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Maintained susceptibility to fosfomycin in extra-hospitalary urinary isolates of *Escherichia coli*. Strong association of fosfomycin resistance with age and ESBL production

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Article history

Received: 9 February 2024; Revision Requested: 1 April 2024; Revision Received: 7 June 2024;
Accepted: 15 June 2024; Published: 20 December 2024

ABSTRACT

Introduction. *Escherichia coli* is isolated in most of uncomplicated community-acquired urinary tract infections (UTI) and fosfomycin is one of the treatments of choice. We analyzed the evolution of fosfomycin resistance in extrahospitalary *E. coli* urinary isolates and whether age and extended spectrum beta-lactamase (ESBL) production were associated to antibiotic resistance.

Methods. A retrospective descriptive study was conducted from January 2017 to December 2022 including *E. coli* isolates from extrahospitalary urine samples.

Results. The susceptibility to fosfomycin remained above 95% during the study period. ESBL production and age above 80 years were significantly associated with increased fosfomycin resistance. We also analyzed the consumption of fosfomycin and it remained stable, although it was higher in the population >65 years.

Conclusions. Greater resistance is observed in ESBL-producing strains and in patients over 65 years of age. A stable consumption of fosfomycin is associated with low resistance percentages maintained over the time.

Keywords: Urinary tract infection, *Escherichia coli*, Fosfomycin, Antibiotic resistance, Antibiotic consumption

Sensibilidad mantenida a fosfomicina en aislados urinarios extrahospitalarios de *Escherichia coli*. Alta asociación de la resistencia a fosfomicina con la edad y la producción de BLEE

RESUMEN

Objetivos. *Escherichia coli* es el patógeno principal en infecciones urinarias comunitarias no complicadas y fosfomicina es uno de los tratamientos de elección. Analizamos la evolución de la resistencia a fosfomicina en aislados urinarios de *E. coli* extrahospitalarios y estudiamos si la edad y la producción de betalactamasas de espectro extendido (BLEE) se asociaban a mayor resistencia.

Material y métodos. Estudio descriptivo retrospectivo desde enero de 2017 hasta diciembre de 2022 que incluyó todos los aislados de *E. coli* de muestras de orina extrahospitalarias.

Resultados. La sensibilidad a fosfomicina fue superior al 95% durante todo el periodo. La producción de BLEE y la edad >80 años se asociaron significativamente con una mayor resistencia. El consumo se mantuvo estable, aunque fue superior en la población >65 años.

Conclusiones. Con un consumo estable de fosfomicina detectamos baja resistencia, siendo mayor en cepas productoras de BLEE y en pacientes > 65 años.

Palabras clave: Infección de tracto urinario, *Escherichia coli*, Fosfomicina, Resistencia antibiótica, Consumo de antibióticos

INTRODUCTION

Escherichia coli remains the most frequent pathogen in urinary tract infections (UTI), isolated in more than 80% of uncomplicated community-acquired infections [1]. These infections are usually treated empirically.

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Guidelines recommend fosfomycin trometamol as one of the treatments of choice, provided that resistance rates of local uropathogens do not exceed 20% [2,3]. In addition, fosfomycin may be useful in the management of multiresistant *E. coli* infections due to the lack of alternatives and its unique mechanism of action without cross-resistance with other groups of antibiotics.

There are few studies about the evolution of resistance to fosfomycin in *E. coli* strains, most of them old and some of them discrepant [4-6].

In this study, we evaluated the evolution of the prevalence of fosfomycin resistance in urinary *E. coli* isolates from primary care in the area of Getafe, Madrid (Spain), with a population of approximately 200,000 inhabitants. Fosfomycin consumption was analyzed and it was also studied whether the age and/or extended spectrum betalactamase (ESBL) production were associated with increased resistance to this antibiotic.

MATERIAL AND METHODS

A retrospective descriptive study was performed including all *E. coli* isolates from extrahospitalary urine samples from January 2017 to December 2022. Data were extracted from the laboratory informatics system (Microb Dynamic, Becton Dickinson SA, Madrid, Spain). A recurrence control was applied excluding isolates with the same susceptibility profile from each patient included in the study, in a period of 3 months

For data analysis, the population was stratified by age in four groups; patients between 14 and 40 years, patients between 41 and 65 years, patients between 66 and 80 and over 80 years, and according to the ESBL production.

Species identification was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry MALDI-TOF (Bruker Daltonics GmbH, Leipzig, Germany), and the susceptibility study was performed by broth microdilution

using Microscan panels (Beckman Coulter, Brea, CA, USA). Antibiotic susceptibility was interpreted considering susceptible those strains with a fosfomycin MIC \leq 32 mg/L and resistant with a MIC $>$ 32 mg/L.

Microscan panels include cefotaxime/clavulanic acid and ceftazidime/clavulanic acid (both from 0.25/4 to 4/4 mg/L). These data allow interpreting a strain as ESBL positive if \geq 8-fold reduction is observed in the MIC of any of the cephalosporins combined with clavulanic acid compared with the MIC of the cephalosporin alone, otherwise the result is interpreted as negative.

Consumption data were obtained from the prescription data billed by family physicians at the ten Primary Care centers in the area of the Hospital Universitario de Getafe. The data analyzed were the total number of containers and the Defined Daily Dose (DDD) of the active ingredient fosfomycin between 2017 and 2022. Subsequently, they were broken down according to the two established age bands; between 14 and 65 years old, and over 65 years old.

Consumption data were expressed as 100 DDDs per 1000 inhabitants/day (100 x DHD). For the detailed analysis of these data, the Business Intelligence program was used.

To determine whether there was statistical significance, the chi-square test and regression model analysis were applied, with a value of $p < 0.05$ being considered significant.

RESULTS

The overall susceptibility to fosfomycin remained above 95% throughout the study period (Table 1), with no significant variation ($r^2=0.19$; $p=0.37$).

In most of the years studied, the strains with the lowest susceptibility to fosfomycin were isolated in patients older than 80 years ($p < 0.01$), with the exception of 2018, when the

Table 1	Total isolates and percentage of susceptibility to fosfomycin throughout the study period and stratified according to age of the patients.					
	2017	2018	2019	2020	2021	2022
Total isolates (N)	2,150	2,212	2,317	1,655	1,883	1,952
Fos-S; n (%S)	2,092 (97.30)	2,148 (97.11)	2,210 (95.38)	1,589 (96.01)	1,820 (96.65)	1,877 (96.16)
14-40 years (N)	420	375	417	284	281	297
Fos-S; n (%S)	416 (99.05)	374 (99.73)	406 (97.36)	281 (98.94)	277 (98.58)	291 (97.98)
41-65 years (N)	640	675	711	455	567	573
Fos-S; n (%S)	634 (99.06)	664 (98.37)	694 (97.61)	440 (96.70)	553 (97.53)	555 (96.86)
66-80 years (N)	729	774	758	537	613	669
Fos-S; n (%S)	705 (96.71)	737 (95.22)	721 (95.12)	521 (97.02)	600 (97.88)	651 (97.31)
>80 years (N)	361	383	429	335	384	381
Fos-S; n (%S)	336 (93.07)	368 (96.08)	387 (90.21)	300 (89.55)	353 (91.93)	349 (91.60)

Fos-S: Fosfomycin-susceptible isolates, %S: percentage of susceptibility to fosfomycin

Table 2 Total ESBL producers isolates stratified according to age, and percentage of susceptibility to fosfomycin throughout the study period stratified according to ESBL production

	2017	2018	2019	2020	2021	2022
ESBL-S total isolates; n (%S)	131 (79.39)	155 (89.03)	197 (76.14)	120 (78.33)	119 (83.19)	127 (80.31)
Non-ESBL producers total isolates; n (%S)	2,019 (98.46)	2,057 (97.72)	2,120 (97.17)	1,535 (97.39)	1,764 (97.56)	1,825 (97.26)
ESBL-S 14-40 years; n (%S)	12 (91.67)	16 (100.00)	21 (95.24)	4 (100.00)	9 (88.89)	14 (85.71)
ESBL-S 41-65 years; n (%S)	19 (100.00)	23 (91.30)	28 (82.14)	27 (81.48)	21 (85.71)	24 (83.33)
ESBL-S 66-80 years; n (%S)	55 (70.91)	59 (86.44)	75 (78.67)	35 (85.71)	28 (85.71)	48 (87.50)
ESBL-S >80 years; n (%S)	44 (77.27)	57 (87.72)	73 (65.75)	54 (71.70)	60 (80.00)	42 (69.05)

ESBL-S: ESBL producers; %S: percentage of susceptibility to fosfomycin.

most resistant strains were isolated in patients aged 66 to 80 years, although this difference was not statistically significant, $p=0.5$ (Table 1).

Similarly, ESBL-producing strains were, in all years studied, less susceptible to fosfomycin compared to non-ESBL-producing strains ($p<0.00001$) (Table 2).

Consumption of fosfomycin in the study period, expressed in DHD x 100 per year, remained constant over the time (21-22 in the 14-65 years old group, and 71-77 in the more than 65 years old group). A higher consumption was observed in the population over 65 years.

DISCUSSION

Susceptibility to fosfomycin in *E. coli* has been higher than 95% throughout the years [4,9-11,13], except in ESBL-producing isolates [5,8].

There is a trend of increasing resistance to fosfomycin related to different factors such as antibiotic consumption [5,11] or ESBL production [6,14]. There are also studies in which the percentages of resistance to fosfomycin were low and without apparent increase [12] which agrees with our results. In our case, there was no change in the consumption data. Moreover, as in previous studies [5-8], ESBL-producing strains were significantly more resistant than non-producing strains. In our study the age was a condition significantly associated with resistance, a fact little developed in other publications [5].

There are some limitations regarding the susceptibility breakpoints used. We consider susceptible those strains with a fosfomycin MIC ≤ 32 mg/L (EUCAST v.10.0). Since 2020, EUCAST has modified the cut-off point to 8 mg/L, specifying its validity only for oral fosfomycin in the treatment of uncomplicated UTI due to *E. coli*. In our center, the cut-off point of EUCAST v.10.0 has been maintained due to the lack of updating of the commercial panels, which at the moment are not adapted to the new cut-off points.

Another limitation of our study is that it was conducted with data from only one health area.

In conclusion, in our experience when stratifying data, greater resistance is observed in ESBL-producing strains, and in isolated strains from patients over 65 years of age, especially in patients over 80 years old. On the other hand, stable consumption is associated with percentages of resistance maintained over time.

Fosfomycin remains an adequate empiric treatment for UTIs, although continuous surveillance of antibiotic resistance pattern by region is important for the appropriate selection of antibiotics for empiric treatment.

FUNDING

None to declare

CONFLICT OF INTEREST

Authors declare no conflict of interest

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