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ORIGINAL ARTICLE

Fosfomycin: A Promising Therapeutic Option for Urinary Tract Infections in the Era of Antibiotic-Resistant Uropathogens

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ABSTRACT

Background: *The distressingly rising antibiotic resistance amongst uropathogens figures a foremost health challenge. The role of fosfomycin in eradicating such superbugs has been rampantly studied nowadays.* ***Objectives:*** *This study was designed to (1) investigate the in vitro susceptibility of Gram negative uropathogens to fosfomycin and (2) compare fosfomycin efficacy with other antibiotics commonly prescribed for treatment of urinary tract infections (UTIs).* ***Methodology:*** *A prospective cohort study was performed over a period of 12 months. Urine samples were collected from patients admitted to the Oncology Center of Mansoura University (OCMU), Egypt, and processed at the Microbiology Diagnostics and Infection Control Unit (MDICU), Faculty of Medicine, Mansoura University, Egypt. Antimicrobial susceptibility was determined by the Kirby-Bauer's disc diffusion method. The minimum inhibitory concentrations (MICs) of fosfomycin were evaluated by agar dilution (AD) method. Phenotypic confirmation of extended spectrum β-lactamase (ESBL) production was done by the double-disc synergy test (DDST). The modified Hodge test (MHT) was used as a screening method for carbapenemase-producing isolates.* ***Results:*** *A total of 171 Gram negative uropathogens were recovered. Fosfomycin was the most active antibiotic with an overall susceptibility of 92.4%. The MICs of fosfomycin ranged from 0.25 to ≥ 256 µg/mL. Amongst the ESBL-producing isolates, 87.5% were fosfomycin-sensitive, while 61.5% of the carbapenemase-producing uropathogens were susceptible.* ***Conclusion:*** *Fosfomycin has a feasible in vitro activity against Gram negative uropathogens, including ESBL- and carbapenemase-producing isolates. Thereby, fosfomycin could be a relevant therapeutic approach for UTIs caused by resistant strains. Nonetheless, future studies should be executed to explore the underlying mechanisms of fosfomycin resistance.*

INTRODUCTION

Urinary tract infections (UTIs) are amidst the most frequently occurring human bacterial infections.[1] Worldwide, about 150 million individuals develop UTIs per annum.[2] Both Gram negative and Gram positive bacteria, along with certain fungal species can cause UTIs. The leading microorganism is uropathogenic *Escherichia coli* (UPEC),[3] followed by *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B *Streptococci* (GBS), *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida* species.[4]

The emergence and spread of antibiotic-resistant uropathogens to the commonly prescribed agents, such as trimethoprim-sulfamethoxazole and fluoroquinolones, led to an escalating concern in finding out other treatment substitutes or reappraisal of the currently available antibiotics for the treatment of UTIs.[5] One such drug is fosfomycin, which was originally discovered in Spain in 1969 from cultures of *Streptomyces* species.[6]

Fosfomycin is a bactericidal antibiotic that interferes with cell wall synthesis by inhibiting phosphoenolpyruvate transferase; the initial enzyme involved in the peptidoglycan biosynthesis.[7] It is a broad spectrum antibiotic with activity against various Gram positive and Gram negative bacterial isolates, including; staphylococci, enterococci, *E. coli* and other Gram negative bacteria.[8] There is no reported cross resistance of this antibiotic with others, thus it can be administered safely in association with other antibiotics.[9] Commercially, fosfomycin is present in two oral formulations; fosfomycin trometamol and fosfomycin calcium, in addition to one intravenous formulation; fosfomycin disodium. Following a single 3-gram dose of fosfomycin trometamol, peak urine concentrations are reached within 4 hours. Urine levels remain high for 1 to 2 days, which is adequate to eradicate most of the uropathogens.[10]

Even though fosfomycin has been in existence for more than four decades ago, a paucity of data are currently available about its efficacy against different uropathogens in Egypt. Accordingly, this study was organized to provide a perception about the *in vitro* susceptibility of Gram negative uropathogens to fosfomycin, as well as to compare its efficacy with other antibiotics generally used for the management of UTIs.

METHODOLOGY

This is a prospective cohort study conducted over a 12-months period (January to December 2016).

Sample collection and processing

Fresh, mid-stream, clean catch urine samples were collected under strict aseptic precautions in sterile containers from patients admitted to the Oncology Center of Mansoura University (OCMU), Egypt. The samples were referred immediately to the microbiology laboratory at the Microbiology Diagnostics and Infection Control Unit (MDICU), Faculty of Medicine, Mansoura University, Egypt for culture and sensitivity testing. The samples were inoculated onto cystine lactose electrolyte deficient (CLED) agar media (Oxoid Ltd., Basingstoke, UK) using calibrated loop (10 µL). The plates were incubated aerobically at 37°C overnight and if required, till 48 hours. Following the guidelines of Kass (2002) in discriminating true bacterial infection from contamination, significant mono-microbial bacteriuria was defined as culture of a single bacterial species from the urine sample at a concentration of $\geq 10^5$ colony-forming unit (cfu)/ml.[11] Different bacterial isolates were identified based on their colony morphology, Gram staining characters and results of standard biochemical reactions.[12]

Antimicrobial susceptibility testing

Antibiotic susceptibility was assessed by the Kirby-Bauer's disc diffusion method on Muller-Hinton agar (MHA) plates (Oxoid Ltd., Basingstoke, UK) in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[13] A set of 18 antibiotic discs (Oxoid Ltd., Basingstoke, UK) was used including amoxicillin (AML; 25 µg), amoxicillin/clavulanic acid (AMC; 20/10 µg), piperacillin/tazobactam (TZP; 100/10 µg), cefuroxime (CXM; 30 µg), ceftriaxone (CRO; 30 µg), ceftazidime (CAZ; 30 µg), cefotaxime (CTX; 30 µg), cefepime (FEP; 30 µg), cefoperazone/sulbactam (SCF; 75/30 µg), aztreonam (ATM; 30 µg), imipenem (IPM; 10 µg), meropenem (MEM; 10 µg), gentamicin (CN; 10 µg), amikacin (AK; 30 µg), trimethoprim/sulfamethoxazole (SXT; 1.25/23.75 µg), ciprofloxacin (CIP; 10 µg), norfloxacin (NOR; 10 µg) and fosfomycin (FOS; 200 µg). *E. coli* ATCC 25922 (American Type Culture Collection, Rockville, MD) was included as a quality control strain.

Determination of the minimum inhibitory concentrations (MICs) of fosfomycin

All strains were verified for the MICs of fosfomycin (Sigma-Aldrich, Italy) using the agar dilution (AD) method as per the CLSI guidelines.[13] MHA plates were prepared according to the manufacturer's instructions followed by the addition of glucose-6-phosphate to a final concentration of 25 µg/mL. Fosfomycin was added to MHA in 2-fold serial dilutions at concentrations ranging from 0.25-256 µg/mL. Few colonies of the test strains were picked with the help of a wire loop and emulsified in 0.9% normal saline in test tubes. The tubes were then incubated for 2 hours at 37°C. The turbidity of the suspensions were matched against the turbidity of 0.5 McFarland turbidity standard. Using a micropipette, these suspensions were spot inoculated on MHA plates which had different concentrations of fosfomycin, in addition to a control plate without antimicrobial agent. After overnight incubation at 37°C, the MIC was interpreted as the lowest concentration of fosfomycin that completely inhibited visible growth as judged by the naked eye. MIC values that inhibited 50% and 90% of the isolates were accepted as MIC_{50} and MIC_{90}, respectively. *E. coli* ATCC 25922 was included concurrently as a control strain in each run of MIC measurements. Breakpoints to define susceptibility for fosfomycin were set to $\leq$ 64 µg/mL (inferred for all *Enterobacteriaceae* from CLSI breakpoint for *E. coli* as has been reported previously).[8]

Phenotypic detection of extended spectrum β-lactamase (ESBL)-producing strains

A screening test for ESBL production was done as part of the routine susceptibility testing according to the criteria set by the CLSI.[13] An inhibition zone of $\leq$ 22 mm for ceftazidime and $\leq$ 27 mm for cefotaxime indicated the possibility of ESBL-producing strain. The confirmatory test for ESBL production was performed using the double-disc synergy test (DDST) in accordance with the guidelines of the CLSI,[13] with discs of amoxicillin-clavulanic acid (20/10 µg) placed in the center of MHA plates. At both sides of the amoxicillin-clavulanic acid disc, discs of cefotaxime (30 µg) and ceftazidime (30 µg) were placed with center to center distance of 30 mm to the centrally placed disc. The plates were incubated for 16-18 hours at 37°C. ESBL production was interpreted if cefotaxime and or ceftazidime disc inhibition zone was increased towards the amoxicillin-clavulanic acid disc or if there was an increase of $\geq$ 5 mm in zone diameter for either antibiotic tested in combination with clavulanic acid *versus* its zone when tested alone. *E. coli* ATCC 25922 (ESBL-negative strain) and *K. pneumoniae* ATCC 700603 (ESBL-positive strain) were used for quality control purposes.

Screening for carbapenemase production

The modified Hodge test (MHT) was used as a screening method for carbapenemase production according to the CLSI recommendations.[13] Briefly, the surfaces of MHA plates were inoculated evenly with a suspension of *E. coli* ATCC 25922 (1:10 dilution of turbidity adjusted to 0.5 McFarland). After brief drying, discs containing 10 µg meropenem were placed at the center of the MHA plates and carbapenem-resistant bacterial isolates from overnight culture plates were streaked from the edge of the disc to the periphery of the plates. The test was considered positive if there was an enhanced growth around the test or quality control

organism (*E. coli* ATCC 25922) streak at the intersection of the streak and the zone of inhibition (a characteristic cloverleaf-like indentation) after overnight incubation at 37°C.

Statistical analyses

All statistical analyses were performed using IBM-SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Data were described in the form of numbers and percentages or as mean ± standard deviation (SD). Comparison of categorical variables was done using Chi- square (χ^2) test. For fosfomycin susceptibility results, categorical agreement between disc diffusion method and AD method was evaluated with the later was used as the reference method.[13] Categorical agreement between both methods was achieved when an isolate was classified within the same category (i.e., susceptible or resistant) by both testing methods based on the CLSI breakpoints (2016). Errors were ranked as minor errors (disc diffusion are susceptible or resistant and AD is intermediate or alternatively, disc diffusion are intermediate and AD is susceptible or resistant); major errors (disc diffusion are resistant and AD is susceptible); very major errors (disc diffusion are susceptible and AD is resistant).[14] The Wilcoxon rank test was used for comparing MIC distributions. A *p*-value ≤ 0.05 was considered to be statistically-significant.

RESULTS

Distribution of bacterial isolates

During the study period, a total of 171 consecutive, non-duplicate (single isolate/patient) Gram negative bacterial isolates were retrieved from urine samples collected from patients admitted to the OCMU, Egypt. Amongst these isolates, *E. coli* was the most predominant uropathogen representing 42.7% (n = 73), followed by *Klebsiella pneumoniae* (32; 18.7%), *Proteus mirabilis* (27; 15.8%) and *Proteus vulgaris* (24; 14%). On the other hand, *Serratia marcescens* was the least frequent one accounting for 8.8% (n = 15) of the isolates. Noteworthy, preponderance of UTI among female patients was observed in this study, where 63.2% (n = 108) of the urinary isolates were related to female samples and the residual 63 strains (36.8%) were from male patients, with a female to male ratio of 1.7:1. The mean age of the involved patients was 37.2 ± 16.3 years (range: 18-61 years).

Results of antimicrobial susceptibility testing

By disc diffusion method, fosfomycin was the most effective antibiotic as compared to other antibiotics tested ($p \leq 0.05$). In sum, 13 (7.6%) of the isolates (3 *E. coli*, 5 *Klebsiella pneumoniae*, 2 *Proteus mirabilis*, 2 *Proteus vulgaris* and 1 *Serratia marcescens*) were fosfomycin-resistant. In addition, 2 *Klebsiella pneumoniae* isolates (1.2% of the total isolates) showed intermediate susceptibility to fosfomycin (had inhibitory zone diameters of 15 mm; the upper end of the intermediate range). Notably, *Klebsiella pneumoniae* isolates exhibited higher resistance rates to fosfomycin in comparison to *E. coli* with a statistically-significant difference (15.6% *versus* 4.1%; $p = 0.01$). The antibiotic susceptibility profiles of the test isolates to other antibiotics are detailed in table 1.

Table 1: Antibiotic susceptibility profiles of the encountered Gram negative bacterial isolates

Antibiotics	*E.coli* n = 73 (%)	*K. pneumoniae* n = 32 (%)	*Pr. mirabilis* n = 27 (%)	*Pr. vulgaris* n = 24 (%)	*S. marcescens* n = 15 (%)	*Total* (%)
FOS	70 (95.9)	27 (84.4)	25 (92.6)	22 (91.7)	14 (93.3)	158 (92.4)
MEM	68 (93.2)	21 (65.6)	23 (85.2)	20 (83.3)	10 (66.7)	142 (83)
TPZ	67 (91.8)	23 (71.9)	21 (77.8)	20 (83.3)	11 (73.3)	142 (83)
IPM	66 (90.4)	20 (62.5)	21 (77.8)	19 (79.2)	10 (66.7)	136 (79.5)
AK	63 (86.3)	20 (62.5)	19 (70.4)	20 (83.3)	10 (66.7)	132 (77.2)
FEP	59 (80.8)	18 (56.3)	21 (77.8)	21 (87.5)	11 (73.3)	130 (76)
CN	59 (80.8)	20 (62.5)	19 (70.4)	17 (70.8)	10 (66.7)	125 (73)
CIP	53 (72.6)	24 (75)	20 (74.1)	18 (75)	9 (60)	124 (72.7)
SCF	57 (78)	17 (53.1)	20 (74.1)	20 (83.3)	10 (66.7)	124 (72.7)
ATM	57 (78)	17 (53.1)	19 (70.4)	20 (83.3)	10 (66.7)	123 (72)
NOR	50 (68.5)	20 (62.5)	19 (70.4)	15 (62.5)	9 (60)	113 (66.1)
CRO	50 (68.5)	16 (50)	17 (63)	13 (54.2)	7 (46.7)	103 (60.2)
CTX	43 (58.9)	15 (46.9)	16 (59.3)	13 (54.2)	6 (40)	93 (54.4)
SXT	39 (53.4)	18 (56.3)	13 (48.1)	14 (58.3)	9 (60)	93 (54.4)
CAZ	41 (56.2)	16 (50)	16 (59.3)	13 (54.2)	5 (33.3)	91 (53.2)
CXM	36 (49.3)	12 (37.5)	13 (48.1)	10 (41.7)	2 (13.3)	73 (42.7)
AMC	27 (37)	12 (37.5)	9 (33.3)	10 (41.7)	0 (0.0)	58 (34)
AML	7 (9.6)	0 (0.0)	3 (11.1)	5 (20.8)	0 (0.0)	15 (8.8)

Abbreviations: n; number, *E. coli*; *Escherichia coli*, *K. pneumoniae*; *Klebsiella pneumoniae*, *Pr. mirabilis*; *Proteus mirabilis*, *Pr. vulgaris*; *Proteus vulgaris*, *S. marcescens*; *Serratia marcescens*, FOS; fosfomycin, MEM; meropenem, TPZ; piperacillin/tazobactam, IPM; imipenem, AK; amikacin, FEP; cefepime, CN; gentamicin, CIP; ciprofloxacin, SCF; cefoperazone/sulbactam, ATM; aztreonam, NOR; norfloxacin, CRO; ceftriaxone, CTX; cefotaxime, SXT; trimethoprim/sulfamethoxazole, CAZ; ceftazidime, CXM; cefuroxime, AMC; amoxicillin/clavulanic acid and AML; amoxicillin.

Results of the MICs of fosfomycin

By AD method, an overall fosfomycin sensitivity of 92.4% (MIC_{50} and MIC_{90}; 2 and 64 µg/mL, respectively) was recognized amongst the test isolates, with MICs ranged from 0.25 to ≥ 64 µg/mL as depicted in table 2. A total of 13 isolates expressed a resistant phenotype with MICs ≥ 256 µg/mL. Outstandingly, *Klebsiella pneumoniae* isolates had higher MICs as compared to *E. coli* (p = 0.02). Categorical agreement between disc diffusion test and AD method was 98.8%, as 2 *Klebsiella pneumoniae* isolates showed intermediate sensitivity by disc diffusion method, but they were susceptible by AD. So, 1.2% minor error was detected, while major errors were not identified in this study.

Table 2: Minimum inhibitory concentrations (MICs) of fosfomycin for the investigated Gram negative uropathogens

Bacterial isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Range (µg/mL)
Escherichia coli **(n=73)**	2	32	0.25 to 256
Klebsiella pneumoniae **(n=32)**	8	64	1 to >256
Proteus mirabilis **(n=27)**	1	32	0.5 to 256
Proteus vulgaris **(n=24)**	0.5	16	0.25 to 256
Serratia marcescens **(n=15)**	0.5	16	0.25 to 256

Abbreviations: MIC_{50}; MIC values that inhibited 50% the isolates, MIC_{90}; MIC values that inhibited 90% the isolates.
Results were interpreted according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI), 2016. Breakpoints to define susceptibility to fosfomycin were set to ≤ 64 µg/mL (settled for all *Enterobacteriaceae* from the CLSI breakpoint for *E. coli*).

Results of the double-disc synergy test (DDST)

Out of the 171 tested bacterial isolates, 42.1% (n = 72) were confirmed to be ESBL-producers by DDST, including 32 *E. coli* (44.4%), 16 *Klebsiella pneumoniae* (22.2%), 11 *Proteus mirabilis* (15.3%), 9 *Proteus vulgaris* (12.5%) and 4 *Serratia marcescens* (5.6%) isolates. It is worth mentioning that higher rates of resistance to fosfomycin were perceived among ESBL-positive strains in comparison to ESBL-negative isolates with a significant difference (12.5% *versus* 4%; p = 0.01). Data are demonstrated in fig. 1.

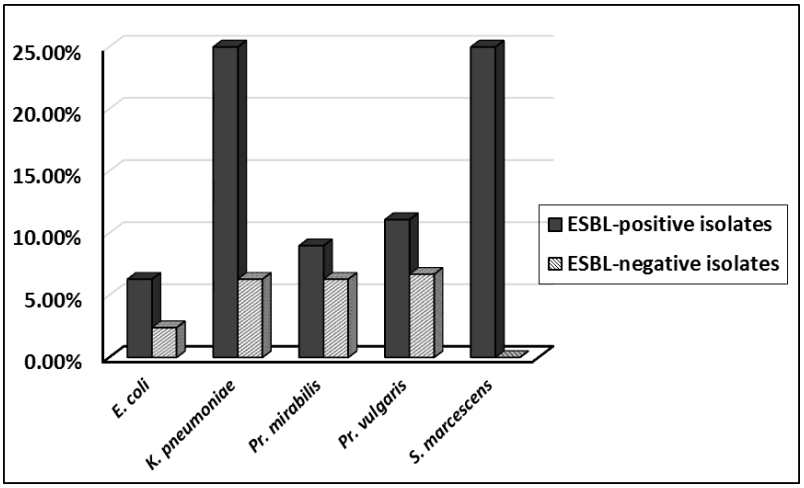

Fig. 1: Resistance patterns of fosfomycin among extended spectrum β-lactamase (ESBL)-positive as compared to ESBL-negative urinary isolates.
Abbreviations: ESBL; extended spectrum β-lactamase, *E. coli*; *Escherichia coli*, *K. pneumoniae*; *Klebsiella pneumoniae*, *Pr. mirabilis*; *Proteus mirabilis*, *Pr. vulgaris*; *Proteus vulgaris* and *S. marcescens*; *Serratia marcescens*.

Results of the modified Hodge test (MHT)

Among the investigated isolates, 20.5% were found to be carbapenem-resistant. The MHT results for imipenem and/meropenem-resistant strains extrapolated that 37.1% of these isolates (13/35) had the carbapenemase phenotype, including 5 *Klebsiella pneumoniae* (38.5%), 3 *E. coli* (23.1%), 2 *Proteus mirabilis* (15.4%), 2 *Proteus vulgaris* (15.4%) and 1 *Serratia marcescens* (7.6%) isolates. About 38.5% (5/13) of the carbapenemase-producing isolates were resistant to fosfomycin compared to 5.1% (8/158) of the carbapenemase-non producers (p = 0.002). Results are illustrated in fig. 2.

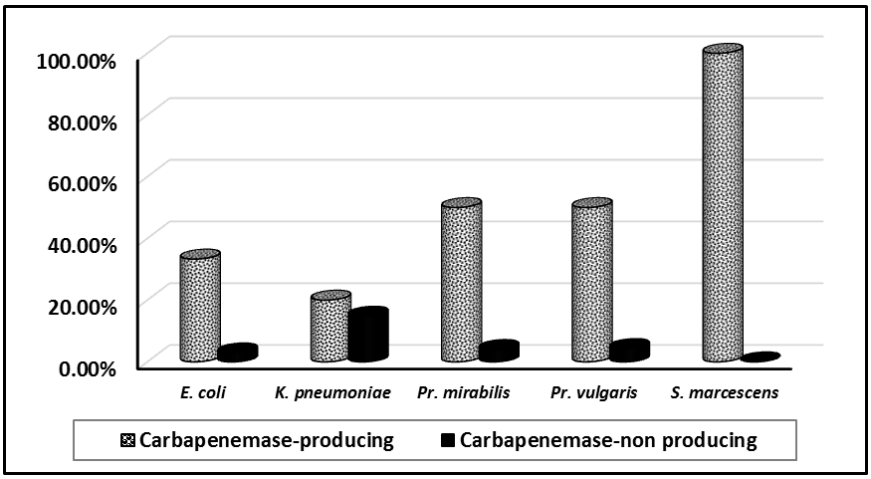

Fig. 2: Resistance patterns of fosfomycin amongst carbapenemase-producing urinary isolates *versus* carbapenemase-non producers.
Abbreviations: *E. coli*; *Escherichia coli*, *K. pneumoniae*; *Klebsiella pneumoniae*, *Pr. mirabilis*; *Proteus mirabilis*, *Pr. vulgaris*; *Proteus vulgaris* and *S. marcescens*; *Serratia marcescens*.

DISCUSSION

The rapid emergence and spread of a plethora of antibiotic-resistant uropathogens, associated with the limited antibiotic arsenal has provoked revisiting of old antibiotic classes. Suchlike drug that has recently attracted attention of therapists is fosfomycin. Therefore, this study was accomplished to evaluate the current status of fosfomycin activity against Gram negative urinary isolates recovered from OCMU, Egypt, and to compare its efficacy with other antibiotics commonly used for the treatment of UTIs.

Based on the *in vitro* antibiotic susceptibility profiles, 92.4% of the investigated Gram negative bacterial isolates were fosfomycin-sensitive, with *E. coli* demonstrating up to 95.9% susceptibility rate, whereas 84.4% of *Klebsiella pneumoniae* isolates were fosfomycin-susceptible ($p = 0.01$). Moreover, *Klebsiella pneumoniae* isolates showed relatively higher fosfomycin MICs than *E. coli* strains ($p = 0.02$), which is congruent with the data presented in a former publication from Germany.[15]

As early as 1997, Dastidar and his collaborators verified the activity of fosfomycin against a group of urinary isolates. Subsequently, they concluded that fosfomycin possess a powerful activity towards *E. coli* and *Klebsiella* species, which agrees with the results of the extant work.[16] Likewise, Demir and his associate stated that 92.5% of their urinary isolates were susceptible to fosfomycin, with *E. coli* displayed higher susceptibility rate for fosfomycin compared to other strains ($p < 0.05$).[17] The comparatively noted low resistance rates to fosfomycin among *E. coli* strains in the existing work as well as in other studies could be attributed to restricted use of fosfomycin for the management of uncomplicated UTIs. Of interest, the susceptibility patterns of fosfomycin among other members of the family *Enterobacteriaceae* have not been extensively delineated, worldwide. In this study, fosfomycin also retained a satisfactory activity against these genera, with 93.3% of *Serratia marcescens*, 92.6% of *Proteus mirabilis* and 91.7% of *Proteus vulgaris* isolates exhibited susceptibility to fosfomycin. In concordance with these findings, Maraki and colleagues explored that fosfomycin sensitivity was observed among 96.7% of their *Proteus mirabilis* isolates.[18]

Trimethoprim-sulfamethoxazole is the drug of choice for treatment of UTIs in situations where the resistance rate is less than 10-20%.[19] Strikingly, 45.6% of the isolates tested in this study were resistant to trimethoprim-sulfamethoxazole. This considerably high rate of resistance could be traced to the erratic use of this antibiotic in the treatment of community-acquired UTIs in developing countries, including Egypt. Concomitant with this result, Alemu and co-workers affirmed that 48.1 % of their urinary isolates from Northwest Ethiopia were resistant to such a drug.[20] On the contrary, the overall rate of trimethoprim-sulfamethoxazole resistance was 13% from another study conducted in the United States.[21] Such a discrepancy in results could be assigned to the regional differences in antibiotic usage policies as well as infection control guidelines.

Although ciprofloxacin was commonly used as first-line antibiotic therapy for UTIs in the last few years,[22] the present data indicated that 27.3% of the urinary isolates were ciprofloxacin-resistant. This high rate of resistance points out to the misguided use of this antibiotic in Egypt, thereby, it is mandatory that ciprofloxacin should be prescribed with caution for the management of UTIs. In accord with this outcome, 29%

resistance to ciprofloxacin was detected among Gram negative urinary isolates from the Czech Republic.[23]

Remarkably, higher rates of resistance to fosfomycin were noticed in this study among ESBL-positive strains compared to ESBL-negative isolates [12.5% *versus* 4%; $p = 0.01$], though fosfomycin susceptibility for isolates with an ESBL-phenotype was significantly higher than that of any other tested antibiotics ($p \leq 0.05$). Linsenmeyer and associates highlighted an overall resistance rate of 19.9% to fosfomycin among their ESBL-producing uropathogens, which is in a range similar to the result of this research.[24]

In the contemporary study, up to 20.5% carbapenem-resistant uropathogens were detected which is markedly higher than that announced from a retrospective cohort study done in the United States.[25] The present finding is upsetting as carbapenems are usually spared as the last resort against infections caused by multi-drug resistant organisms.[26] In addition, 37.1% of the carbapenem-resistant uropathogens (13/35) harbored the carbapenemase phenotype, of which 38.5% were fosfomycin-resistant. This result is supported by that of Livermore and his group, whereby fosfomycin resistance was discovered in 33.3% of the carbapenemase-producing *Enterobacteriaceae*.[27] However, the current finding is relatively higher than that extrapolated by Pogue and colleagues where fosfomycin resistance was recognized among 22% of their carbapenemase-producing urinary isolates.[28] Despite approximately one third of the carbapenemase-producing urinary isolates in this study were fosfomycin-resistant, a proportion of patients contracting these infections can still get benefit from fosfomycin therapy because of the restricted treatment options for such worrisome infections.

Study Limitations

A limitation of this study is that it is an *in vitro* study, thereby patients from which the isolates were retrieved did not essentially receive fosfomycin therapy, accordingly clinical correlations could not be established. Besides, the underlying mechanisms of fosfomycin resistance were not elucidated and were apart from the purpose of this research. Finally, all of the investigated isolates were obtained from a single medical center, so future studies need to be organized elsewhere to provide a more inclusive insight.

CONCLUSION

In short, the present study asserted that fosfomycin has a worthy *in vitro* activity against Gram negative urinary isolates, including ESBL-producing, as well as carbapenemase-producing uropathogens. Thus, fosfomycin is a potential candidate for the management of UTIs caused by antibiotic-resistant superbugs, and being administered orally, it could be used to reserve parenteral antibiotics, such as carbapenems. Yet, extension of the currently available antibiotic armamentarium by newer agents, together with strict adherence to infection control strategies is mandatory to overwhelm the rapid evolution of bacterial resistance.

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Conflict of interest

The author declares no conflicts of interest.

Ethical approval

The protocol of this study was reviewed and approved by the local institutional review board.

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