ORIGINAL ARTICLE

Annals of Agricultural and Environmental Medicine
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Fosfomycin susceptibility of uropathogens resistant to antibiotics used in peri-operative prophylaxis of urinary tract infection among patients after urogynaecological surgery

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Wawrysiuk SP, Bogusiewicz M, Pachciński O, Grywalska E, Miotła P. Fosfomycin susceptibility of uropathogens resistant to antibiotics used in peri-operative prophylaxis of urinary tract infection among patients after urogynaecological surgery. Ann Agric Environ Med. doi:10.26444/aaem/211322.

Abstract

Introduction and Objective. Antibiotic prophylaxis is one of the methods for preventing urinary tract infection (UTI) after urogynecological surgeries. Fosfomycin trometamol (FT) has emerged as a promising option in cases involving multidrug-resistant (MDR) pathogens in which previous antibiotics have failed. The aim of the study is to analyze the susceptibility to FT of common uropathogens, resistant to other antibiotics in patients with post-operative UTI.
Materials and Method. A retrospective study of susceptibility and resistance to commonly used antibiotics was performed by examining the results of urine analysis (n=173) of women with UTI after urogynaecological surgeries. The agar dilution method with glucose-6-phosphate for MIC determination were used for resistance and susceptibility testing in positive urine cultures (≥105 colony forming units (CFUs)/mL). Resistance to commonly used antibiotics was analyzed in comparison to resistance to FT.
Results. In 173 results of urine analysis, 95.95% of the total isolates were found to be susceptible to FT. Among isolates resistant to amoxicillin/clavulanic acid, ampicillin, cephalexin, trimethoprim/sulfamethoxazole, ciprofloxacin, nitrofurantoin; respectively, 80.00%, 94.44%, 77.78%, 96.30%, 90.91%, and 84.38% were susceptible to FT.
Conclusions. Peri-operative prophylaxis of UTI with FT is a promising alternative to classic antibiotics due to the high susceptibility of uropathogens, including MDR isolates. The decision about the prophylaxis method should be made based on the epidemiological updated recommendations. The study shows the need for ongoing observation of antibiotic resistance patterns in order to guide prophylaxis recommendations, especially in the era of MDR pathogens.

Key words

urinary tract infection, antibiotic resistance, fosfomycin trometamol, post-operative prophylaxis, multidrug-resistant pathogens

INTRODUCTION

Globally, antimicrobial-resistance (AMR) has been recognized as one of the top public health challenges, with the WHO prioritizing actions to mitigate its impact [1]. Urinary tract infections, especially in surgical contexts, contribute significantly to the burden of AMR due to the widespread use of prophylactic antibiotics. Addressing multidrug-resistant (MDR) pathogens in such cases is crucial for safeguarding the efficacy of existing antimicrobials and reducing healthcare-associated costs.

One of the most frequent causes of gynaecological visits among women, regardless of age, is urinary tract infection (UTI) [2]. This pathology can emerge as a sporadic or recurrent infection, and is a common complication of surgical interventions in urogynaecology [3]. The mid-urethral sling procedure (MUS) in stress urinary incontinence (SUI) and reconstructive surgery for pelvic organ prolapse (POP) are some of the most commonly performed surgeries in gynaecology with a lifetime risk of surgery being 13.6% and 19%, respectively [4]. The incidence of UTI after MUS is estimated to be 7–32% [5], while the risk of UTI in the case of reconstructive surgery for POP reaches 10–64% [6].

The most frequently isolated uropathogens include *Uropathogenic Escherichia coli* (UPEC) (47.8%), *Enterococcus faecalis* (10.4%) and *Klebsiella penumoniae* (9%) [7]. Due to the extensive use of antibiotics for prophylaxis and treatment of UTI, resistance has increased significantly. In consequence, other uropathogens have been isolated: extended-spectrum beta-lactamase (ESBL) *Escherichia coli*, ESBL *Klebsiella penumoniae* and vancomycin-resistant (VRE) *Enterococcus faecium* [7]. The increase in the rate of UTI triggered by multidrug-resistant pathogens (MDR), renders prophylaxis and treatment with the traditional antibiotics increasingly futile [8].

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Received: 13.03.2025; Revised: 08.09.2025; Accepted: 24.09.2025; Online first:13.10.2025

Fosfomycin trometamol is a phosphoric acid derivative which has emerged as a promising option in cases involving MDR pathogens in which previous antibiotics have failed. A good activity of FT against MDR bacteria has been observed in comparison with other first-line antibiotics, such as ampicillin, cefuroxime, ciprofloxacin, co-trimoxazole, and nitrofurantoin [9]. The main mechanism of resistance includes mutations in MurA and alterations in GlpT and UhpT transport systems, which initiates peptidoglycan (PG) biosynthesis of the bacterial cell wall [10]. MurA mutation is one of the resistance mechanisms to FT displayed by only several bacteria [10].

The aim of the study is to analyze the susceptibility to FT of common uropathogens resistant to other antibiotics (amoxicillin/clavulanic acid, ampicillin, cephalexin, trimethoprim/sulfamethoxazole, ciprofloxacin, nitrofurantoin) in patients with post-operative UTI.

MATERIALS AND METHOD

The study protocol was approved by the local institutional Ethical Committee. A retrospective analysis included 2,430 patients undergoing MUS and pelvic organ prolapse reconstruction in the Second Gynaecology Department of Independent Public Clinical Hospital No. 4 in Lublin, Poland, hospitalized between January 2017-January 2020 – this period was selected for consistency in hospital data collection protocols. The only pelvic organ prolapse surgeries included were vaginal plastic surgery and the Manchester procedure (both from the vaginal access). Prior to the surgery, each patient received 2gm of cefazolin or 0.5gm of metronidazole (for patients reporting allergies to cefazolin) as the standard method of surgical infection prevention.

The main exclusion criteria were symptoms of a recurrent UTI, patients with a proven UTI within the four weeks before enrolment, any antibiotic intake within the period between surgery and the ambulatory visit in the Clinic, and immunosuppression. The final inclusion into the statistical analysis of the study was a positive urine analysis result within 30 days after the surgery on a follow-up visit, or the presence of UTI symptoms at any point during that period, both with the following positive urine culture. The study of susceptibility and resistance to commonly used antibiotics was performed by examining the results of the urine culture of women with UTI after MUS and pelvic organ prolapse reconstruction.

Positive cultures performed as a part of ambulatory visits in the case of post-operative UTI symptoms were found in 172 patients. Urine cultures with ≥ 105 colony forming units (CFUs)/mL were considered positive. Resistance and susceptibility testing was performed with a agar dilution method with glucose-6-phosphate for MIC determination. Only the results from disc-diffusion tests were used for resistance and susceptibility testing in positive urine cultures. Resistance to amoxicillin/clavulanic acid, ampicillin, cephalexin, trimethoprim/sulfamethoxazole, ciprofloxacin and nitrofurantoin was analyzed in comparison to resistance to fosfomycin trometamol. Application of appropriate discs, including ampicillin (10 µg), trimethoprim/sulfamethoxazole (11.25 µg/23.75 µg), ciprofloxacin (5 µg), amoxicillin/clavulanic acid (20 µg/10 µg), nitrofurantoin (100 µg), cephalexin (30 µg), and cefuroxime (30 µg) was performed. Specific polymerase chain reaction (PCR) and sequencing was used to identify extended-spectrum β-lactamase (ESBL) isolates [11]. The obtained isolates were identified using standard methods, via a commercial bacterial identification system (Vitek 2 Compact, BioMérieux, France). All analyses were performed at the same laboratory. Statistical analysis was performed with Statistica 12.0 (Tulsa, OK, USA), using the $\chi 2$ test. A $p < 0.05$ was considered statistically significant.

RESULTS

The most frequently isolated pathogens were Escherichia coli and Enterococcus faecalis (Tab. 1). Only 4.0% of pathogens were resistant to FT, whereas resistance to other agents varied between 15.7% – 32.5% (Table 2). Resistance to FT was found in three (4.5%) of Escherichia coli strains, two (40%) of Proteus mirabilis strains, as well as in one (100%) Enterobacter aerogene and one (100%) Enterococcus faecium strain.

Table 1. List of bacteria isolated from urine samples

Bacteria	No. of positive cultures
Escherichia coli	84
Enterococcus faecalis	66
Escherichia coli ESBL	5
Proteus mirabilis	5
Cirrobacter freundii	4
Enteroccocus spp.	4
Klebsiella pneumoniae	2
Enterobacter aerogenes	1
Enterococcus faecium	1

Table 2. Total resistance rates to all antimicrobial agents.

Antimicrobial agent	Resistance rates		
	n	Percentage	95% CI
Fosfomycin trometamol	7	4.0	1.6; 8.2
Amoxicillin/clavulanic acid	25	30.1	25.5; 41.2
Ampicillin	18	15.7	9.6; 23.8
Cefuroxime	18	21.7	13.4; 32.0
Cephalexin	18	23.4	14.5; 34.4
Ciprofloxacin	22	26.5	17.4; 37.4
Nitrofurantoin	32	19.2	13.5; 26.0
Trimethoprim/sulfamethoxazole	27	32.5	22.7; 43.7

In 172 results of urine analysis (172/2430; 7.1%), 96% of the total isolates were found to be susceptible to FT. Among isolates resistant to amoxicillin/clavulanic acid, ampicillin, cefuroxime, cephalexin, ciprofloxacin, nitrofurantoin and trimethoprim/sulfamethoxazole, respectively, 80.0%, 94.4%, 88.9%, 77.8%, 90.9%, 84.4% and 96.3% were susceptible to FT (Tab. 3). However, no significant difference was found in total resistance to all uropathogens in terms of FT versus trimethoprim/sulfamethoxazole and ciprofloxacin (Tab. 3).

Table 3. Total antimicrobial resistance of all uropathogens isolated from urine samples

Group of antimicrobial agents		Fosfomycin trometamol (%)		No. of urine samples	Stastical significance
		R	S		
Amoxicillin/ clavulanic acid	R	20.0	1.7	83	$\chi 2 = 8.87$ $p = 0.003$
	S	80.0	98.3		
Ampicillin	R	5.6	0	114	$\chi 2 = 5.38$ $p = 0.020$
	S	94.4	100.0		
Cephalexin	R	22.2	1.7	77	$\chi 2 = 9.57$ $p = 0.002$
	S	77.8	98.3		
Trimethoprim/ sulfamethoxazole	R	3.7	8.9	83	$\chi 2 = 0.74$ $p = 0.389$
	S	96.3	91.1		
Ciprofloxacin	R	9.1	6.6	83	$\chi 2 = 0.15$ $p = 0.694$
	S	90.9	93.4		
Cefuroxime	R	11.1	6.2	83	$\chi 2 = 19.81$ $p < 0.001$
	S	88.9	93.9		
Nitrofurantoin	R	15.6	0.7	167	$\chi 2 = 16.55$ $p < 0.001$
	S	84.4	99.3		

R = resistant; S = sensitive.

DISCUSSION

The study highlights the need for integrating fosfomycin into broader public health strategies, especially in hospital settings where MDR infections are prevalent. Policy changes, such as incorporating FT into standardized prophylaxis guidelines, could reduce the reliance on antibiotics with higher resistance rates. Additionally, enhanced surveillance systems to monitor resistance patterns could further support effective antimicrobial stewardship programmes.

Urinary tract infections are a frequent post-operative complication of both SUI (7–24%) and POP (6.4–31%) surgeries [12, 8]. There are several factors responsible for increased risk of UTI after such procedures, with UTI accounting for about 40% of nosocomial infections. Even up to 80% are caused by catheterization of the patients (CAUTI) [13]. Also, elevated post-void residual volume in the bladder, together with catheterization, increases the risk of UTI [5]. Placement of a Foley catheter during surgery contributes to the mechanical imposition of uropathogenes in the ureter and bladder, and additionally weakens the epithelial defence through microtrauma. The bacterial flora in the region of urethra can be also influenced by the infected vaginal mucosa at the ste of the *midurethral* incision.

Depending on the clinical situation, the antibiotics are used either in peri-operative prophylaxis of UTI or in the treatment of diagnosed UTI. The most common class of antibiotic administered to patients in the prophylaxis of UTI, are first generation cephalosporins (20.6% of all antibiotics applied in UTI), then nitrofuran derivatives, sulfonamides and trimethoprim, followed by other antibacterials (17.8%). The first-line drugs recommended in uncomplicated UTI are nitrofurantoin and trimethoprim-sulfamethoxazole. In complicated UTI (with CAUTI or pyelonephritis during its course), fluoroquinolones are typically prescribed. It is important to mention, that fluoroquinolones are not recomended in uncomplicated UTI because of an increasing rate of infections caused by fluoroquinolone resistant pathogens [14]. Additionally, the US Food and Drug Administration determined numerous side-effects, concurrent with damage to connective tissue, e.g. rupture of an aneurysm of the abdominal aorta, and damage to tendons, joints and muscles. Fluoroquinolones may also negatively affect the central nervous system [15].

According to the National Institute for Health and Care Excellence (NICE), antibiotic prophylaxis is recommended in clean-contaminated surgery [16], whereas prophylaxis of UTI seems to be reasonable in any urogynaecological surgeries. However, the efficacy of prophylaxis is unclear; some studies showed significant reduction in the incidence of post-operative UTI after mid-urethral slings [17], while other studies do not advocate the use of prophylaxis [18]. The study conducted by Wawrysiuk et al. shows equal efficacy of FT and a phytotherapeutic drug used after sling or vaginal plastic surgery in the prophylaxis of UTI [19]. Due to the different approaches to UTI diagnosis used in these studies, it is impossible to draw a definitive conclusion. Moreover, considering the fact that different antibiotics were used in each study, different rates of resistance to each antibiotic could have influenced the effectiveness of the prophylaxis. Perhaps the use of FT which presents low resistance rates (4% in the current study) would improve post-operative prophylaxis of UTI. FT is recommended as the first line treatment in UTI by the European Association of Urology and American Infectious Diseases Society [20, 21], therefore FT is a promising candidate for both the treatment and prophylaxis of UTI.

The study was a retrospective, single-centre analysis from a tertiary hospital, and reflects local practice and resistance patterns; generalisability to other settings may therefore be limited. Only women who became symptomatic post-operatively and had a positive urine culture were analysed (172/2430; 7.1%), which may introduce some selection/ spectrum bias. The susceptibility panel followed routine laboratory practice in which cefazolin testing for urinary isolates was not performed, and metronidazole was not applied for typical aerobic uropathogens; therefore a direct comparison with the exact surgical prophylaxis regimen was not available. The study describes the *in vitro* activity of fosfomycin trometamol rather than its clinical prophylactic effectiveness. In this respect, it would be valuable to address this by conducting prospective comparative studies. Finally, the study period (2017–2020) precedes potential temporal shifts in resistance, underscoring the need for ongoing local surveillance.

Urogynaecolgical surgery complicated with UTI is a factor for treatment failure due to improper tissue healing, the development of urinary urge, and recurrence of SUI that may require reoperation, mesh revision, or even mesh removal [22]. In the study conducted by Svenningsen et al. where antibiotic prophylaxis was used in 9,131 versus no prophylaxis in 19,556 patients, surgical site infection occurred significantly more frequently in the women not given antibiotic prophylaxis. However, no significant difference was found in terms of *de novo* or persistent urgency urinary incontinence or treatment satisfaction [18]. Routine antibiotic prophylaxis also increases the risk of uropathogen resistance, as well as possible adverse events connected to the change in the urinary and vaginal microbiome [23].

Considering the above, there is a need to determine the effectiveness of an alternative antimicrobial that could be used in infections with MDR pathogens. FT – a phosphonic acid derivative – has a unique mechanism of action which affects the process of bacterial cell wall synthesis in both Gram-negative and Gram-positive [24]. FT enters the microbial cell by the l-α-glycerophosphate transport system (GlpT) or the hexose–phosphate uptake system (UhpT), and subsequently blocks the cascade of peptidoglycan formation, even MDR bacteria like ESBL *Escherichia coli* or *Klebsiella pneumoniae* [25]. In the study of urinary samples of patients with uncomplicated UTI, and despite the constant use of FT, no increase in resistance has been observed in Europe during the last eight years [26].

CONCLUSIONS

To address the global threat of MDR infections, it is imperative to implement evidence-based guidelines that incorporate fosfomycin as a key prophylactic agent. The findings from the current study can assist with hospital infection control protocols, reduce healthcare costs associated with MDR UTIs, and support international efforts to curb AMR.

Peri-operative prophylaxis of UTI with FT is a promising alternative to classic antibiotics due to the high susceptibility of uropathogens, including MDR isolates. Given the high *in vitro* susceptibility observed, fosfomycin trometamol may be considered in antimicrobial stewardship discussions where resistance to standard agents is prevalent; definitive recommendations for peri-operative prophylaxis require prospective comparative trials. The decision on use of the prophylaxis method should be based on the epidemiological updated recommendations. The study shows the need for ongoing observation of antibiotic resistance patterns in order to guide prophylaxis recommendations, especially in the era of MDR pathogens. Antimicrobial resistance is a vast threat to global health, which necessitates a re-evaluation of aspects of antibiotic administration, especially in terms of antibiotic prophylaxis.

Funding information
This research was funded by the Medical University of Lublin from the statutory funds DS321.

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