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Evaluation of fosfomycin, furazidin, and gentamicin impact on growth of uropathogenic ESBL-producing *Escherichia coli*

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Introduction: Urinary tract infections are a prevalent health issue, significantly impacting both patient well-being and healthcare systems. The rise of antibiotic resistance, particularly among Gram– bacilii, complicates treatment protocols. This study assesses the inhibitory effect of 3 antimicrobials – fosfomycin, furazidin, and gentamicin – against both wild-type and extended-spectrum β-lactamase (ESBL)-producing uropathogenic *Escherichia coli* clinical strains.

Materials and methods: Sixty *E. coli* isolates (30 ESBL-producing and 30 wild-type) were collected from clinical urine samples. Identification and antimicrobial susceptibility were assessed using MALDI-TOF MS and VITEK 2 systems. Growth inhibition by antibiotics was measured in Mueller-Hinton broth at optical density 600 nm over 24 h. Extended-spectrum β-lactamase genes were identified via polymerase chain reaction targeting bla_{CTX-M}, bla_{SHV}, bla_{TEM}, bla_{PER}, bla_{VEB} and bla_{GES} genes. Statistical analysis was performed using the Friedman test with Dunn's correction.

Results: Fosfomycin exhibited significant growth inhibition against both wild-type and ESBL-producing *E. coli*, particularly those harboring bla_{CTX-M} genes. Furazidin and gentamicin were effective against wild-type strains but not against ESBL producers. Statistically significant inhibition for wild-type strains was observed with fosfomycin ($p = 0.004$), furazidin ($p = 0.007$), and gentamicin ($p = 0.008$). For ESBL producers, significant inhibition was noted only with fosfomycin ($p < 0.001$).

Conclusions: Fosfomycin shows strong efficacy against both wild-type and ESBL-producing *E. coli*, suggesting its potential as a first-line treatment for urinary tract infections amidst rising antibiotic resistance. Furazidin and gentamicin, while effective against wild-type strains, are less effective against ESBL-producing strains, underscoring the need for targeted antibiotic use. Further research is recommended to validate these findings and optimize clinical treatment guidelines.

Keywords: fitness cost; extended-spectrum β-lactamase; urinary tract infection; *Escherichia coli*; antimicrobials.

INTRODUCTION

Urinary tract infection (UTI) is an inflammatory response of the urothelium to pathogenic microorganisms that colonize the urinary tract [1]. Urinary tract infections are commonly present with dysuria and increased urinary frequency [2]. However, UTI can lead to life-threatening conditions such as severe sepsis or septic shock. In the United States, UTI was reported as the source in 40% of patients who presented to the emergency department with septic shock and 25% of hospitalized patients who developed septic shock [3]. Kumar et al. published a retrospective study based on 2 cohorts of adult patients admitted to intensive care units in 3 countries (Canada, United States, and Saudi Arabia) between 1996–2007. They estimated that the UTI was a source of sepsis in 15–18% of cases [4]. Urinary tract infection is also a significant economic problem. It has been reported that UTI are responsible for approx. 8 mln visits in outpatient settings. It generates enormous costs, reaching even $1.5 billion per year [5]. Urinary tract infection are more prevalent among women, with nearly 50–60% of women likely to experience this kind of infection at some point in their lives [6].

The causative agents of UTI span a diverse group of pathogens, but *Escherichia coli* remains the predominant etiological agent [1]). This bacterium's ability to adhere to the urothelium, resistance to rinsing by urine flow, and the arsenal of virulence factors contribute significantly to its pathogenicity [7]. Treatment of UTI is based on antibiotic therapy. Practitioner guidelines may be a bit different from country to country. Based on European guidelines, the first-line antibiotic in UTI therapy includes fosfomycin, pivmecillinam, cephalosporins (e.g., cefadroxil), trimethoprim with sulfamethoxazole, and nitrofurantoin [8].

However, the treatment of UTIs has been complicated by the escalating trend of antibiotic resistance, particularly by the emergence of extended-spectrum β-lactamase (ESBL) producing strains that confer resistance to many β-lactam antibiotics [8]. The ESBL-producing *E. coli* strains represent a remarkably challenging group of pathogens, as they often exhibit resistance to multiple drug classes and are associated with higher rates of recurrence, treatment failures, and increased healthcare costs [9]. This resistance mechanism is mediated by several genes, such as *CTX-M*, *SHV*, *TEM*, *PER*, and others, which are often plasmid-borne, facilitating their rapid dissemination among bacterial populations [10, 11].

The clinical response to the rising tide of antibiotic resistance includes a renewed interest in older antibiotics, such as fosfomycin or nitrofurantoin, and the development of new treatment strategies, like combined therapy [12]. Fosfomycin has been recognized for its efficacy against a broad spectrum of pathogens, including

ESBL-producing *E. coli*, making it a valuable option for empirical treatment in uncomplicated UTIs [13]. Nitrofurantoin remains effective for many strains of *E. coli* but, due to its pharmacokinetic properties, it is recommended for lower UTI [8]. Analyzes of cumulative antibiograms performed in Polish hospitals revealed that also aminoglycosides (e.g., gentamicin or amikacin) had high effectiveness against uropathogens, next to nitrofuran derivatives (e.g., nitrofurantoin or furazidin) and fosfomycin. These drugs could be a good choice in the empirical therapy of UTI [14, 15].

In this context, our study aims to critically evaluate the effectiveness of fosfomycin, furazidin, and gentamicin against ESBL-producing uropathogenic *E. coli* strains, providing insights that may influence future guidelines and therapeutic approaches.

MATERIALS AND METHODS

The study group consisted of 60 *E. coli* clinical isolates (30 ESBLs and 30 wild-types) from the Department of Microbiology and Medical Laboratory Immunology culture collection at the Medical University of Lodz in Poland. Strains were previously secured from positive urine samples obtained between February and August 2021 from the Medical Microbiology Laboratory at the Central Teaching Hospital of the Medical University of Lodz. They were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) system VITEK MS (bioMérieux, France) and tested for antimicrobial susceptibility with automated microbiological system VITEK 2 (bioMérieux, France). Every ESBL mechanism was confirmed phenotypically with a double disc synergy test [16]. All bacteria were stored in Viabank storage beads (Medical Wire & Equipment, UK) at –80°C maximum and regenerated on Columbia Agar with 5% sheep blood (Thermo Fisher Scientific, USA), 18 ±2 h at 35 ±1°C in atmospheric conditions.

To determine the effect of antibiotics on ESBL and wild-type *E. coli* growth, the strains were incubated at 37 ±1°C in Mueller–Hinton broth with or without antibiotics in MultiskanGO (Thermo Fisher Scientific, USA). Measurements were taken every hour for 24 h at optical density (OD) = 600 nm. The study investigated antibiotics commonly used to treat UTI: (1) fosfomycin, (2) gentamicin, and (3) furazidin. Furazidin is an analog of nitrofurantoin, which, due to the lack of availability of nitrofurantoin, is used as its substitute. This is justified because cross-resistance between these drugs has been observed [17]. The concentration of antibiotics in the tested samples was 1/2 the minimum inhibitory concentration (MIC), determined individually for each of the tested strains previously. Minimum inhibitory concentration values were determined using the broth microdilution method according to the procedure described in ISO 20776-1:2019 [18], as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The determined MICs are presented in Table 1.

TABLE 1. Minimum inhibitory concentration values of the tested antibiotics against the examined *Escherichia coli* isolates

Isolate number	Minimum inhibitory concentration (mg/mL)		
	furazidin	gentamicin	fosfomycin
A1	4	0.5	8
A2	8	2	2
A3	16	2	16
A4	256	1	16
A5	16	2	8
A6	8	2	4
A7	16	2	2
A8	64	0.5	2
A9	256	0.5	4
A10	256	2	4
A11	64	2	16
A12	16	1	8
A13	128	2	4
A14	4	2	2
A15	128	1	4
A16	4	8	3
A17	8	2	4
A18	64	0.5	4
A19	8	1	8
A20	32	2	1
A21	8	2	8
A22	4	0.25	128

TABLE 2. Minimum inhibitory concentration values of the tested antibiotics against the examined *Escherichia coli* isolates

Isolate number	Minimum inhibitory concentration (mg/mL)		
	furazidin	gentamicin	fosfomycin
A23	16	2	8
A24	8	8	4
A25	16	2	5
A26	1	0.5	8
A27	4	1	2
A28	8	0.5	16
A29	64	1	8
A30	32	1	16
B1	32	2	2
B2	16	1	8
B3	32	2	4
B4	16	2	2
B5	32	1	2
B6	4	2	4
B7	16	2	2
B8	64	16	4
B9	8	8	2
B10	256	2	4
B11	128	2	8
B12	16	4	8
B13	4	8	4
B14	32	16	8
B15	4	2	4
B16	8	2	2
B17	32	8	4
B18	64	8	16
B19	128	1	8
B20	4	8	4
B21	4	16	8
B22	4	8	16
B23	1	0.5	4
B24	2	16	2
B25	8	1	4
B26	512	16	8
B27	16	8	4
B28	32	8	2
B29	8	2	2
B30	16	16	4

A – wild-type; B – ESBL-producing

Stock solutions (5120 mg/L) of all tested antibiotics were prepared using pure substance powders purchased from the manufacturer (Selleck Chemicals, USA). Fosfomycin (Catalog No. S5048) and gentamicin (Catalog No. S6289) were dissolved in distilled water, whereas furazidin (Catalog No. S3709) was first dissolved in DMSO (Thermo Fisher Scientific, USA)

and then diluted with distilled water. Finally, furazidin solution contained ~10% DMSO. A control broth microdilution assay containing DMSO alone confirmed that this concentration did not interfere with the growth of the tested bacteria.

Additionally, an analysis of the ESBL-producing strains genotype was performed to investigate the existence of possible associations related to the occurrence of specific ESBL resistance genes. For this purpose, the genetic material of *E. coli* strains was isolated directly from pure bacterial cultures on Columbia Agar with 5% sheep blood (Thermo Fisher Scientific, USA). Bacterial genomic DNA was obtained using the Genomic Mini AX Bacteria Spin kit (A&A Biotechnology, Poland), cat. no. 060-100S, according to the manufacturer's instruction. DNA was amplified using HS PCR Kit 1 (A&A Biotechnology, Gdynia, Poland), cat. no. 1201-1000H. The sequences of primers used for detection of genes responsible for ESBL resistance (bla_{CTX-M}, bla_{SHV}, bla_{TEM}, bla_{PER}, and bla_{VEB}) are listed in Table 2. Polymerase chain reaction reaction was performed as follows: initial denaturation at 95°C for 2 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 50°C for 1 min, extension at 72°C for 2 min and final extension at 72°C for 10 min. Polymerase chain reaction products were analyzed by gel electrophoresis with 100 bp marker (antibiotic resistance identification). The gels were visualized under ultraviolet light transilluminator.

All collected data were analyzed using Microsoft Excel (Microsoft Corporation, USA), GraphPad Prism 8 (GraphPad Software, USA), and the online tool CompareCurves [23, 24]. Normality of data distribution was verified with the Shapiro–Wilk test, which demonstrated that the data were not normally distributed. Therefore, all subsequent analyses were performed using non-parametric tests. To compare bacterial growth in the presence and absence of antibiotics, the Friedman test with Dunn's multiple comparison correction was applied. The CompareCurves algorithm was additionally used to evaluate differences between entire bacterial growth curves for each antibiotic. This method compares the overall shape of kinetic curves using a global similarity test based on integrated deviations between the curves and provides an overall p-value indicating whether growth profiles differ significantly. All experiments were performed in triplicate for each of the 30 isolates per group, and results were expressed as mean optical density (OD_{600}) ± standard deviation at each time point. A p-value < 0.05 was considered statistically significant in all analyses.

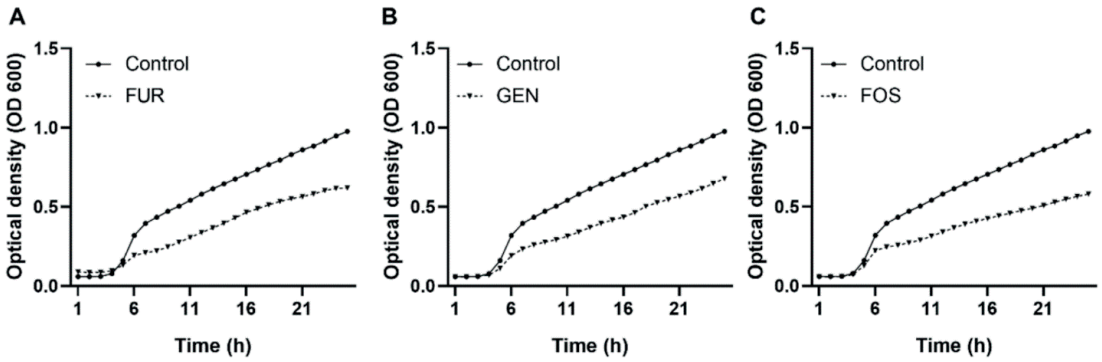
RESULTS

The bacterial growth curves in the presence of studied antibiotics are presented in Figures 1 and 2. Each point on the curves represents the mean OD ± SD calculated from 30 individual bacterial strains.

In Figure 1, the mean values of all wild-type strains' growth curves in broth only (control group) were compared with the same strains in the presence of antibiotics in 1/2 of MIC. The statistically significant inhibition of bacterial growth was obtained in each group: furazidin (p = 0.007), gentamicin (p = 0.008), and fosfomycin (p = 0.004). The growth profiles for all 3 antibiotics showed a comparable pattern of inhibition (Fig. 1). Each antibiotic examined in this analysis exhibits satisfactory effectiveness against wild-type uropathogenic *E. coli* strains.

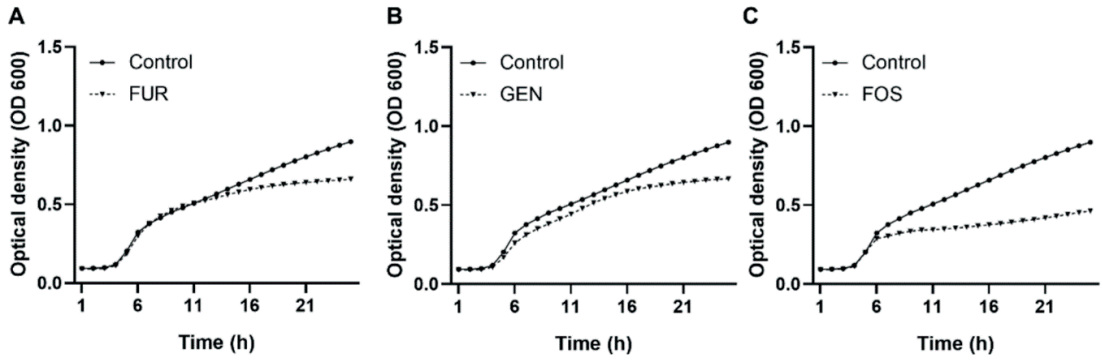
TABLE 3. Details of the oligonucleotide primers used in the study

Gene	Primer sequences	Product size (bp)	References
$bla_{CTX-M-15}$	Forward: 5′-ATGTGCACCAGTAARGT-3′ Reverse: 5′-TGGGTRAARTARGTSACCAGA-3′	593	[19]
bla_{SHV}	Forward: 5′-ATTTGTCGCTTCTTTACTCGCC-3′ Reverse: 5′-TTCACCACCATCATTACCGACC-3′	1016	[20]
bla_{TEM}	Forward: 5′-GTGCGCGGAACCCCTATT-3′ Reverse: 5′-GGGATTTTGGTCATGAGATTATC-3′	717	[20]
bla_{PER}	Forward: 5′-AATTTGGGCTTAGGGCAGAA-3′ Reverse: 5′-ATGAATGTCATTATAAAAGC-3′	924	[19]
bla_{VEB}	Forward: 5′-CGACTTCCATTTCCCGATGC-3′ Reverse: 5′-GGACTCTGCAACAAATACGC-3′	642	[21]
bla_{GES}	Forward: 5′-ATGCGCTTCATTCACGCAC-3′ Reverse: 5′-CTATTTGTCCGTGCTCAGG-3′	864	[20]
bla_{CTX-M} group 1	Forward: 5′-AAAAATCACTGCGCCAGTTC-3′ Reverse: 5′-AGCTTATTCATCGCCACGTT-3′	415	[22]
bla_{CTX-M} group 2	Forward: 5′-CGACGCTACCCCTGCTATT-3′ Reverse: 5′-CCAGCGTCAGATTTTTCAGG-3′	552	[22]
bla_{CTX-M} group 8	Forward: 5′-TCGCGTTAAGCGGATGATGC-3′ Reverse: 5′-AACCCACGATGTGGGTAGC-3′	666	[22]
bla_{CTX-M} group 9	Forward: 5′-CAAAGAGAGTGCAACGGATG-3′ Reverse: 5′-ATTGGAAAGCGTTCATCACC-3′	205	[22]
bla_{CTX-M} group 25	Forward: 5′-GCA CGA TGA CAT TCG GG-3′ Reverse: 5′-AACCCACGATGTGGGTAGC-3′	327	[22]



FOS – fosfomycin; FUR – furazidin; GEN – gentamicin

FIGURE 1. Growth curves of studied wild-type *Escherichia coli* strains (n = 30) in the presence of studied antibiotics compared to the growth curves without the presence of antimicrobials



FOS – fosfomycin; FUR – furazidin; GEN – gentamicin

FIGURE 2. Growth curves of studied ESBL-producing *Escherichia coli* strains (n = 30) in the presence of studied antibiotics compared to growth curves without the presence of antimicrobials

The analysis of antibiotics' effectiveness against ESBL-producing *E. coli* strains is presented in Figure 2. Statistically significant inhibition of bacterial growth was obtained only in group with fosfomycin ($p < 0.001$). Furazidin and gentamycin did not show the expected effect ($p = 0.319$ and $p = 0.201$, respectively).

For wild-type *E. coli* (Fig. 1), the growth kinetics in antibiotic-containing media showed delayed exponential phases and lower stationary-phase plateaus compared to the antibiotic-free control. Despite the different antibiotic mechanisms, the overall growth profiles were highly similar, as confirmed by CompareCurves analysis ($p \approx 1.0$). In contrast, for ESBL-producing strains (Fig. 2), only fosfomycin caused a distinct suppression of growth throughout the incubation period ($p < 0.001$), while furazidin and gentamicin curves closely overlapped with the control group, indicating limited inhibitory activity against these resistant isolates.

In addition to growth curve analysis, the genetic determinants of ESBL resistance were identified. Among 30 ESBL-producing *E. coli* strains, the genes coding ESBL resistance were identified in 16 cases: 12 $bla_{CTX\text{-}M}$ group 1 genes (including 8 $bla_{CTX\text{-}M\text{-}15}$), 3 bla_{SHV} *gene*, 3 bla_{TEM}, and 1 bla_{VEB}. For 14 strains the molecular background of antibiotic resistance remained unknown.

We did not perform a comparative analysis of bacterial growth curves depending on the detected resistance genes due to the small number of isolates within each genetic subgroup.

DISCUSSION

The number of ESBL-producing *E. coli* strains in the population is still growing [25]. ESBL resistance has significant clinical implications in such infection treatment. It has been reported that UTIs triggered by ESBL strains are characterized by higher mortality compared to infections caused by wild-type strains [26]. It makes empiric therapy of UTI more difficult. Some studies even investigated prediction rules to predict ESBL-triggered infection in patients with suspected UTI [27, 28].

The emergence of antibiotic resistance, particularly among uropathogenic *E. coli* strains, represents a significant challenge in the management of UTIs. The results of this study underline the variable efficacy of fosfomycin, furazidin, and gentamicin against both wild-type and ESBL-producing strains. Notably, fosfomycin demonstrated a consistent inhibitory effect on bacterial growth, aligning with other studies that highlight its potent action against multidrug-resistant bacteria [12].

In contrast, the performance of furazidin and gentamicin was less consistent, which may be indicative of the selective pressure exerted by the use of aminoglycosides and other related antibiotics over the years. A study by Mwakyoma et al. noted that resistance to gentamicin has been increasing, particularly in ESBL-producing strains [29]. This could explain the diminished response observed in our ESBL samples, suggesting a need for cautious use of gentamicin in empirical therapy.

TABLE 4. Identified ESBL genes the examined Escherichia coli isolates. No samples resulted positive for presence of bla_{PER}, bla_{GES}, and bla_{CTX-M} groups 2, 8, 9, 25 genes

Isolate number	Identified genes				
	$bla_{CTX-M-15}$	bla_{SHV}	bla_{TEM}	bla_{VEB}	bla_{CTX-M} group 1
B1		+			
B3			+		
B4					+
B5	+	+			+
B8				+	
B11					+
B12			+		
B17					+
B20	+				+
B22	+				+
B23	+		+		+
B24	+				+
B25	+				+
B26	+	+			+
B27					+
B29	+				+

Our findings align with the broader literature that advocates reassessing old antibiotics like fosfomycin in the face of growing resistance. For instance, Karageorgopoulos et al. [13] reviewed the efficacy of fosfomycin against ESBL-producing pathogens and found it a reliable option in many geographical regions. Fosfomycin is a broad-spectrum bactericidal antibiotic that remains highly effective against both Gram– and Gram+ pathogens, including multidrug-resistant *E. coli* strains. Its unique mechanism of action differentiates it from other agents used against UTI. Fosfomycin irreversibly inactivates the enzyme MurA by covalently binding to the cysteine residue in its active site, thereby blocking the first committed step of peptidoglycan biosynthesis [30]. Unlike β-lactam antibiotics, which target penicillin-binding proteins (PBPs) at later stages of cell wall cross-linking, fosfomycin acts upstream of PBP-mediated reactions, resulting in early interruption of the cell wall precursor pathway and rapid bacterial lysis [31]. This mechanism explains its sustained activity against ESBL--producing isolates, since β-lactamase enzymes do not inactivate fosfomycin's molecular target [32]. In addition, plasmid-mediated *fosA*, *fosB*, and *fosC2* genes – encoding glutathione S-transferases that inactivate fosfomycin – have emerged sporadically in ESBL--producing *E. coli* strains [33, 34]. Nevertheless, global surveillance data still confirm a low prevalence of acquired resistance (<5%) in uropathogenic *E. coli* populations, even in countries with extensive antibiotic use [15, 35, 36]. These properties explain the strong and consistent inhibitory effect observed in our study for fosfomycin-treated *E. coli* isolates, in contrast to the diminished response seen with furazidin or gentamicin.

The most frequently identified gene, in the ESBL-producing *E. coli* group we studied, was bla_{CTX-M} which reflects the global trend described in recent epidemiological reports. Historically, *TEM* and *SHV* variants dominated as ESBLs derived from point mutations in early penicillinases, but they have now been largely replaced by *CTX-M*-type enzymes, which originated from *Kluyvera* spp. and spread through plasmid-mediated transfer. In contrast, bla_{TEM}, bla_{SHV}, bla_{PER}, bla_{VEB}, and bla_{GES} are now relatively rare in *E. coli*, typically confined to hospital outbreaks in other Gram– species [11, 37]. The dominance of *CTX-M*-type ESBLs in our isolates therefore aligns with international surveillance data nd highlights the ongoing "*CTX-M* pandemic" as the leading driver of β-lactam resistance in *E. coli* populations worldwide. [38]. The absence of bla_{PER}, bla_{VEB}, and bla_{GES} genes in our collection suggests that these ESBL variants remain rare among community-acquired uropathogenic *E. coli* in Poland.

It is worth noting that, although we identified twelve *E. coli* isolates carrying the bla_{CTX-M} group 1 genes (including 8 $bla_{CTX-M-15}$), the growth curves for individual isolates were not analyzed separately. This decision was based on the small sample size and the aim to present population-level growth dynamics. However, preliminary visual inspection of the raw data suggests subtle variability among individual bla_{CTX-M}-positive isolates, which might reflect differences in the *CTX-M* variants represented in our collection. Future studies using whole-gene sequencing and curve-based phenotypic clustering could clarify whether distinct bla_{CTX-M} subtypes are associated with specific growth patterns or fitness costs.

CONCLUSIONS

In summary, furazidin, gentamicin, and fosfomycin are antibiotics effective in the treatment of cystitis caused by wild-type *E. coli* strains, which is the most common etiological factor of

UTI. However, in the case of cystitis caused by ESBL-producing *E. coli* strains, fosfomycin exhibits the best effect on bacterial multiplication. Given its sustained activity against ESBL-producing *E. coli*, fosfomycin should be considered a first-line agent in the empirical treatment of uncomplicated cystitis.

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