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Is there a rise in resistance rates to fosfomycin and other commonly used antibiotics in *Escherichia coli*-mediated urinary tract infections? A perspective for 2004 – 2011

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Aim: Resistance patterns of *Escherichia coli* to fosfomycin, ciprofloxacin, amikacin, and cotrimoxazole were evaluated in 2 different studies held in 2004 and 2005. In this study, it was aimed to compare the changes in the susceptibility patterns of uropathogenic *E. coli* strains to the above-mentioned antibiotics after 6 years.

Materials and methods: Between February and April 2011, *E. coli* strains isolated from urine samples were included prospectively in the study.

Results: A total of 502 *E. coli* strains (358 from outpatients and 144 from inpatients) were isolated from urine specimens between February and April 2011. Extended spectrum beta-lactamase (ESBL)-producer *E. coli* rate was 35%. Resistances to cotrimoxazole, ciprofloxacin, amikacin, and fosfomycin were 54.5%, 49.8%, 22.7%, and 1.4%, respectively. When we compared ESBL-producer E. coli strains isolated in 2005 and 2011, amikacin resistance increased (11% to 22.7%, P = 0.0001), whereas cotrimoxazole resistance decreased significantly (74% to 62.9%, P = 0.0063). When we compared resistance patterns of non-ESBL–producer *E. coli* in relation to 2004 and 2011, there was no significant change in the resistance to fosfomycin, cotrimoxazole, ciprofloxacin, and amikacin. Pooled analysis of fosfomycin studies from Turkey revealed 1.6% fosfomycin resistance in a total of 6439 strains.

Conclusion: Our results suggest that despite common usage, there is not an increase in the resistance to fosfomycin. We conclude that fosfomycin can be used as one of the primary choices in the empirical therapy of urinary tract infections.

Key words: Resistance, fosfomycin, urinary tract infection

1. Introduction

Community- and hospital-acquired urinary tract infections (UTIs) are among the most frequently encountered infectious diseases. According to the Turkish Statistical Institute, UTIs were the third most common infection in Turkey (the first being respiratory tract infections and the second gastrointestinal infections) (1). *Escherichia coli* is the most important bacterium that causes this infection. Fosfomycin tromethamine (FT), trimethoprim/sulfamethoxazole (cotrimoxazole), ciprofloxacin, and amino glycosides are the most commonly preferred antibacterial drugs for the treatment of community-acquired UTIs. Increasing antimicrobial resistance is a major problem in bacteria isolated from both community-acquired and nosocomial UTIs**.** Extended spectrum beta-lactamase (ESBL)-producing *E. coli* and *Klebsiella pneumoniae* are major growing problems in almost every country. Therefore, treatment options should be considered due to the changing epidemiology and resistant rates.

The resistant rates of uropathogenic *E. coli* strains to fosfomycin, ciprofloxacin, amikacin, and cotrimoxazole were determined by 2 separate studies in our hospital between 2004 and 2005 (2,3). We have also conducted studies about fosfomycin use in complicated lower UTIs caused by ESBL-producing *E. coli* (4,5). Fosfomycin usage rates have increased, especially in the treatment of lower UTIs, after detected low resistance rates against fosfomycin in these studies. In our center, fosfomycin has been at the forefront of empirical treatment in daily practice.

In this study, we aimed to evaluate the effect of widespread use of fosfomycin in the treatment of UTIs on antibiotic susceptibility patterns in the last 6 years.

2. Materials and methods

In February, March, and April 2011, mid-stream urine samples that were collected in a sterile container were

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inoculated onto 5% sheep blood agar and eosin methylene blue agar by using a quantitative method. The bacteria were defined by conventional and automated methods (API / VITEK 2, BioMérieux, Marcy-l'Étoile, France) in samples in which bacterial growth was detected. Antibiotic susceptibility to amikacin (30 μg), ciprofloxacin (5 μg), trimethoprim-sulfamethoxazole (1.25/23.75 μg), and fosfomycin (200 μg) was determined via disk diffusion tests with antibiotic-containing disks (Oxoid Ltd., Basingstoke, Hampshire, UK) on Mueller-Hinton agar plates. The results were expressed as susceptible or resistant according to criteria recommended by the Clinical and Laboratory Standards Institute (CLSI) (6). ESBL production was detected using the double disk synergy test.

E. coli ATCC 25922 was used as the control strain. Only one isolate from each patient was included in the study; recurrent isolates were excluded. Resistance patterns from 2004–2005 and 2011 were compared by chi-square test.

To find the published series of the last 5 years, 3 Turkish national (ULAKBİM, http://www.turkishmedline.com, and http://medline.pleksus.com.tr) and 2 international (PubMed and Science Citation Index-Expanded) databases were searched. Key words were "fosfomycin", "*Escherichia coli*", "*E. coli*", and "Turkey". In cases of presentations from a single study with intersecting periods, that covering a longer period was chosen. Articles published before 2007 were excluded.

3. Results

A total of 502 *E. coli* isolates were included in the study. Of the 502 *E. coli* isolates, 358 were isolated from outpatients while 144 were isolated from inpatients. The resistance rates were determined to be 1.4% for FT, 49.8% for ciprofloxacin, 22.7% for amikacin, and 54.5% for trimethoprim-sulfamethoxazole. ESBL-producing *E. coli* strains were found in 35% of the isolates.

The resistance rates of ESBL-producing *E. coli* strains in 2005 versus 2011 are summarized in Table 1. The resistance rates of non-ESBL–producing *E. coli* strains in 2004 versus 2011 are shown in Table 2.

From 2005 to 2011, ESBL-producing *E. coli* strains showed a significant rise in resistance to amikacin (P = 0.0001) and a significant decline in resistance to trimethoprim/sulfamethoxazole (cotrimoxazole) (P = 0.0063), while no statistically significant difference was observed in resistance to fosfomycin and ciprofloxacin.

For non-ESBL–producing *E. coli* strains, evaluation of resistance rates from 2004 to 2011 revealed no significant difference between data from 2005 and 2011 in terms of resistance to fosfomycin, cotrimoxazole, ciprofloxacin, and amikacin.

Of the past studies conducted in Turkey, including data on resistance to fosfomycin, 10 studies were determined to be eligible to be analyzed in the present study. Overall, as summarized in Table 3, the average resistance rate of the 6439 *E. coli* strains included in these studies was determined to be 1.9% (resistance rate of 0.5% in non-ESBL–producing *E. coli* strains and 5% in ESBL-producing *E. coli* strains).

4. Discussion

UTIs are among the infectious diseases associated with the most frequent use of antibiotics. Quinolones, cotrimoxazole, amino glycosides, and nitrofurantoin (NFT) are the first choices for the treatment of uncomplicated UTIs. NFT is indicated in the treatment of uncomplicated lower UTIs and is effective in vitro against *E. coli* strains, including ESBL-producers. Resistance rates to NFT in ESBL-negative and ESBL-producing *E. coli* were reported to be 6.6% and 23.2%, respectively, from a tertiary care educational hospital in Turkey (17,18). Sensitivity of strains to NFT has not been investigated in this study. A recent study from Turkey detected that the lowest resistance rates of community-acquired *E. coli* strains were isolated from urinary system infections for NFT (0.9%) and fosfomycin (3.6%) (19). However, ever-increasing antibiotic resistance of *E. coli* strains isolated from these infections together with a particular rise in ESBL-producing strains in recent years seriously challenges the treatment (13,14). The likelihood of treatment failure with cotrimoxazole and quinolones due to plasmid-mediated resistance renders carbapenems as the primary therapeutic option (5,7). In this regard, investigations continue in search of new antibiotics to replace broad-spectrum, costly antibiotics like quinolones that require hospitalization. Being recently introduced into the market in Turkey, fosfomycin occupies a particularly important place among these antibiotics given that high concentrations were achieved in urine a short time after

Table 1. Resistance in ESBL-producing *E. coli* strains [n (%)].

Antibiotics	2005 (n = 344)	2011 (n = 178)	P-value
Ciprofloxacin (5 μg)	263 (76.4)	132 (74.1)	0.3359
Amikacin (30 μg)	38 (11.0)	62 (34.8)	0.0001
Cotrimoxazole (25 μg)	256 (74.4)	112 (62.9)	0.0063
Fosfomycin (50 μg)	12 (3.4)	4 (2.2)	0.4355

Table 2. Resistance in non-ESBL–producing *E. coli* strains [n (%)].

Antibiotics	2004 (n = 72)	2011 (n = 324)	P-value
Ciprofloxacin (5 μg)	28 (39.0)	118 (36.4)	0.6945
Amikacin (30 μg)	5 (7.0)	53 (16.3)	0.0527
Cotrimoxazole (25 μg)	31 (43.0)	162 (50.0)	0.2863
Fosfomycin (50 μg)	0 (0.0)	3 (0.9)	0.4124

administration, along with low cost, low resistance rates, and applicability without hospitalization (5,7).

The present study aimed to determine the influence of more common usage of fosfomycin in UTIs during the past 6 years and the alteration in sensitivity parameters of antibiotics used as the first-line therapy of UTIs. Comparison of *E. coli* strains isolated in 3 distinct time points in terms of resistance rates in the present study revealed a statistically significant increase in resistance rates to amikacin and a decrease in resistance rates to cotrimoxazole. There was no significant alteration in resistance rates of other antibiotics evaluated.

Based on data from recent studies conducted in Turkey, it is worth noting that amino glycosides still have considerable priority in the empirical treatment of UTIs (2,9,10,13,15). Likewise, in another study from our team, pooled analysis of resistance rates of *E. coli* strains isolated from UTIs revealed a high sensitivity to amino glycosides with an average resistance rate of 6.1% to amikacin in a total of 7960 *E. coli* strains derived from outpatients (20). It seems likely that more frequent use of amikacin due to low resistance rates determined in the recent period has a role in the relative rise in resistance to drugs established in 2011.

Ciprofloxacin is one of the most frequently administered antibiotics in empirical approaches as well as in causative agent-based treatment of UTIs. However, rise in resistance rates to ciprofloxacin and increasingly encountered ESBL-producing strains seem to restrict the use of this antibiotic (5). Evaluation of past studies published before 2007 revealed that resistance to ciprofloxacin was 20.1% in a total of 15,221 *E. coli* strains derived from outpatients (20). Resistance rates in subsequent years have been reported to range from 27% to 69% (7,9,10,13). Notably, ESBL-producing *E. coli* strains have been associated with higher resistance rates to ciprofloxacin. Accordingly, the high resistance rates to ciprofloxacin determined in the 3 periods in the present study seem remarkable. Nevertheless, the likelihood of microbiological eradication even in the resistant strains should be taken into consideration for this drug given its high urinary concentrations.

Cotrimoxazole has long been used as a safe treatment in UTIs. However, high rates of resistance that developed in relation to common use restrict the empirical use of this agent. In a pooled analysis of 53 publications, the resistance rate to cotrimoxazole was reported to be 47.1% in a total of 17,533 *E. coli* strains derived from outpatients (20). Resistance to cotrimoxazole was also determined to be considerably high in the present study. Data from past studies in Turkey indicate that resistance to cotrimoxazole ranges from 47% to 72% (9,13). Hence, these high rates of resistance support that the empirical use of this agent is not reasonable.

In our previous study concerning antibiotics frequently used in UTIs, no resistance to fosfomycin was identified in 72 *E. coli* strains in 2004, while in 2005 the resistance rate to fosfomycin was reported to be 3% in a total of 344 ESBL-producing *E. coli* strains. Accordingly, empirical use of this agent in UTIs has begun to gain wide currency. Administration of a single dose of fosfomycin repeated every other day 3 times was reported to be effective in patients with UTIs in which the causative agent was an ESBL-producing *E. coli* strain and the clinical picture was accompanied with no systemic findings or complicating factors (4). Similarly, fosfomycin (every other day, 1 × 1, 3 times) was reported to be similar to meropenem (3 × 1/day, 14 days) in terms of microbiological and clinical success in the treatment of ESBL-producing *E. coli* strains related to complicated lower UTI (5). Afterwards, this treatment protocol became routinely applied at our hospital, particularly in the infectious diseases, urology, physical therapy and rehabilitation, and obstetrics and gynecology clinics. Feedback on the administration of similar treatment protocols has also been received from other centers in Turkey. Fosfomycin has also been reported to be very effective in the treatment of uncomplicated cystitis in recent publications (12,21,22).

Resistance to fosfomycin was determined to be 1.4% in 2011. Evaluation of subgroups revealed resistance to fosfomycin in 12 of 344 ESBL-producing *E. coli* strains in 2005 while 4 of 178 ESBL-producing *E. coli* strains showed resistance to fosfomycin in 2011, which may be related to

Table 3. Resistance to fosfomycin: data from previous studies conducted in Turkey.

Studies			*E. coli* strains			
			Overall number	Resistance		
Investigator (reference)	Year	Province		Non-ESBL–producing	ESBL-producing	Total
			N	n/N (%)		
Yaşar et al. (7)	2011	İstanbul	416	7/312 (2.2)	5/104 (4.8)	12/416 (2.9)
Mengeloğlu et al. (8)	2011	Siirt	105	0/71 (0.0)	0/34 (0.0)	0/105 (0.0)
Bayram et al. (9)	2011	Van	375	13/263 (5.0)	17/112 (15.0)	30/375 (8.0)
Deveci et al. (10)	2010	Mardin	57	0/31 (0.0)	0/26 (0.0)	0/57 (0.0)
Ceran et al. (11)	2010	İstanbul	117	4/110 (3.6)	0/7 (0.0)	4/117 (3.4)
Hoşbul et al. (12)	2009	Ankara	771	0/621 (0.0)	3/150 (2.0)	3/771 (0.4)
Uyanık et al. (13)	2009	Erzurum	139	0/103 (0.0)	0/36 (0.0)	0/139 (0.0)
Aşık et al. (14)	2008	Afyon	80	–	1/80 (1.2)	1/80 (1.2)
Akyar et al. (15)	2007	İstanbul	1100	0/968 (0.0)	0/132 (0.0)	0/1100 (0.0)
Tekin et al. (16)	2006–2011	Diyarbakır	3279	0/2033 (0.0)	71/1246 (5.7)	71/3279 (2.2)
Total	2006–2012	Turkey	6439	24/4512 (0.5)	97/1927 (5.0)	121/6439 (1.9)

the limited number of cases and shorter time period in 2011. On the contrary, none of non-ESBL–producing *E. coli* strains showed resistance to fosfomycin in 2004, while resistance was determined in 3 non-ESBL–producing *E. coli* strains in 2011. Two of these 3 strains were isolated from bedridden patients who were undergoing 6-month fosfomycin treatment due to recurrent UTIs. Data from recently conducted studies in Turkey indicate low resistance rates to fosfomycin in *E. coli* strains, with an average resistance of 1.9% (range: 0%–15%) (7–16).

A limitation of this study seems to be the minor differences in the included studies from 3 different periods. While only community-acquired UTI cases were included in the study conducted in 2004, resistance rates of ESBL-producing *E. coli* strains were determined regardless of the discrimination of community- or hospital-acquired infection in 2005. Moreover, data from 2011 included evaluation of strains with respect to outpatient versus inpatient origin. Nevertheless, despite these differences, all 3 studies provide substantial data considering resistance rates specific to our region.

Data from the studies about fosfomycin cover a relatively long period of time, starting from the introduction of fosfomycin in clinical practice in the early 1970s. The studies have not shown a major difference in the susceptibility to fosfomycin between the first and the last year of the study period (23). In conclusion, our findings revealed no increase in resistance rates to fosfomycin

despite its more common use in UTIs for the past 6 years as well as no significant differences in resistance rates to other antibiotics. Accordingly, fosfomycin seems to be a safe remedy that continues to hold its ranking among the first treatment choices of both empirical and causative agent-based treatment of UTIs.

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