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Antimicrobial Susceptibility Profile of Fosfomycin and Nitrofurantoin despite Dissemination of Fluoroquinolones and Trimethoprim/ Sulfamethoxazole Resistant Urinary Tract Isolates

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

The widespread growth of multidrug-resistant (MDR), extended drug resistant (XDR) uropathogens and the shortage of new antimicrobials are the most significant obstacles challenging the treatment of urinary tract infections. The study is aimed to identify the antimicrobial susceptibility profile against MDR and XDR uropathogens. A total of 2485 urine samples were processed from 2267 patients, 361 uropathogens were grown. The antimicrobial susceptibility was determined by the Kirby-Bauer disk diffusion method, following the Clinical and Laboratory Standards Institute's guidelines. Eighty-nine percent of the samples had Multidrug-resistant microorganisms, while 32% had XDR uropathogens. In comparison to fluoroquinolones and trimethoprim/sulfamethoxazole, fosfomycin and nitrofurantoin demonstrated a significantly higher sensitivity rate against uropathogens, including MDR and XDR uropathogens, in both gender groups with community-acquired and nosocomial UTIs (P<0.001). Fosfomycin revealed the highest sensitivity rate, about 94.8%. Klebsiella pneumonia and *E. coli* showed the highest resistance rate against fosfomycin in 3.7% and 3.4% of the cases. Nitrofurantoin showed a similar sensitivity rate both in community and hospitalized patients in 86.1%. Fluoroquinolones (61%) and trimethoprim/sulfamethoxazole

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(86.6%) revealed the highest resistance rate against uropathogens. The prevalence of extended-spectrum beta-lactamases producing pathogens was 10.2%. Fosfomycin and nitrofurantoin revealed a higher sensitivity rate against gram-negative MDR uropathogens in community and nosocomial UTIs compared to fluoroquinolones and trimethoprim/sulfamethoxazole.

Keywords: Urinary tract infection; fosfomycin; nitrofurantoin; multidrug-resistant microorganisms; extensive drug-resistant microorganisms.

ABBREVIATIONS

CDC : Centers for Disease Control and Prevention
CLSI : Clinical and Laboratory Standards Institute's
EMB : Eosin Methylene Blue Agar
ESBL : Extended-Spectrum Beta-Lactamases
FQ : Fluoroquinolone
MDR : Multidrug-Resistant
UTI : Urinary Tract İnfection
XDR : Extensive Drug-resistant

1. INTRODUCTION

Urinary tract infections (UTIs) are one of the common infections in both community and nosocomial infections [1,2]. Globally, over 150 million UTI cases occur each year, costing the global economy over $6 billion US dollars [3]. The possibility of colonization and progression to symptomatic UTIs is responsible for host factors, including anatomical or functional abnormalities and genetic predisposition, and microbial factors such as virulence, adhesins, iron scavenger receptors, secreted toxins, capsule, flagella, outer membrane proteins and lipopolysaccharide (LPS) [4]. The widespread growth of multidrug-resistant (MDR) and extensively drug-resistant (XDR) uropathogens and the shortage of new antimicrobials against such pathogens are the most significant obstacles challenging the treatment of bacterial infections [5]. Despite the spread of antimicrobial resistance and the lack of new antimicrobials, physicians reverted to older antimicrobials such as fosfomycin and nitrofurantoin, which gained favor due to their activity against gram-positive and gram-negative uropathogens [6]. Extended-spectrum beta-Lactamase (ESBL)-producing uropathogens is increasing in community and hospitalized patients [7]. Escherichia coli is the most frequently isolated uropathogen in uncomplicated and complicated urinary tract infections. It is resistant to most oral antibiotics, including fluoroquinolones, trimethoprim-sulfamethoxazole, and beta-lactam antibiotics [8]. Other common uropathogens include Klebsiella spp, Staphylococcus, Pseudomonas Aeruginosa, Proteus mirabilis, and Candida spp [9].

Antimicrobial resistance is a global problem considerably in developing countries [10,11]. Fluoroquinolone (FQ) is a widely used antimicrobial drug in UTI patients, although various up-to-date articles had identified an alarming increasing resistance toward FQs [12]. Fosfomycin is an antibiotic with a broad spectrum of activity against Gram-positive pathogens such as Staphylococcus aureus and Enterococcus and Gram-negative bacteria such as Pseudomonas aeruginosa and Klebsiella pneumonia. Fosfomycin has adequate distribution into tissues, and it is a well-tolerated drug with a low incidence of adverse events [13]. Nitrofurantoin is another helpful drug with potent bactericidal properties against various multidrug-resistant gram-positive and gram-negative uropathogens. It is used to prevent and treat urinary tract infections [14]. As a result of frequent use of fosfomycin and NF, an increased antimicrobial resistance rate was reported recently. To the best our konwledge, this is the first study reported from Somalia. The main objective of the study is to identify the antimicrobial susceptibility profile of Fosfomycin and NF against MDR and XDR uropathogens.

2. MATERIALS AND METHODS

This retrospective study has reviewed a total of 2485 urine cultures performed in the microbiology unit of Mogadishu Somali Turkish Training and Research Hospital between 2020-2021. The urine samples were obtained from suspected patients in clean-catch midstream urine specimens and collected, transported, and stored safely in the laboratory unit. Bacterial identification was made by the phenotypic study of the culture, looking for typical characteristics and gram staining, and a series of standard biochemical analyses to recognize the bacteria of interest was also done [15, 16]. The antimicrobial susceptibility had been determined by the Kirby-Bauer disk diffusion method following the Clinical and Laboratory Standards Institute's (CLSI)

guidelines. Eosin methylene blue agar had used for the identification of uropathogens. Antimicrobial sensitivity and resistance were assessed by Mueller-Hinton agar. The antimicrobials studied against uropathogens were nitrofurantoin (300 mcg), and fosfomycin (200 mcg), ciprofloxacin (5mcg), levofloxacin (5mcg), and Trimethoprim/Sulfamethoxazole (1.25/23.75 mcg). For confirming the findings of AmpC production, E-test strips were used. Uropathogens that were resistant to two or more antibiotic classes were considered multidrug-resistant microorganisms (MDR). The extended-spectrum beta-lactamase production screening test had done according to CLSI recommendations. Analyzed parameters included age, gender, uropathogens obtained from the culture, antibiotic sensitivity, and resistance spectrum. Data were collected from medical records, and no potential harm to the patients.

The findings were analyzed in descriptive univariate cross-tabulations using SPSS software for Windows (version 23 SPSS).

3. RESULTS

A total of 2485 urine samples were processed for culture and 361 uropathogens were grown. The mean age of the patients was 50 $\pm$ 8.4years. Females constitute 51% of the cases, while males were 49%,. *Escherichia coli* was the most common uropathogen (63.4%), followed by *Klebsiella pneumonia* in 13.3% of the samples. Table 1 shows the distribution of uropathogens identified from urine culture. Eighty-nine percent of the patients had Multidrug-resistant microorganisms. *A*cinetobacter baumannii has the most MDR and XDR patterns in 69.1% of cases, while Escherichia coli and K. pneumonia showed a similar MDR spectrum in 35.2% of the cases.

Fosfomycin exhibited the highest sensitivity rate against MDR and XDR uropathogens in 94.8% in community-acquired and nosocomial UTIs. In our study, patients classified into two groups; inpatients accounted for 44.3% of the cases, and outpatients were 65.7% of the patients. Ninety-six percent of fosfomycin was sensitive against nosocomial uropathogens. A slight evolving resistance against fosfomycin was seen in community-acquired UTI about 5.7% despite their higher sensitivity rate (Fig. 1).

Klebsiella pneumonia and *E. coli* revealed the highest resistance rate against fosfomycin in 3.7% and 3.4% of the cases sequentially. Pseudomonas Aeruginosa and Acinetobacter Baumannii were the most multidrug-resistant and extensively drug resistant uropathogens, but fortunately, they produced a zero resistance rate against fosfomycin (Table 2). One-quarter of extended-spectrum beta-lactamases producing pathogens had shown resistance toward fosfomycin.

Nitrofurantoin showed a higher sensitivity rate against extended-spectrum beta-lactamases producing uropathogens. Nitrofurantoin had an 86.1% sensitivity rate against uropathogens, and the drug showed a nearly similar sensitivity rate in patients with the community and hospital-acquired UTIs. As cited above, Klebsiella pneumonia produced the most resistance rate against nitrofurantoin in 27.6% that was three times more than *E. coli* that developed a resistance rate against nitrofurantoin in 9.4% of the cases. More than two-thirds of resistance against nitrofurantoin is produced by ESBL pathogens.

Fluoroquinolones with relation to fosfomycin and nitrofurantoin showed a lesser sensitivity rate toward uropathogens in both gender groups, uncomplicated and complicated UTIs (Fig. 2). Ciprofloxacin had a 67.7% resistance rate in total cases. Acitinobacter Buaminni (100%), *E. coli* (68%), Klebsiella Pneumonia (60.6%), and Pseudomonas Aeruginosa in 60% resistance pattern against Ciprofloxacin had gained through the study. Levofloxacin showed a resistance level near that of Ciprofloxacin but slight inferiority regarding the total resistance rate of about 54.2%of the cases. Moreover, levofloxacin was better in community and hospital-acquired UTIs and cases of ESBL producing pathogens. Trimethoprim/sulfamethoxazole showed the highest resistance rate against uropathogens in 86.6% of the cases. Fosfomycin and nitrofurantoin with relation to fluoroquinolones and trimethoprim/sulfamethoxazole showed a higher sensitivity rate against uropathogens, including multidrug-resistant and extensively drug-resistant uropathogens in both gender groups with community-acquired and nosocomial UTIs ($P<0.001$).

Out of 361 urine cultures that showed growth, 37 cases produced extended-spectrum beta-lactamases producing pathogens that make a prevalence of 10.2%. *E. coli* was the leading ESBL uropathogens in about 70.3%, followed by Klebsiella pneumonia in 27% and Enterobacter

cloacae in 2.7%. Patients with hospital-acquired urinary tract infections were more susceptible to develop multidrug-resistant and ESBL producing uropathogens.

4. DISCUSSION

The main challenges confronting the treatment of urinary tract infections are disseminating multidrug-resistant gram-negative uropathogens and the lack of new antimicrobials against such pathogens (5). The main objective of the study is to identify the antimicrobial susceptibility profile against MDR and XDR uropathogens.

The prevalence of MDR uropathogens in our study was 89% of the cases that is three times higher than previously reported studies [17]. Overprescription and improper use of antibiotics are the leading factors that contribute to the widespread antimicrobial resistance. In our study, the urine cultures that showed bacterial growth were 361 (14.5%) cases out of 2485 patients who enrolled in our study that corresponds to other previous studies [18]. According to the gender distribution of pathogens, females were more vulnerable to UTI (57.2%) compared to males (42.8%), which matches in the previously reported studies [18].

Table 1. Distribution of uropathogens that shown growth

Pathogen	No. of patients	Percentage %
E. coli	229	63.4%
ESBL	26	
Klebsiella Pneumonia	48	13.3%
ESBL	10	
Pseudomonas Aeruginosa	14	3.9%
Staph Aureus	13	3.6%
Acinetobacter Baumannii	7	1.9%
Enterobacter cloacae	5	1.4%
ESBL	1	
Enterococcus faecium	5	1.3%
Streptococcus species	2	0.6%
Citrobacter freundii	2	0.6%
Staphylococcus haemolyticus	1	0.3%
Cedecea lapagei	1	0.3%
Candida	34	9.4%
Total	361	100.0%

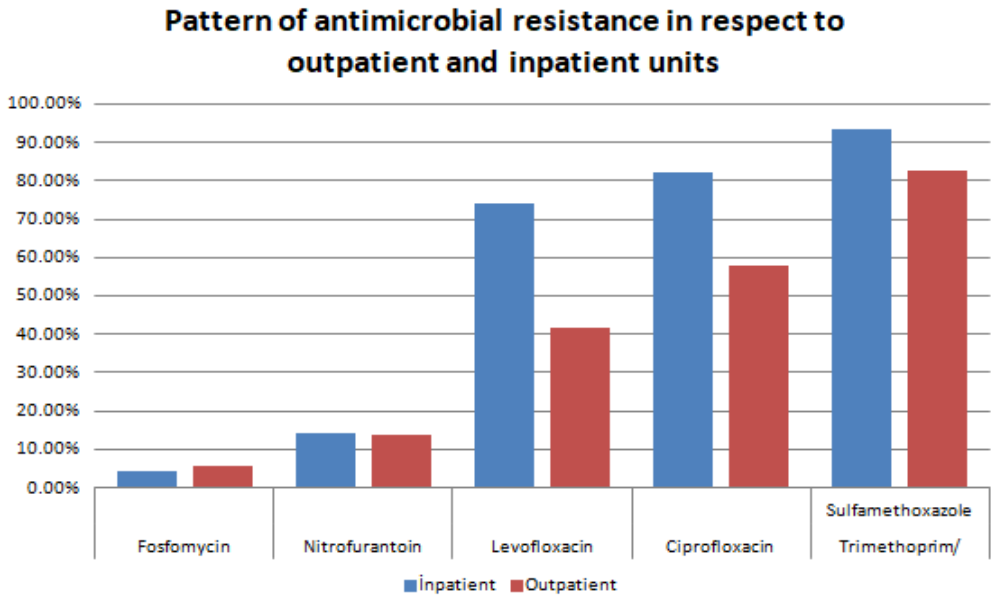

Fig. 1. Pattern of antimicrobial resistance in respect to outpatient and inpatient units

Table 2. Antimicrobial resistance pattern against uropathogen including extended-spectrum beta-lactamase producing uropathogens

Medications	Resistance Rate %	Resistant Level against individual pathogens				ESBL
		E. coli	Klebsiella Pneumonia	Pseudomonas Aeruginosa	Acinetobacter Baumannii	
Ciprofloxacin	67.7%	68%	60.6%	60%	100%	84.2%
Levofloxacin	54.2%	62.5%	25%	50%	100%	72.4%
Fosfomycin	5.2%	3.4%	3.7%	0%	0%	25%
Nitrofurantoin	13.9%	9.4%	27.6%	0%	0%	34.7%
Trimethoprim/Sulfamethoxazole	86.6%	84.2%	84.7%	92.8%	100%	83%

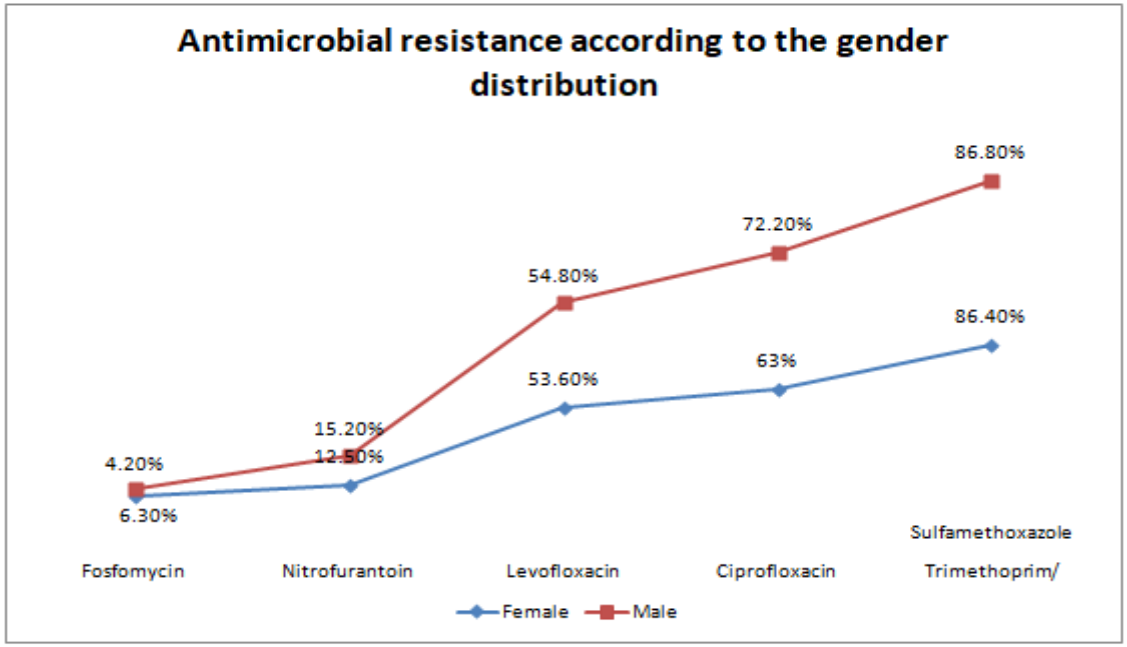

Fig. 2. Antimicrobial resistance according to the gender distribution

Fosfomycin had a potential antimicrobial activity against ESBL producing uropathogens in both inpatient and outpatient settings which corresponds to the previous studies [19,20]. Fosfomycin showed significant efficacy against uropathogens (ESBL, Enterobacter, Enterococcus, gram-positive and gram-negative bacteria MDR, and XDR) and gained a sensitivity rate of 94.8% of the cases but expressed an evolving resistance in community-acquired UTIs about 5.7% [21]. Klebsiella pneumonia and *E. coli* revealed the highest resistance rate against fosfomycin in 3.7% and 3.4% of the cases sequentially that oppose a study reported by Annika I. Nilsson and colleagues [22].

Nitrofurantoin showed a satisfactory sensitivity rate against ESBL uropathogens in all age groups. 34.7% resistance rate toward Nitrofurantoin against ESBL expressed in our study that matches research reported by J. Garau from Canada and the USA [23]. The authors reported a 9.4% nitrofurantoin resistance rate against *E. coli* that opposes Kashanian J and associates study from the USA that reported a 2.3% resistance rate [24].

In the present study, *E. coli* was the leading cause of ESBL producing uropathogens in 70.3% of the total cases, followed by Klebsiella pneumonia in 27%. ESBLs-producing E. coli are the most common cause of increased morbidity in patients with UTI. ESBL-producing organisms are known to show significant resistance implications to antimicrobial drugs such as Fluoroquinolones. Regarding the antibiotic susceptibility pattern, ESBL-producing E. coli showed higher resistance against Ciprofloxacin (68%) and Levofloxacin (62.54%). This higher resistance is in contrast to the other previous studies and could be the overuse of fluoroquinolones in the community and hospital-acquired UTIs before the initial empirical therapy [25,26].

5. CONCLUSION

Fosfomycin and nitrofurantoin revealed a higher sensitivity rate against gram-negative MDR uropathogens in community and nosocomial UTIs compared to fluoroquinolones and trimethoprim/sulfamethoxazole. Pseudomonas Aeruginosa and Acinetobacter Baumannii were the most multidrug-resistant and extensively drug-resistant uropathogens. Fortunately, they exhibited a zero resistance rate toward fosfomycin and nitrofurantoin.

Limitations of the study: 1. This a retrospective study using electronic medical records of the patients, 2. The study only focused on the antimicrobial sensitivity and resistance pattern based on culture results, but further prospective studies are needed to evaluate the efficacy and safety of these drugs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

All patients obtained informed consent.

ETHICAL APPROVAL

This retrospective study received medical ethical committee approval from the institutional review board of Mogadishu Somalia-Turkey Recep Tayyip Erdogan Training and Research Hospital, Mogadishu, Somalia (Ref. MSTH-4127).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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