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# Experience with fosfomycin in the treatment of complicated urinary tract infections caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae

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***Abstract***

***Background:*** The aim of this study was to evaluate the efficacy of fosfomycin in the treatment of complicated urinary tract infections (cUTIs) caused by extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae.

***Methods:*** We retrospectively evaluated 42 ambulatory patients with cUTIs caused by ESBL-producing Enterobacteriaceae at the Outpatient Internal Medicine Clinic of the University Clinical Hospital Centre Zagreb in the period from June 2012 to June 2014. ESBL production was confirmed by double disk synergy test according to Jarlier. *In vitro* susceptibility to fosfomycin of ESBL-producing *Escherichia coli, Klebsiella pneumoniae* and *Citrobacter freundii* isolates was tested according to the European Committee on Antimicrobial Susceptibility Testing methodology.

***Results:*** In 42 patients with cUTIs, 43 urinary pathogens susceptible to fosfomycin were isolated in the urine cultures, including 34 *E. coli* ESBL, seven *K. pneumoniae* ESBL and two *C. freundii* ESBL isolates. On average, patients had 2.2 complicating factors (CFs) and received 3.6 fosfomycin doses per treatment course. The overall microbiological cure was 50%, clinical cure was 71% and ESBL eradication rate was 74%. Patients with between zero and one CFs received significantly fewer fosfomycin doses than patients with two or more CFs ($p = 0.022$). Three kidney transplant patients achieved microbiological cure following prolonged fosfomycin administration. No statistically significant correlation was found between the presence of individual CFs and treatment outcome.

***Conclusions:*** Fosfomycin may be a valid option for oral treatment of cUTIs caused by ESBL-producing pathogens. The optimal duration of fosfomycin treatment for cUTIs remains to be determined.

***Keywords:*** complicated urinary tract infections, extended-spectrum beta-lactamase, ESBL, fosfomycin

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## Introduction

Treatment of complicated urinary tract infections (cUTIs) caused by bacterial strains producing extended-spectrum beta-lactamases (ESBLs) represents a major therapeutic problem. The prevalence of ESBL production among the most common urinary pathogens, namely *Escherichia coli* (E. coli) and *Klebsiella pneumoniae* (K. pneumoniae), was 8% and 32%, respectively, in Croatia in 2016.[1] According to the Annual report of the European Antimicrobial Resistance Surveillance Network, the percentages of ESBL-producing *E. coli* and *K. pneumoniae* remained high in 2016, reaching more than 25% in *E. coli*

and more than 50% in *K. pneumoniae* isolates in certain Southern European countries. ESBL production is often seen in combination with resistance to multiple antimicrobial groups, leaving few remaining antimicrobial treatment options available.[2] More frequent prescribing of fosfomycin in appropriate indications represents one of the carbapenem-sparing strategies, and is promoted by the leading experts.[3] Infections caused by ESBL-producing pathogens have worse outcomes and lead to longer hospitalisations.[4,5] Carbapenems remain the antibiotics of first choice for the treatment of these infections. However, the increase in carbapenem resistance, and the need for parenteral administration preclude their widespread use for the treatment of cUTIs caused by ESBL-producing urinary pathogens. Hence, there is a growing interest in older antibiotics like fosfomycin, especially due to its rapid bactericidal activity, low resistance rates, oral administration and low cost. The aim of this study was to evaluate the efficacy of fosfomycin in the treatment of cUTIs caused by ESBL-producing Enterobacteriaceae.

## Patients and methods

Fosfomycin efficacy in the treatment of cUTIs caused by ESBL-producing Enterobacteriaceae was retrospectively evaluated in ambulatory patients at the Outpatient Internal Medicine Clinic (OIMC) of the University Clinical Hospital Centre Zagreb in the period from June 2012 to June 2014; the first 3 years of fosfomycin availability on the market in Croatia.

### *Definitions*

Urinary complicating factors (CFs) were defined as clinical factors that decrease the likelihood of microbiological and clinical cure. These included history of recurrent UTIs, presence of a urinary Foley catheter, chronic kidney disease, diabetes mellitus, urolithiasis, renal transplantation, immunosuppression, urinary tract tumour, urological surgery in the previous 6 months, benign prostatic hyperplasia, malignancy outside the urinary tract and neurogenic bladder. Immunosuppression was defined as having a solid organ or bone marrow transplant, receipt of chemotherapy in the previous 30 days, 30 mg prednisone or equivalent daily, or other immunosuppressive agents. Recurrent UTI was defined as having had at least two infections in the previous 6 months. Microbiological cure was defined as the presence of a documented sterile urine culture 7–9 days after the end of antibiotic treatment.[6–9] ESBL-producing urinary pathogen eradication was defined as the absence of ESBL-producing Enterobacteriaceae growth in control urine taken 7–9 days after the completion of fosfomycin treatment. Clinical cure was defined as the absence of signs and symptoms of UTI 7–9 days after the end of treatment.[6–9]

*Inclusion criteria used to define patients with lower cUTIs caused by ESBL-producing Enterobacteriaceae:*

1. Urine culture positive for ESBL-producing Enterobacteriaceae $\geqslant 10^5$ colony forming units/ml in clean-catch, midstream urine sample.
2. *In vitro* susceptibility of urinary pathogen to fosfomycin as determined by the agar-dilution method and according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.[10]
3. Symptoms and/or signs of UTI (patient must have one or more of the following: dysuria, pollakisuria, urgency, suprapubic tenderness, low-grade fever, haematuria).
4. Pathological result of semiquantitative urine analysis (positive leukocyte esterase and/or positive nitrites).

*Exclusion criteria:*

1. Axillary temperature >37.5°C, poor overall clinical condition, nausea and/or vomiting.
2. Leukocytosis or left-shift in complete blood count.
3. Positive costovertebral angle tenderness.
4. Creatinine clearance <10 ml/min or chronic haemodialysis (fosfomycin trometamol is contraindicated in these patients as it is eliminated by the kidney).

The first three exclusion criteria were used to exclude patients with the possibility of upper UTI and/or urinary sepsis, as in both of these conditions parenteral antibiotic treatment (i.e. with carbapenems) is mandatory. Patients with possible acute pyelonephritis and/or urinary sepsis were excluded, as oral fosfomycin is indicated only for the treatment of lower UTIs.[11]

All patients received fosfomycin trometamol 3 g orally with a number of doses as prescribed by the treating physician. Fosfomycin doses were

administered every other day, or every third day, depending on the creatinine clearance value.

### *Microbiological methods*

Causative urinary pathogens were identified to the species level by conventional biochemical testing (Kligler, Citrate, Motility-Indole-Lysine, Phenylalanine). ESBL production was confirmed by double disk synergy test according to Jarlier.[12] Deformation of the inhibition zones around the cephalosporin disks towards the central disk containing clavulanic acid was considered a positive result. *In vitro* susceptibility of ESBL-producing *E. coli*, *K. pneumoniae* and *Citrobacter freundii* (C. freundii) isolates to fosfomycin was tested according to EUCAST methodology. Thus, the minimum inhibitory concentration (MIC) susceptibility breakpoint for fosfomycin was defined as 32 mg/l. Fosfomycin MIC breakpoints were determined by the agar dilution method.[10]

### *Statistical methods*

Pearson Chi square and student's *t* tests were used for the statistical analysis; $p < 0.05$ was considered significant.

## Results

In the study period, 42 patients with cUTIs caused by ESBL-producing Enterobacteriaceae were treated with fosfomycin at the OIMC. The majority of 42 patients treated with fosfomycin (37/42; 88.1%) were elderly females with recurrent cUTIs (Table 1).

Overall, microbiological and clinical cure was achieved in 21/42 (50%) and 30/42 (71.4%) patients, respectively. Eradication of the ESBL strain was achieved in 31/42 (73.8%) patients. Initial clinical improvement occurred in all patients, but 12 patients experienced a recurrence of symptoms 7–9 days following treatment termination. Microbiological eradication was not achieved in 21 out of 42 patients with cUTIs caused by ESBL-producing Enterobacteriaceae. In 11 patients, of whom 7 were symptomatic, the causative ESBL-producing pathogen persisted in the control urine culture (nine ESBL-producing *E. coli* and two ESBL-producing *K. pneumoniae* isolates). In the remaining 10 patients, the initial ESBL-producing pathogen was eradicated but the following organisms were isolated in the follow-up urine cultures: *Pseudomonas aeruginosa* ($n = 3$), non-ESBL *K. pneumoniae* ($n = 3$), *Enterococcus faecalis* ($n = 2$), *Providencia rettgeri* ($n = 1$) and *Proteus mirabilis* ($n = 1$). Among these 10 patients, 5 were symptomatic at the follow-up visit (Table 2).

While the average number of CFs was 2.2, two patients had no identifiable CFs (other than being infected with a multiresistant Gram negative pathogen), while two had 5 and two had 6 CFs. Three of those four patients had a transplanted kidney. All four patients had been treated successfully with prolonged fosfomycin administration and achieved microbiological cure; on average, they received five fosfomycin doses.

All patients treated with fosfomycin had ESBL-producing urinary pathogens *in vitro* susceptible to fosfomycin: 34 *E. coli*, seven *K. pneumoniae* and two *C. freundii* ESBL-producing isolates were found (in one patient, both *E. coli* and *K. pneumoniae* were isolated from the urine culture). Fosfomycin MIC ranged from 0.5 to 32 mg/l, while MIC50 was 4 mg/l. Fosfomycin had the best *in vitro* activity against two *C. freundii* isolates (MIC range 0.5–1 mg/ml, MIC50 0.5 mg/l) and a lower, but still very good, activity, against *E. coli* (MIC range 0.5–32 mg/l, MIC50 2 mg/l) and *K. pneumoniae* isolates (MIC range 4–32 mg/l, MIC50 16 mg/l). All of the isolates were multidrug-resistant as described previously by Magiorakos and colleagues.[13] In addition to fosfomycin, all ESBL-producing isolates were also susceptible to carbapenems (meropenem, imipenem and ertapenem) *in vitro*. All the other tested antibiotics had a much lower *in vitro* activity against ESBL-producing Enterobacteriaceae, with the number of susceptible isolates as follows: piperacillin/tazobactam 22/43 (51.2%), gentamicin 21/43 (48.8%), amoxicillin/clavulanic acid 18/43 (41.9%), cefepime 11/43 (25.6%), trimethoprim/sulfamethoxazole 7/43 (16.3%) and ciprofloxacin 3/43 (7%). All isolates were resistant to cefalexin, cefuroxime and ceftriaxone. According to EUCAST standards, nitrofurantoin was tested against 34 ESBL-producing *E. coli* isolates of which 19 (55.9%) were susceptible.[10]

In 5/42 isolates, fosfomycin was the only available oral therapeutic option. Among these were two ESBL-producing *C. freundii* and three

**Table 1.** Patient clinical characteristics ($n = 42$).

| Patient characteristics | (range) |
|---|---|
| Average age; age span (years) | 71.8 (19–93) |
| Sex: female | 33 |
| male | 9 |
| Causative pathogen: *Escherichia coli* ESBL | 34 |
| *Klebsiella pneumoniae* ESBL | 7 |
| *Citrobacter freundii* ESBL | 2 |
| $MIC_{50}$ (mg/l): *E. coli* ESBL | 2 |
| *K. pneumoniae* ESBL | 16 |
| *C. freundii* ESBL | 0.5 |
| Microbiological cure | 21/42 |
| ESBL eradication | 31/42 |
| Clinical cure | 30/42 |
| Average no. of fosfomycin doses | 3.6 (1–11) |
| Average no. of complicating factors | 2.2 (0–6) |
| Complicating factors: recurrent UTI | 37/42 |
| chronic kidney disease | 9/42 |
| urinary catheter | 8/42 |
| diabetes mellitus | 8/42 |
| urolithiasis | 8/42 |
| immunosuppression | 5/42 |
| renal transplantation | 4/42 |
| recent urological operation | 4/42 |
| neurogenic bladder | 3/42 |
| benign prostatic hyperplasia | 2/42 |
| extra-urogenital malignant tumour | 2/42 |
| tumour of the urinary tract | 1/42 |

ESBL-producing *E. coli* isolates. The *C. freundii* isolates were resistant to all antibiotics tested except carbapenems and fosfomycin with low MICs for the latter (0.5 and 1 mg/l). The mentioned three *E. coli* isolates were susceptible to carbapenems, one was also susceptible to all aminoglycosides and one only to amikacin.

On average, patients received 3.6 doses of oral fosfomycin trometamol; 20 patients were treated with three doses, while the others received between 1 and 11 consecutive fosfomycin doses (Table 2).

The emergence of urinary pathogen resistance to fosfomycin was detected in 2/42 (4.8%) treated patients. One *E. coli* and one *K. pneumoniae* isolate became resistant after treatment with three and seven fosfomycin doses, respectively. Both isolates had MIC 8 mg/l before treatment, and in the control urine culture both had MICs >64 mg/l.

With a rise in the number of CFs, the proportion of patients with microbiological cure decreased, in spite of the higher number of fosfomycin doses administered. There was no significant correlation between the number of CFs and microbiological cure ($p = 0.116$). The correlation with clinical cure was also low ($p = 0.921$). No significant association was found between the presence of individual CFs and the treatment outcome. We found no correlation between fosfomycin MIC of the causative pathogens and the rate of microbiological and/or clinical cure.

The number of fosfomycin doses in patients with between zero and one CF was found to be significantly lower than in those having two or more CFs ($p = 0.022$).

In our study 3/42 (7.1%) patients reported side effects, which were all nonserious (nausea, headache, insomnia) and in accordance with the good safety profile of the drug.[14]

## Discussion

Together with nitrofurantoin and trimethoprim-sulfamethoxazole, fosfomycin in a single 3 g dose is a preferred choice for empirical treatment of acute uncomplicated cystitis.[15] The use of fosfomycin in the treatment of cUTIs represents off-label prescribing. However, fosfomycin is attractive to practicing physicians since susceptibility rates of ESBL-producing Enterobacteriaceae to oral antibiotics keep declining.[2] Moreover, fosfomycin is administered orally and its pharmacokinetics is ideal for the treatment of UTIs. After hydrolysis from trometamol, fosfomycin is excreted unchanged by glomerular filtration and achieves high peak urinary concentrations.[16] Owing to very high urine drug concentrations,

**Table 2.** Patients' ($n = 42$) isolates with their respective susceptibilities and treatment outcomes.

| Pt. no. | Pt. age | Gender | No. of CFs | Type of CFs | ESBL-producing pathogen | FOS MIC (mg/l) | No. of FOS doses | Clinical cure (yes/no) | Micro-biological cure (yes/no) | ESBL eradication (yes/no) | Overgrowth of new pathogen /patient symptomatic (yes/no) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 91 | F | 1 | Recurrent cUTI | *K. pneumoniae* | 16 | 1 | No | No | Yes | *P. mirabilis*/yes |
| 2 | 79 | F | 3 | CKD, DM, recurrent cUTI | *E. coli* | 2 | 3 | No | No | Yes | *P. aeruginosa*/yes |
| 3 | 84 | F | 1 | Recurrent cUTI | *E. coli* | 8 | 3 | No | No | No | - |
| 4 | 78 | F | 1 | Recurrent cUTI | *E. coli* | 1 | 1 | Yes | Yes | Yes | - |
| 5 | 92 | F | 3 | DM, malignancy*, recurrent cUTI | *E. coli* | 1 | 3 | No | No | No | - |
| 6 | 88 | F | 1 | Recurrent cUTI | *E. coli* | 2 | 1 | Yes | Yes | Yes | - |
| 7 | 91 | F | 3 | DM, Foley catheter, recurrent cUTI | *E. coli* | 1 | 3 | Yes | No | No | - |
| 8 | 65 | F | 2 | Foley catheter, recurrent cUTI | *E. coli and K. pneumoniae* | 4 | 3 | No | No | Yes | *P. aeruginosa*/yes |
| 9 | 63 | F | 2 | Recurrent cUTI, urolithiasis | *E. coli* | 8 | 5 | Yes | No | Yes | *K. pneumoniae*/no |
| 10 | 59 | F | 1 | Recurrent cUTI | *E. coli* | 32 | 3 | Yes | Yes | Yes | - |
| 11 | 79 | F | 1 | Recurrent cUTI | *E. coli* | 32 | 3 | Yes | Yes | Yes | - |
| 12 | 63 | M | 6 | CKD, DM, immunosuppression, recent urological operation, recurrent cUTI, renal transplantation | *E. coli* | 8 | 5 | Yes | Yes | Yes | - |
| 13 | 74 | M | 5 | CKD, DM, recent urological operation, recurrent cUTI, urolithiasis | *C. freundii* | 1 | 7 | Yes | Yes | Yes | - |
| 14 | 27 | F | 1 | Recurrent cUTI | *E. coli* | 2 | 3 | Yes | Yes | Yes | - |
| 15 | 93 | F | 1 | Recurrent cUTI | *E. coli* | 8 | 3 | Yes | Yes | Yes | - |
| 16 | 51 | F | 2 | Malignancy*, recurrent cUTI | *E. coli* | 4 | 3 | Yes | No | No | - |
| 17 | 88 | F | 2 | DM, recurrent cUTI | *E. coli* | 2 | 3 | Yes | Yes | Yes | - |

*(Continued)*

**Table 2.** (Continued)

| Pt. no. | Pt. age | Gender | No. of CFs | Type of CFs | ESBL-producing pathogen | FOS MIC (mg/l) | No. of FOS doses | Clinical cure (yes/no) | Micro-biological cure (yes/no) | ESBL eradication (yes/no) | Overgrowth of new pathogen /patient symptomatic (yes/no) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | 53 | F | 5 | CKD, immunosuppression, recent urological operation, recurrent cUTI, renal transplantation | *E. coli* | 1 | 5 | Yes | Yes | Yes | - |
| 19 | 86 | F | 2 | Foley catheter, recurrent cUTI | *E. coli* | 16 | 1 | Yes | No | Yes | *K. pneumoniae*/no |
| 20 | 48 | F | 1 | Urolithiasis | *K. pneumoniae* | 8 | 3 | Yes | Yes | Yes | - |
| 21 | 49 | F | 2 | Immunosuppression recurrent cUTI | *E. coli* | 1 | 3 | Yes | Yes | Yes | - |
| 22 | 80 | F | 1 | Recurrent cUTI | *E. coli* | 1 | 3 | Yes | Yes | Yes | - |
| 23 | 86 | F | 2 | Foley catheter, recurrent cUTI | *E. coli* | 8 | 1 | Yes | Yes | Yes | - |
| 24 | 88 | M | 3 | BPH, DM, Recurrent cUTI | *E. coli* | 1 | 3 | No | No | No | - |
| 25 | 19 | F | 4 | Foley catheter, neurogenic bladder, recurrent cUTI, urolithiasis | *E. coli* | 4 | 11 | No | No | No | - |
| 26 | 73 | F | 2 | CKD, DM | *E. coli* | 4 | 1 | Yes | No | No | - |
| 27 | 73 | F | 1 | Recurrent cUTI | *E. coli* | 8 | 1 | Yes | No | Yes | *E. faecalis*/no |
| 28 | 53 | F | 2 | Foley catheter, neurogenic bladder | *E. coli* | 1 | 3 | Yes | No | Yes | *P. aeruginosa*/no |
| 29 | 81 | F | 0 | - | *E. coli* | 0.5 | 1 | Yes | Yes | Yes | - |
| 30 | 93 | F | 0 | - | *E. coli* | 1 | 3 | No | No | No | - |
| 31 | 92 | F | 2 | CKD, recurrent cUTI | *E. coli* | 1 | 3 | No | No | Yes | *K. pneumoniae*/ yes |
| 32 | 77 | F | 3 | CKD, recurrent cUTI, urolithiasis | *E. coli* | 1 | 1 | Yes | Yes | Yes | - |
| 33 | 61 | M | 6 | BPH, CKD, immunosuppression, recent urological operation, recurrent cUTI, renal transplantation | *K. pneumoniae* | 16 | 3 | Yes | Yes | Yes | - |

**Table 2.** (Continued)

| Pt. no. | Pt. age | Gender | No. of CFs | Type of CFs | ESBL-producing pathogen | FOS MIC (mg/l) | No. of FOS doses | Clinical cure (yes/no) | Micro-biological cure (yes/no) | ESBL eradication (yes/no) | Overgrowth of new pathogen /patient symptomatic (yes/no) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 34 | 48 | M | 2 | Recurrent cUTI, urolithiasis | *K. pneumoniae* | 32 | 11 | No | No | No | - |
| 35 | 87 | F | 1 | Recurrent cUTI | *E. coli* | 8 | 6 | No | No | No | - |
| 36 | 69 | M | 4 | CKD, Foley catheter, neurogenic bladder, recurrent cUTI | *E. coli* | 4 | 5 | Yes | Yes | Yes | - |
| 37 | 83 | F | 2 | Recurrent cUTI, urolithiasis | *E. coli* | 8 | 6 | Yes | Yes | Yes | - |
| 38 | 65 | M | 3 | Immunosuppression, recurrent cUTI, renal transplantation | *K. pneumoniae* | 8 | 7 | Yes | No | No | - |
| 39 | 61 | M | 1 | Recurrent cUTI | *K. pneumoniae* | 32 | 3 | Yes | Yes | Yes | - |
| 40 | 66 | F | 1 | Recurrent cUTI | *E. coli* | 1 | 6 | No | No | Yes | *P. rettgeri*/yes |
| 41 | 85 | M | 4 | Foley catheter, recurrent cUTI, tumour of the urinary tract, urolithiasis | *C. freundii* | 0.5 | 7 | Yes | No | Yes | *E. faecalis*/no |
| 42 | 74 | F | 1 | Recurrent cUTI | *E. coli* | 1 | 1 | Yes | Yes | Yes | - |

BPH, benign prostatic hyperplasia; CF, complicating factor; CKD, chronic kidney disease; cUTI, complicated urinary tract infection; DM, diabetes mellitus; *E. faecalis, Enterococcus faecalis; E. faecium, Enterococcus faecium*; F, female; FOS, fosfomycin; *K. pneumoniae, Klebsiella pneumoniae*; M, male; No., number; *P. aeruginosa, Pseudomonas aeruginosa; P. mirabilis, Proteus mirabilis; P. rettgeri, Providencia rettgeri*; Pt., patient.
*Outside of the urinary tract.

depending on the renal function, if administered repeatedly, it only needs to be given once every second or third day to be effective.[14,17]

The emergence of fosfomycin resistance during prolonged treatment has been reported in the literature, and is quoted as one of the main concerns regarding clinical utility of this drug.[18] In our study population, only 2/43 (4.7%) ESBL-producing isolates, one *E. coli* and one *K. pneumoniae*, acquired resistance to fosfomycin after treatment for 5 and 13 days, respectively.

Data about the clinical efficacy of fosfomycin in the treatment of cUTIs caused by ESBL-producing Enterobacteriaceae is scarce, and limited mainly to small retrospective studies. To date, this is the second largest retrospective study on fosfomycin efficacy in the treatment of cUTIs caused by ESBL-producing Enterobacteriaceae with microbiological and clinical cure rates achieved in 50% and 71.4% of patients, respectively. The rate of ESBL-producing pathogen eradication was higher than the rate of microbiological cure (73.8% *versus* 50%), reflecting 10 patients with an overgrowth of different organisms in the control urine cultures (Table 2). This can be explained by the fact that 9 of those 10 patients had recurrent cUTIs as a CF. In about one-quarter of our patients (11/42, 26.2%) the ESBL-producing strain was not eradicated, but regrew in the follow-up urine cultures in a short period of 7–9 days. This occurred in spite of the prompt but temporary relief of symptoms at the beginning of treatment, implicating the fosfomycin effect *in vivo*. Possible explanations include a rapid growth of resistant bacterial subpopulations and/or the presence of a bacterial biofilm being resistant to degradation by fosfomycin.[19,20] Potential solutions from the clinical viewpoint could include combination antimicrobial treatment and/or prolonged fosfomycin administration.

Our patient population involved predominantly elderly females with a relatively high number of CFs and a variable duration of fosfomycin treatment. The average age of our patients (72 years) likely reflects the increasing risk of UTIs in this age and gender group.

Pullukcu and colleagues retrospectively evaluated the efficacy of fosfomycin (3 g every other day, three times) in the treatment of ESBL-producing *E. coli*-related lower UTI and reported microbiological and clinical success in 41/52 (78.5%) and 49/52 (94.3%) patients, respectively. This was the first, and thus far the largest, study on fosfomycin efficacy in the treatment of ESBL-producing *E. coli*-related UTIs.[7] The differences in microbiological (79% *versus* 50%) and clinical cure rates (94% *versus* 71%) between that and our study are probably related to the variability in the average age of the patients (55 *versus* 72 years) and the number of CFs. In the study by Pullukcu, 16/52 (30.8%) patients did not have any CFs, and the average number of CFs was 0.7. In our study, all except two patients had at least one CF, with 2.2 CFs on average.

Senol and colleagues compared the effect of fosfomycin and carbapenems (meropenem or imipenem-cilastatin) in an observational prospective study of ESBL-producing *E. coli*-related cUTIs. The fosfomycin treatment regimen was the same as in the study by Pullukcu and colleagues. Carbapenem therapy lasted 14 days, that is, twice as long as the fosfomycin treatment, provided that the effect of the third fosfomycin dose is assumed to last for 2–3 days. Clinical and microbiological success rates in the carbapenem and fosfomycin groups were similar (19/20 (95%) *versus* 21/27 (78%) and 16/20 (80%) *versus* 16/27 (59%), respectively, $p > 0.05$). The microbiological and clinical success in that study was thus similar to our results (59% *versus* 50% and 78% *versus* 71%, respectively). The patients' characteristics were also rather similar to those in our study.[8]

Neuner and colleagues reported the results of fosfomycin treatment in 41 hospitalised patients with urine cultures positive for a multidrug-resistant urinary pathogen. Of these, seven were ESBL-producers and four achieved microbiological cure. The exact number of fosfomycin doses in those patients was not specified, but the average number of doses among all 41 patients was 2.9.[21]

In a retrospective cohort study, Matthews and colleagues analysed 75 adult patients (average age 73 years) with UTI who received 151 episodes of treatment with fosfomycin. Out of those 75 patients, 37 had UTIs caused by ESBL-producing Enterobacteriaceae (31 *E. coli* and 6 *K. pneumoniae*). Of the 40 cases that could be classified, 21 (53 %) met the criteria for microbiological cure

(sterile follow-up urine). Among those 21 UTIs, 12 were caused by ESBL-producing pathogens, while in the 19 cases with microbiological failure, 10 were caused by ESBL-producers. Microbiological failure was not associated with either ESBL production or other risk factors.[22]

In a retrospective analysis by Seroy and colleagues, patients with cUTIs received a variable number of fosfomycin doses: 1–6 for 20 *E. coli* ESBL-related (3 on average) and 1–14 for 8 *K. pneumoniae* ESBL-related cUTIs (4.6 on average). Of 20 patients with *E. coli* ESBL-related cUTIs, 8 had persistence or recurrence of infection, as did 4 out of 8 patients with *K. pneumoniae* ESBL-related cUTIs.[23]

A three-dose fosfomycin regimen for the treatment of patients with different types of UTIs was evaluated in a prospective, uncontrolled study in 12 medical centres in China. In the whole sample of patients there were 31 patients with cUTI and microbiological eradication was achieved in 23 patients (74.2%).[24] However, the exact causative pathogens or CFs were not specified.

All ESBL-producing urinary isolates in our study were susceptible to fosfomycin and carbapenems *in vitro*, whereas other antibiotics had a much lower activity. It is important to note that trimethoprim/sulfamethoxazole and ciprofloxacin, other possible oral antibiotics for the treatment of ESBL-related cUTIs, were active *in vitro* against only 16.3% and 7% of ESBL-producing isolates, respectively. Nitrofurantoin preserved activity against 55.9% of ESBL-producing *E. coli* isolates but it is licensed for uncomplicated UTIs only.[25,26] The *in vitro* activities of antibiotics tested against urinary ESBL-producing isolates (except for carbapenems and fosfomycin) in our study were lower than in the majority of other published studies.[27–29] The antibiotic resistance profile of ESBL-producing isolates in our study probably reflects acquired resistance due to previous antibiotic treatments for recurrent cUTIs.[30] The relatively high number of CFs and comorbidities in our patients is related to high rates of antimicrobial resistance, as in healthcare-associated UTIs.[31]

Treatment of cUTIs caused by ESBL-producing Enterobacteriaceae remains challenging, especially in the elderly and in immunocompromised patients in whom increased numbers of CFs decrease the chances of treatment success. Our results indicate that fosfomycin treatment courses of a longer duration than the most commonly recommended three doses may be necessary in order to eradicate the causative pathogen. Our patients with between zero and one CF received a significantly lower number of fosfomycin doses than patients with two or more CFs ($p = 0.022$). Hence, it seems that the treating physicians considered the patients with two or more CFs to have a higher risk of treatment failure.

The correlation between outcomes in terms of microbiological and clinical cure in the patient groups with zero to one CFs *versus* two or more CFs did not reach statistical significance for either microbiological ($p = 0.116$) or clinical cure ($p = 0.921$). It is possible that statistically significant differences would have been achieved with a larger patient sample. Since clinical cure is easier to achieve than microbiological cure, irrespective of treatment duration and the number of CFs, it can be speculated that even larger samples of study patients would be needed to reach statistically significant differences in that regard.

The main limitations of our study are its retrospective nature, the relatively small number of patients and the use of variable dosing regimens.

In conclusion, we believe fosfomycin may be a valid option for oral treatment of cUTIs caused by ESBL-producing pathogens for which very few antibiotic options remain. In five of our patients, fosfomycin was the only oral therapeutic option available, which makes this old drug a valuable member of the antibiotic armamentarium. All patients experienced temporary relief of their symptoms at the beginning of the treatment; however, in a significant number of them, microbiological eradication was not achieved. This is probably due to the fact that our patients were predominantly elderly females with recurrent cUTIs. The optimal duration of fosfomycin treatment for cUTIs remains to be determined.

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## Contributorship statement

BL collected and analysed the data and wrote the manuscript, LR defined the research problem, planned the study, collected the data and performed a critical review of the manuscript. Both coauthors approved the final version of the manuscript and met the ICMJE authorship criteria.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

## Research involving human participants and/or animals

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and followed the guidelines of the 1964 Helsinki declaration and its later amendments.

## Informed consent statement

Our study was approved by the Ethics Committee of the University of Zagreb School of Medicine - Register number: 380-59-10106-18-111/27, Class: 641-01/18-02/01. All patients provided written informed consent prior to enrolment in the study.

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