous tissue disorders; however, it is proposed as a separate PT, and no studies examining the correlation between lip oedema and fosfomycin, which warrants further attention. Fosfomycin is generally used to treat dysentery; however, it can also lead to antibiotic-associated pseudomembranous colitis (*6*). This raises the possibility that fosfomycin may disrupt the normal gut flora, resulting in dysentery-like symptoms, which needs further investigation.

The median TTO was 2 days, and the hazard rate decreased over time, indicating that the fosfomycin associated AEs were early onset. Although some unexpected AEs were found in this study, close monitoring during the early stages of treatment can significantly reduce the risk.

Our study, while providing valuable insights into fosfomycin safety, has several limitations: (1) Potential biases inherent to FAERS' passive surveillance system, including reporting inaccuracies and delays; (2) Inability to determine AE incidence rates due to unavailable total patient exposure data; (3) Demonstration of statistical associations rather than established biological causality. Future research should employ prospective designs integrating epidemiological and clinical trial data to better characterize the drug's safety profile.

5. Conclusion

This study methodically assessed fosfomycin associated AEs through a comprehensive analysis of the FAERS database from Q1 2004 to Q3 2024. Our investigation not only validated known safety information but also uncovered potential risks, including off-label reports of several novel and unexpected AEs such as dyspnoea, dizziness, lip oedema, and dysentery. Our research provides valuable insights for medical practice and public health decision making, and further studies are needed to confirm these findings.

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