



Original article

Effectiveness and tolerability of intravenous fosfomycin in treating complicated urinary tract infections caused by *Escherichia coli*: a prospective cohort study from the FOSFOMIC project

Elisa Moreno-Mellado^{1,2,3}, Abdullah Tarik Aslan⁴, Murat Akova⁴, Eva León^{2,5}, Nicolás Merchante^{2,5}, David Vinuesa⁶, Encarnación Moral-Escudero⁷, Svetlana Sadyrbaeva-Dolgova⁸, Salvador López-Cárdenas⁹, Ángela Cano-Yuste^{3,10}, Matteo Rinaldi^{11,12}, María Núñez-Núñez⁶, Maddalena Giannella^{11,12}, Jesús Sojo-Dorado^{1,2,3}, Ana Cristina Antolí-Royo¹³, Natalia Chacón^{1,2,3,9}, Vicente Merino-Bohórquez¹⁴, Inés Portillo^{1,15}, Jesús Rodríguez-Baño^{1,2,3}, Fernando Docobo-Pérez^{1,15,†}, Belén Gutiérrez-Gutiérrez^{1,2,3,*}, FOSFOMIC team*

¹ Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Seville, Spain

² Departamento de Medicina, Universidad de Sevilla/Instituto de Biomedicina de Sevilla/Centro Superior de Investigaciones Científicas (CSIC), Seville, Spain

³ Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain

⁴ Department of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey

⁵ Unidad de Enfermedades Infecciosas y Microbiología, Hospital Universitario de Valme, Seville, Spain

⁶ Unidad de Enfermedades Infecciosas, Hospital Universitario San Cecilio, Instituto de Investigación Biosanitario de Granada, Granada, Spain

⁷ Department of Infectious Medicine, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

⁸ Unidad de Enfermedades Infecciosas, Hospital Universitario Virgen de las Nieves, Instituto de Investigación Biosanitario de Granada, Granada, Spain

⁹ Unit of Infectious Diseases and Clinical Microbiology, Jerez de la Frontera University Hospital, Jerez de la Frontera, Cádiz, Spain

¹⁰ Servicio de Enfermedades Infecciosas, Hospital Universitario Reina Sofía/Instituto Maimónides de Investigación Biomédica de Córdoba/Universidad de Córdoba (Departamento de Ciencias Médicas y Quirúrgicas), Córdoba, Spain

¹¹ Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

¹² Infectious Diseases Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico Sant'Orsola, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

¹³ Department of Internal Medicine, Complejo Asistencial de Ávila, Ávila, Spain

¹⁴ Unidad Clínica de Farmacia, Hospital Universitario Virgen Macarena and Departamento de Farmacología, Universidad de Sevilla, Seville, Spain

¹⁵ Departamento de Microbiología, Facultad de Medicina, Universidad de Sevilla/Instituto de Biomedicina de Sevilla/CSIC, Seville, Spain

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ABSTRACT

Objectives: The FOSFOMIC study assessed the clinical and microbiological effectiveness, and safety of intravenous fosfomycin in treating complicated urinary tract infections (cUTIs) caused by *Escherichia coli*, in comparison with other intravenous antimicrobials.

Methods: A prospective, multinational matched cohorts study involving adults with community-acquired cUTIs and receiving targeted therapy with intravenous fosfomycin or other first-line drugs (beta-lactams or fluoroquinolones) was conducted from November 2019 to May 2023 in ten centres from Spain, Italy, and Türkiye. Matching criteria included type of infection acquisition, Charlson and Pitt scores. Endpoints were clinical and microbiological cure, mortality, recurrence, and adverse effects. Analyses used conditional logistic regression and desirability of outcome ranking (DOOR).

Results: Overall, 155 matched pairs were included. Clinical and microbiological cure rates were 65.2% (101/155; 95% CI, 57.4–72.2) and 63.2% (98/155; 95% CI, 55.4–70.4) with fosfomycin and comparators, respectively (adjusted OR, 1.09; 95% CI, 0.68–1.73; *p* 0.73). Mortality rates were 1.9% (3/155; 95% CI, 0.7–5.5) and 5.8% (9/155; 95% CI, 3.1–10.7), respectively (*p* 0.11). Recurrence rates were 14.2% (22/155; 95% CI, 9.6–20.6) in the fosfomycin group vs. 10.3% (16/155; 95% CI, 6.1–16.1) (*p* 0.39). Severe adverse effects

* Corresponding author. Belén Gutiérrez-Gutiérrez, Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Avda Dr Fedriani 3, Seville 41009, Spain.

E-mail address: bgutierrez2@us.es (B. Gutiérrez-Gutiérrez).

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† Belén Gutiérrez-Gutiérrez and Fernando Docobo-Pérez contributed equally as senior authors.

Pyelonephritis
Safety

occurred in 1.9% (3/155; 95% CI, 0.7–5.5) of patients treated with fosfomycin vs. 0.6% (1/155; 95% CI, 0.0–3.3) in the control group (p 0.62). Non-severe adverse effects were more frequent with fosfomycin, affecting 23.3% (36/155; 95% CI, 17.0–30.7) compared with 7.7% (12/155; 95% CI, 4.1–13.1) in the control group (adjusted OR, 5.36; 95% CI, 2.04–14.1; p < 0.001). In DOOR analysis, fosfomycin demonstrated comparable effectiveness in treating pyelonephritis (probability of better DOOR, 54.0%; 95% CI, 48.5–59.6) and in comparison with ceftriaxone (50.3%; 95% CI, 44.7–55.8), without evidence of inferiority in bacteraemic urinary tract infections (DOOR, 47.3%; 95% CI, 41.7–52.8).

Discussion: Fosfomycin is a viable option for treating cUTIs caused by *E. coli*, allowing for diversification in the treatment of these high-incidence infections. **Elisa Moreno-Mellado, *Clin Microbiol Infect* 2025;31:839**

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Introduction

The global spread of antimicrobial-resistant microorganisms, particularly among Gram-negative bacteria, poses a significant public health challenge [1]. Urinary tract infections (UTIs) caused by *E. coli* are the most common, highlighting the need for diverse treatments with low ecological impact. This has renewed interest in older antimicrobial agents overshadowed by broad-spectrum antibiotics [2].

Complicated UTIs (cUTIs) have shown increasing prevalence, resulting in considerable morbidity and significant healthcare expenses. Fosfomycin, with over four decades of clinical use, disrupts bacterial cell wall biosynthesis by inhibiting peptidoglycan synthesis. It is effective against a wide array of Enterobacterales, including strains-producing extended-spectrum β -lactamases (ESBLs), AmpC or carbapenemases [3]. Although its use has increased mainly for uncomplicated UTIs [4], fosfomycin continues to exhibit low resistance rates against *E. coli*.

The intravenous form of fosfomycin (fosfomycin disodium) is approved in numerous countries for treating various infections, including cUTIs and bloodstream infections, but remains unavailable in several countries, including the United States, which limits its global applicability. Moreover, aspects of its clinical applicability remain uncertain because of less rigorous regulatory standards at the time of its introduction, leading the European Medicines Agency to recommend usage restrictions in 2020 [5].

Despite these limitations, recent studies, including randomized trials, have underscored the potential usefulness of fosfomycin in managing diverse infections [6–8], particularly cUTIs.

Additionally, there is evidence suggesting that oral fosfomycin may be a reasonable option as step-down therapy in cUTI [9,10]. This study contributes to the understanding of fosfomycin treatment by evaluating not only its efficacy but also its tolerability and safety in a real-world setting. This approach provides a more comprehensive perspective on the drug's use in routine clinical practice, complementing findings from controlled clinical trials.

This study aimed to evaluate the efficacy of fosfomycin in community-acquired cUTIs caused by *E. coli* using an observational design, complementing recent data from randomized trials.

Methods

Study design and population

The FOSFOMIC study (ClinicalTrials.gov Identifier: NCT04076436) is a prospective, multicentre, matched-cohort study conducted across ten centres in Spain, Italy, and Türkiye from November 2019 to May 2023. Patients over 18 years admitted with community-acquired cUTIs caused by *E. coli* were eligible if receiving

intravenous targeted therapy with the drugs of interest. cUTIs were defined according to Food and Drug Administration (FDA) criteria [11], characterized by pyuria, microbial detection in urine or blood cultures, and symptoms like fever, chills, and lower back pain. Pyelonephritis was considered a specific subgroup of cUTIs [11].

The fosfomycin cohort included adult patients who received intravenous fosfomycin for cUTI as targeted monotherapy, initiated within 24 hours of antibiogram results, and continued for at least 72 hours. The control cohort included patients meeting the same age criteria who were treated with intravenous beta-lactams, fluoroquinolones, or other antimicrobials included in the antimicrobial guidelines of the participating centres to treat these infections, as targeted monotherapy, following the same time criteria. Treatment decisions were made exclusively by attending physicians. Matching criteria included infection acquisition type, Charlson Comorbidity Index (± 2 points) [12], and Pitt score (± 1 point) [13]. Thus, for each patient in the fosfomycin group who met the inclusion criteria, a matched control was selected based on these criteria, with both being included in the study for prospective follow-up. Exclusion criteria were palliative care, lack of informed consent, age under 18, prostatitis and nosocomial cUTI.

We evaluated the efficacy and tolerability of fosfomycin across three matched subgroups: patients with pyelonephritis, patients with bacteraemia, and patients treated with ceftriaxone as targeted therapy. In all subgroups, fosfomycin-treated cases were matched with control cases. The consideration of these subgroups was based on their significant clinical interest and the availability of a sufficient sample size of matched pairs to allow for their analysis.

Ethical approval was granted by the Ethics Committee of Biomedical Research of Andalusia (0046/19 EPA-SP) and other participating centres as per local requirements. All participants provided written informed consent. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14] (Table S1).

Study outcomes, variables, and definitions

The primary outcome was clinical and microbiological cure at day 21 from infection diagnosis. Secondary outcomes included 30-day mortality, recurrence until day 30, and occurrence of severe and non-severe adverse effects.

Infections were classified as community acquired if they occurred in a patient not hospitalized in the preceding week or began within 72 hours of hospital admission, encompassing both community-acquired and non-nosocomial healthcare-related infections.

Clinical and microbiological cure entailed the disappearance of all new symptoms or signs related to the UTI, coupled with a negative urine culture conducted at day 21. Isolation of urinary

pathogens other than the initial causative organism was considered as microbiological cure only if not accompanied by symptoms and deemed asymptomatic bacteriuria. Recurrence during follow-up was defined as the re-emergence of signs and symptoms related to an *E. coli* UTI, post-treatment completion and until day 30. Adverse effects encompassed any adverse or unfavourable occurrences in study participants, including signs, symptoms, or illnesses, regardless of their relation to the administered drug. Severe adverse effects were those with potential for significant health harm, such as risk of death or necessitating hospitalization.

Explanatory variables included age, gender, chronic diseases (e.g. diabetes, heart or renal failure, liver disease, and cancer), Charlson Comorbidity Index, immunosuppression, creatinine clearance, Pitt score, severe sepsis/shock [15], and Sequential Organ Failure Assessment (SOFA) score. The type of UTI was categorized into several groups: pyelonephritis, renal abscess, cystitis, non-localizable infections; with or without bacteraemia; device-associated or not; with or without hydronephrosis. Treatment aspects such as empirical or targeted therapy, MIC, dosage, duration, and reasons for treatment change (including clinical or microbiological failure, intolerance, new infections, or switching to oral route) were thoroughly recorded. Patients' visits were scheduled for days 0 (initial assessment with clinical criteria for UTI and collection of blood and urine cultures), 2, 5, 7, 14, the cure test (day 21), and day 30. Subsequent visits focused on tracking clinical progress, evaluating adverse effects, and collecting urine cultures. If a patient was discharged before day 21, a study investigator scheduled an appointment and provided instructions for the patient to return on day 21 for the "test of cure" visit and urine culture collection. Patients who did not attend this day-21 visit were recorded as lost to follow-up and the episode was not considered. On day 30, a visit or phone call assessed mortality and other secondary variables like recurrences and adverse effects.

Microbiology methods

Microbial identification was performed using Matrix-Assisted Laser Desorption/Ionization-Time Of Flight (MALDI-TOF) mass spectrometry. Susceptibility testing for fosfomycin was conducted using agar dilution in triplicate, following the 2023 European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations [16]. The Epsilon test was also employed. Isolates were considered ESBL producers if at least one phenotypic confirmatory test was positive according to EUCAST criteria or confirmed by molecular methods.

Statistical analysis

Missing data were assessed using Little's Missing Completely at Random (MCAR) test, and multiple imputation via the Markov Chain Monte Carlo method was applied to address missingness. Univariable and multivariable analyses were conducted using conditional logistic regression to account for matched data, adjusting for potential confounders identified in univariate analysis ($p < 0.10$).

Potential interactions were identified through TreeNet analysis (Salford Predictive software) and included in the models if they were statistically significant ($p < 0.05$) and clinically relevant. Collinearity was assessed using the variance inflation factor (< 2) to ensure model stability. Variable selection for the final multivariable models followed a backward stepwise approach, guided by the Akaike information criterion.

The results of the multivariable analyses, including adjusted OR (aOR) with 95% CIs, are reported in accordance with guidelines for multivariable regression model reporting [17] (Table S2).

Finally, desirability of outcome ranking (DOOR) analysis [18] compared fosfomycin and control treatments across the entire cohort and in the three previously defined matched subgroups of cases and controls. This analysis established four mutually exclusive hierarchical levels of outcomes in descending order of desirability: (a) clinical and microbiological cure on day 21 without the appearance of recurrences or severe adverse effects, (b) no clinical-microbiological cure on day 21 and/or recurrences, (c) severe adverse effects on day 30, and (d) death on day 30. In a secondary analysis, for cases that achieved cure at day 21, the presence of non-severe adverse effects was used as a tiebreaker. The proportion and 95% CIs of cases treated with fosfomycin showing a better DOOR compared with those treated with controls were calculated.

The statistical analyses were conducted using multiple software platforms, including R software (version 4.4.1), SPSS 26.0 (SPSS Inc.), and the Salford Predictive Modeler software 8.3.4.

Results

Characteristics of the study cohorts

Overall, 386 patients were eligible; 182 received intravenous fosfomycin treatment, and 204 other active intravenous antimicrobials. A total of 155 patients treated with targeted fosfomycin were matched with their controls according to predefined criteria (Fig. 1). Table 1 details the clinical and microbiological profiles of the patients. The median age was 62 years (interquartile range [IQR], 46–73) in the fosfomycin group and 65 years (IQR, 48.5–75.5) in the control group ($p 0.11$), and both groups included a majority of women. The median Charlson comorbidity index was 1.00 in each group (IQR, 0–3; $p 0.08$). Most infections in both groups were strictly community acquired, accounting for 90.3% (140/155). The predominant UTIs were pyelonephritis, observed in 60.6% (94/155) of fosfomycin-treated patients and 59.4% (92/155) of control-treated patients ($p 0.82$), and cystitis, present in 20.0% (31/155) of patients in the fosfomycin group vs. 17.4% (27/155) in the control group ($p 0.45$).

Overall, there were no significant differences between the groups regarding demographics, baseline comorbidities, infection acquisition type, urinary infection type, bacteraemia development, infection severity, ESBL-producing organism infection, or receipt of appropriate empirical treatment. The most used intravenous antimicrobials in the control group were ceftriaxone, prescribed to 55.4% (86/155) of patients, followed by ciprofloxacin (10.3%; 16/155), amoxicillin/clavulanic acid (9.0%; 14/155), piperacillin–tazobactam (7.1%; 11/155), meropenem (7.1%; 11/155), ertapenem (5.2%; 8/155), and others (5.9%; 9/155).

The predominant dosing regimens for fosfomycin (adjusted for renal function) were 4 g every 6 hours (80.0%; 124/155), 4 g every 8 hours (14.8%; 23/155), and 4 g every 12 hours (5.2%; 8/155). A description of the empirical therapy administered, including the type of antibiotics used and the duration of treatment, is provided in Table S3.

Outcomes

Clinical and microbiological cure rates at day 21 were similar between patients treated with fosfomycin (65.2%; 101/155; 95% CI, 57.4–72.2) and those treated with other drugs (63.2%; 98/155; 95% CI, 55.4–70.4; $p 0.69$). Mortality rates were 1.9% (3/155; 95% CI, 0.7–5.5) in the fosfomycin group compared with 5.8% (9/155; 95% CI, 3.1–10.7) in the control group ($p 0.08$). Recurrence occurred in 14.2% of fosfomycin-treated patients (22/155; 95% CI, 9.6–20.6) and 10.3% of control-treated patients (16/155; 95% CI, 6.1–16.1; $p 0.26$). Severe adverse effects were reported in 1.9% of patients in the

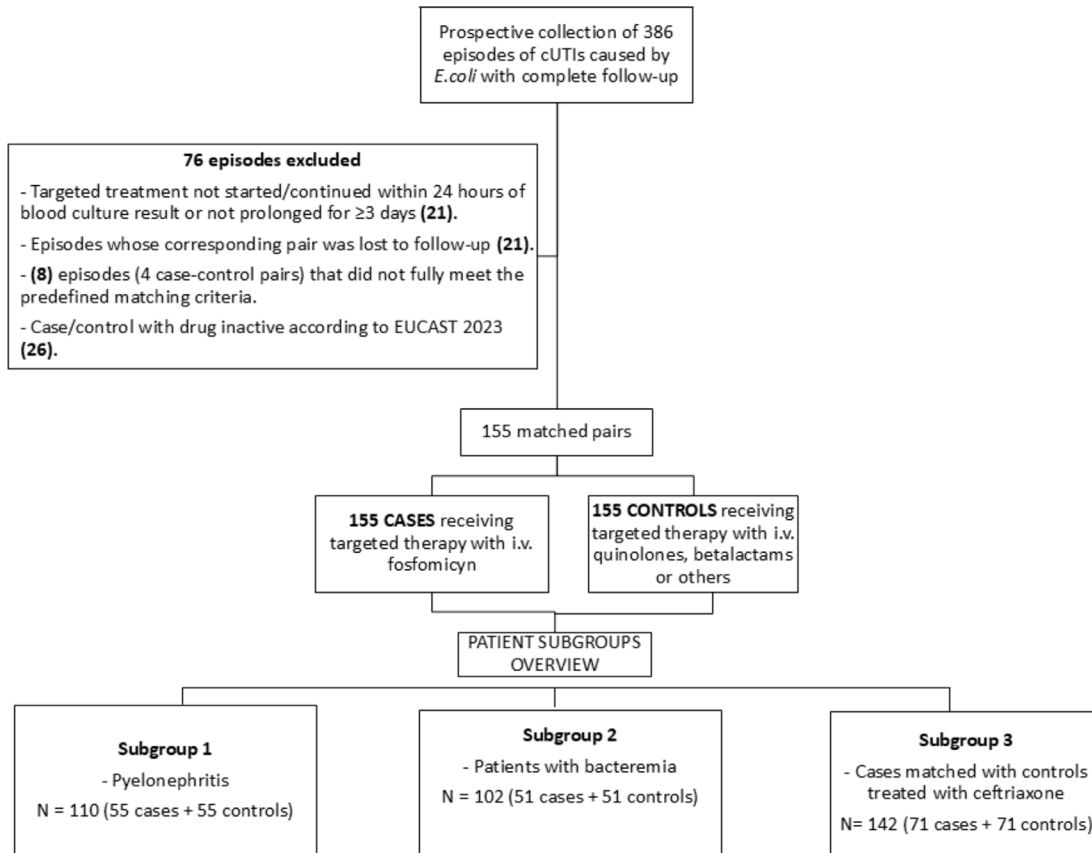


Fig. 1. Flow chart. cUTI, complicated urinary tract infection; i.v., intravenous; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

fosfomycin group (3/155; 95% CI, 0.7–5.5) and 0.6% in the control group (1/155; 95% CI, 0.0–3.3; p 0.34, Table 2). However, non-severe adverse effects were more frequent among fosfomycin-treated patients, occurring in 23.2% (36/155; 95% CI, 17.0–30.7) compared with 7.7% (12/155; 95% CI, 4.1–13.1) in the control group ($p < 0.001$). Details regarding the types of non-severe adverse effects are provided in a footnote in Table 2.

Adjusted multivariate analysis and DOOR analysis

In the adjusted multivariate analyses using conditional logistic regression for matched pairs (Table S4), no significant differences in clinical and microbiological cure on day 21 were found between patients treated with fosfomycin or matched controls (aOR, 1.09; 95% CI, 0.69–1.73; p 0.73) or recurrence (aOR, 1.12; 95% CI, 0.47–2.69; p 0.80). However, targeted treatment with fosfomycin was significantly associated with a higher risk of non-severe adverse effects (aOR, 5.36; 95% CI, 2.04–14.1; $p < 0.001$). The proportion of cases with a better DOOR among those treated with fosfomycin was 50.5% (95% CI, 45.0–56.1%; Table 3 and Fig. 2).

Sensitivity analysis in different patient subgroups

Table S4 outlines the occurrence percentages of various analysed variables in cases and controls across the three defined matched subgroups, along with the adjusted OR for those treated with fosfomycin compared with other intravenous drugs. No significant differences were observed in terms of clinical and microbiological cure across the subgroups: in the pyelonephritis subgroup (55 pairs, Table S5), the aOR was 1.54 (95% CI, 0.67–3.52, p 0.31); in the bacteraemia subgroup (51 pairs, Table S6), the aOR

was 0.69 (95% CI, 0.29–1.62, p 0.40); and in the subgroup of cases matched with controls treated with ceftriaxone (71 pairs, Table S7), the aOR was 0.94 (95% CI, 0.42–2.09, p 0.88).

The proportion of cases with a better DOOR among those treated with fosfomycin was 54.0% (48.5–59.6%) in the pyelonephritis subgroup; 47.3% (41.7–52.8%) in the bacteraemia subgroup; and 50.3% (44.7–55.8%) in the subgroup of cases matched with controls treated with ceftriaxone (Table 3 and Fig. 1). When non-severe adverse effects were considered as a tiebreaker for cases and controls achieving clinical and microbiological cure, the percentage of fosfomycin-treated cases with a better DOOR decreased across both the overall cohort and the subgroups. Even in this scenario, the upper CI did not fall below 50% in any subgroup, suggesting that fosfomycin cannot be inferred to be a worse option compared with controls (Table S8 and Fig. S1).

Discussion

Our study strongly suggests that targeted fosfomycin treatment for cUTIs caused by *E. coli* is not associated with worse outcomes compared with standard therapies. However, it was linked to an increased incidence of non-severe adverse effects, primarily gastrointestinal.

The ZEUS [7] and FOREST [8] randomized clinical trials confirmed fosfomycin's efficacy while also noting increased adverse events. Complementing these studies, our research provides a comprehensive evaluation of fosfomycin's effectiveness, safety, and tolerability, particularly for community-acquired cUTIs caused by *E. coli*. Using DOOR analysis, we assessed multiple outcomes, including mortality, clinical and microbiological cure, recurrence, and adverse events.

Table 1
Clinical characteristics of matched patients with complicated urinary tract infections caused by *Escherichia coli*^a

Characteristic	Treatment with fosfomycin (n = 155)	Treatment with other drugs (n = 155)	p
Age, median (IQR) (y)	62 (46–73)	65 (48.5–75.5)	0.11
Female sex	103 (66.5)	103 (66.5)	>0.99
Charlson index, median (IQR)	1.00 (0.00–3.00)	1.00 (0.00–3.00)	0.08
Congestive heart failure	8 (5.2)	17 (11.0)	0.06
Connective tissue disease	9 (5.8)	13 (8.4)	0.35
Dementia	4 (2.6)	5 (3.2)	0.74
Diabetes			0.47
No	111 (71.6)	112 (72.3)	
With no end-organ damage	35 (22.6)	39 (25.2)	
With end-organ damage	9 (5.8)	4 (2.6)	
Hemiplegia or paraplegia	4 (2.6)	2 (1.3)	0.42
Liver disease			0.42
No	141 (91.6)	145 (93.5)	
Mild	9 (5.8)	7 (4.5)	
Moderate or severe	4 (2.6)	3 (1.9)	
Lymphoma	1 (0.6)	3 (1.9)	0.34
Tumour without metastasis	26 (16.8)	25 (16.1)	0.86
Metastatic solid tumour	3 (1.9)	2 (1.3)	0.57
Myocardial infarction	5 (3.2)	14 (9.0)	0.04
Peptic ulcer disease	6 (3.9)	10 (6.5)	0.29
Peripheral vascular disease	8 (5.2)	15 (9.7)	0.12
Renal disease moderate or severe	17 (11.0)	28 (18.1)	0.06
Immunosuppressor treatment	137 (88.4)	137 (88.4)	>0.99
Strictly community-acquired infection	140 (90.3)	140 (90.3)	>0.99
Ward of admission			0.68
Medical	107 (69.0)	108 (69.7)	
Emergency	8 (5.2)	10 (6.5)	
Surgical	1 (0.6)	2 (1.3)	
ICU	39 (25.2)	35 (22.6)	
Features of the urinary tract infection			
Cystitis	31 (20.0)	27 (17.4)	0.56
Not localizable UTI	8 (5.2)	15 (9.7)	0.13
Pyelonephritis	94 (60.6)	92 (59.4)	0.82
Renal abscess	3 (1.9)	4 (2.6)	0.71
Associated with a device	14 (9.0)	13 (8.4)	0.84
Other feature	5 (3.2)	4 (2.6)	>0.99
With hydronephrosis	10 (6.5)	5 (3.2)	0.21
With bacteraemia	69 (44.5)	70 (45.2)	0.91
Severe sepsis or shock	40 (25.8)	37 (23.9)	0.65
CRP at day 0, median (IQR)	156.10 (89.60–246.40)	159.90 (98.85–240.15)	0.98
CRP at day 2, median (IQR)	148.40 (78.55–236.50)	129.70 (70.75–228.95)	0.12
CRP variation in 48 h in percentage, median (IQR)	−0.07 (−0.37 to 0.44)	−0.16 (−0.46 to 0.29)	0.27
SOFA at day 0 ≥ 2	52 (33.5)	50 (32.3)	0.90
Pitt score at day 0, median (IQR)	1.00 (0.00–2.00)	1.00 (0.00–2.00)	0.84
ESBL-producer	26 (16.8)	19 (12.3)	0.24
Empirical appropriate treatment	142 (91.6)	149 (96.1)	0.07
Length of intravenous therapy with study drug (d), median (IQR)	4.0 (3.0–6.0)	5.0 (4.0–7.0)	0.03
Length of antibiotic therapy (d), median (IQR)	9.0 (7.0–13.0)	9.0 (6.0–11.0)	0.08
Oral antibiotic therapy after intravenous therapy	123 (79.4)	95 (61.3)	<0.001

ESBL; extended-spectrum β-lactamase; IQR, interquartile range; UTI, urinary tract infection; CRP, C-reactive protein; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment.

^a Data are presented as median (IQR) or no. (percentage). P values were calculated using conditional logistic regression.

Table 2
Outcomes of matched patients with complicated urinary tract infections caused by *Escherichia coli*^a

Outcome	Treatment with fosfomycin (n = 155)	Treatment with other drugs (n = 155)	Treatment difference (95% CI) ^b	p
Clinical and microbiological cure at day 21 ^c	101 (65.2)	98 (63.2)	+2.0 (−8.7 to 12.6)	0.69
Recurrence until day 30	22 (14.2)	16 (10.3)	+3.9 (−3.4 to 11.1)	0.26
Severe adverse effects ^d	3 (1.9)	1 (0.6)	+1.3 (−1.2 to 3.8)	0.34
Non-severe adverse effects ^e	36 (23.2)	12 (7.7)	+15.6 (7.6–23.3)	<0.001
Mortality at day 30	3 (1.9)	9 (5.8)	−3.9 (−8.1 to 0.4)	0.08

^a Data are presented as no. of cases (percentage). p values were calculated using conditional logistic regression.

^b Differences in outcomes between fosfomycin and control cohorts, with 95% CIs calculated without continuity correction.

^c Clinical cure rates at day 21 were 145 (93.5%) in patients treated with fosfomycin and 140 (90.3%) in those treated with other drugs (p 0.30).

^d Severe adverse effects during follow-up were: fosfomycin group, liver toxicity (1), hypertensive crisis (1), heart failure (1); other drugs group, ceftriaxone-associated *Clostridioides difficile* diarrhoea (1).

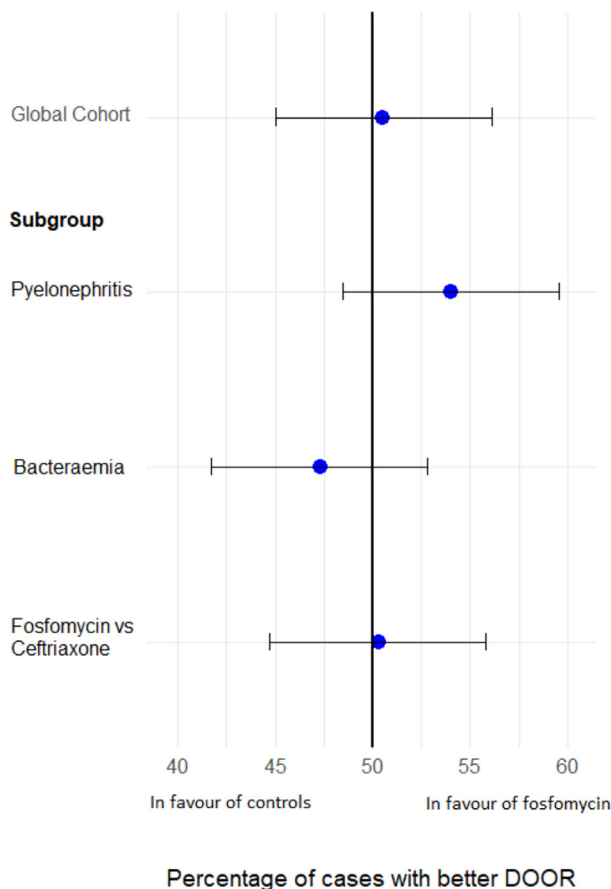
^e Non-severe adverse effects observed during administration of targeted intravenous therapy were: fosfomycin group, nausea (16), phlebitis (5), abdominal discomfort (10), headache (5); other drugs group: pruritus (3), diarrhoea (6), nausea (3). Among these, 19.4% (7/36) of cases in the fosfomycin group and 25% (3/12) of cases in the other drugs group resulted in treatment discontinuation. The majority of non-severe adverse events—83.3% (30/36) in the fosfomycin group and 75% (9/12) in the other drugs group—occurred during the intravenous targeted treatment phase or within 48 hours of its completion.

Table 3

Classification of fosfomycin-treated cases and controls by desirability of outcome ranking across four categories in the global cohort and patient-specific subgroups

DOOR rank	Outcome	Global cohort		Subgroup of matched cases and controls with pyelonephritis		Subgroup of matched cases and controls with bacteraemia		Subgroup of cases matched with controls treated with ceftriaxone	
		Case (n = 155)	Control (n = 155)	Case (n = 55)	Control (n = 55)	Case (n = 51)	Control (n = 51)	Case (n = 71)	Control (n = 71)
1	Clinical and microbiological cure at day 21 without the occurrence of adverse effects and/or recurrence	94	94	35	30	24	27	44	44
2	No clinical-microbiological cure on day 21 and/or recurrence until day 30	55	51	18	24	24	21	24	23
3	Severe adverse effects	3	1	0	0	2	1	1	1
4	Mortality at day 30	3	9	2	1	1	2	2	3
	% Cases with better DOOR than controls (95% CI)	50.5 (45.0–56.1) %		54.0 (48.5–59.6) %		47.3 (41.7–52.8) %		50.3 (44.7–55.8) %	

DOOR, desirability of outcome ranking.

**Fig. 2.** Lollipop chart displaying the percentage of cases (and CIs) treated with fosfomycin achieving better DOOR outcomes than controls, both in the overall cohort and across the four analysed patient profiles. Considering four categories of DOOR. DOOR, desirability of outcome ranking.

Similarly to the ZEUS trial, where over 50% of cases involved pyelonephritis, fosfomycin demonstrated higher effectiveness in cUTIs despite an increased rate of adverse events. Our results suggest that fosfomycin could be an effective option for treating pyelonephritis, consistent with findings from other published studies [7,19]. The strong performance of fosfomycin, particularly in its intravenous form, in treating pyelonephritis may be attributed

to its adequate tissue penetration, including renal tissue, which is crucial for effectively treating this type of cUTI [20,21].

Conversely, in the treatment of bacteraemic UTIs, our findings align with the FOREST study [8], where fosfomycin did not demonstrate non-inferiority compared with other treatments for bacteraemic UTIs caused by multidrug-resistant *E. coli*. This was primarily because of a higher rate of adverse event-related discontinuations, rather than a lack of efficacy.

Fosfomycin may reduce the ecological impact of broad-spectrum antimicrobials like quinolones, carbapenems, and cephalosporins [22–24], supporting antimicrobial stewardship by limiting selective pressure for multidrug resistance. Moreover, by diversifying treatment options for one of the most prevalent infections—cUTIs caused by *E. coli* [25]—fosfomycin helps preserve future therapeutic options at both population and individual levels, particularly for infections that are often recurrent [26].

Our study has limitations, including a small sample size in some patient subgroups and a 30-day follow-up period. Moreover, as an observational study, it carries inherent risks of unmeasured variables and residual confounding because of the lack of randomization. Furthermore, the inclusion of middle-aged patients with relatively low comorbidity may have reduced the likelihood of observing severe adverse events. Additionally, the lower representation of patients with significant cardiovascular or kidney impairments in the fosfomycin group, likely because of caution in prescribing this drug, limits the extrapolation of our findings to these higher-risk groups. Lastly, the study focused exclusively on cUTIs caused by *E. coli*, excluding other urinary pathogens for which fosfomycin may also be effective. However, it benefits from a prospective, international, multicentre design and the inclusion of matched case-control pairs based on comorbidity, acquisition, and infection severity, which contribute to making the study methodologically robust. These elements enhance the reliability and relevance of our findings. Additionally, to our knowledge, this is the first published study to simultaneously analyse, in a real-world setting, various outcomes related to the effectiveness and safety of intravenous fosfomycin compared with other antimicrobials commonly used for cUTIs caused by *E. coli*, in both a global international cohort and across different matched subgroups.

Conclusion

In conclusion, targeted intravenous fosfomycin is a viable option for cUTIs caused by *E. coli*, allowing for diversification in the treatment of these high-incidence infections.

Author contributions

J.R.-B., F.D.-P., and B.G.-G. conceived and designed the study. B.G.-G. obtained funding. E.M.-M. and I.P. were involved in study coordination and data curation. F.D.-P. and B.G.-G. supervised the global study. E.M.-M., J.R.-B., and B.G.-G. analysed and interpreted the data. E.M.-M. and B.G.-G. did the statistical analysis and drafted the manuscript. All other authors were directly involved in study supervision at each of the participating centres and in critical revision of the manuscript for important intellectual content. All other authors acknowledged as investigators from the CIBER-INFEC/FOSFOMIC Group participated in data collection at their respective institutions. F.D.-P. and B.G.-G. contributed equally to this work.

Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

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Data availability

Individual, anonymized data would be shared after a signed agreement with Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla if requested with the objective of performing a meta-analysis with individual patients’ data. Requests should be submitted to the corresponding author. Interested researchers should obtain the approval of the Ethic Committee CEIM Provincial de Sevilla. A database in SPSS file with the requested data and a dictionary of terms would be provided.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2025.01.007>.

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