

Susceptibility pattern of oral antimicrobials in uncomplicated UTI: Does fosfomycin still stand effective?

Priyam Batra¹, Amit K. Abrol¹, Stuti Gupta¹, Preeti Pushpan¹,
Rajendra Kumar¹

¹Department of Lab Medicine, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Introduction: Urinary tract infections (UTIs) are a leading cause of morbidity amongst all age groups and most patients with uncomplicated UTI who visit the OPD are treated with empirical antibiotics without doing any culture analysis. Of all the oral antibiotics used in UTI, fosfomycin is well excreted in the urine and is being used for the treatment of UTIs with a single oral dose. **Methodology:** The current study was planned to determine the resistance amongst uropathogens to various oral antibiotics including fosfomycin isolated over a 4-year period (April 2015 to March 2019). **Results:** A total of 22,546 urine samples were received from OPD patients over 4 years and of these, 7,295 isolates were obtained from patients with uncomplicated UTI. About 82% of the isolates were gram-negative bacilli (GNBs). The most common isolate was *E. coli* 1023 (67.2%) followed by *Klebsiella* spp 254 (16.7%), and *Pseudomonas* spp 63 (4.1%). Of all the antibiotics tested, maximum sensitivity in the year 2018 was found to fosfomycin followed by nitrofurantoin for all the isolates tested. There was a statistically significant increase in the resistance pattern for almost all antibiotics tested in gram-negative bacteria (both Enterobacteriaceae and non-fermenters) whereas the increase in the resistance was not statistically significant in gram-positive cocci. **Conclusion:** It can be easily seen that the level of antibiotic resistance has been increasing even in the community with the rampant injudicious use of antibiotics in humans as well as livestock. As the level of resistance to fosfomycin is still low in the community, it can play a promising role in the treatment of infection in patients with uncomplicated UTI.

Keywords: Antibiotic resistance, fosfomycin, urinary tract infections

Introduction

Urinary tract infections (UTIs) are a leading cause of morbidity amongst all age groups accounting for nearly 8.3 million outpatient visits, more than 1 million hospitalizations, and an annual cost of more than 1 billion USD.^[1] Nearly, 1–3% of medical consultations in the UK are due to UTI.^[2] Most patients with uncomplicated UTI who visit the OPD are

treated with empirical antibiotics without culture.^[3] This overuse and misuse of antibiotics have led to the percolation of antibiotic resistance in the community making most of the available oral antibiotics ineffective for use. Fosfomycin, an oral phosphonic acid derivative disrupting cell wall synthesis, was introduced first in the year 1969 from cultures of *Streptomyces* species.^[4] Since it is well excreted in the urine achieving a urine concentration of 2000 µg/mL, single-dose oral therapy has been recommended for the treatment of uncomplicated UTI.^[5,6] The 2010 IDSA guidelines for the treatment of uncomplicated UTI recommend the use of nitrofurantoin and cotrimoxazole as the first-line agents followed by fosfomycin,

Address for correspondence: Dr. Priyam Batra,
Department of Lab Medicine, All India Institute of Medical
Sciences, New Delhi - 110 029, India.
E-mail: dr.priyambatra@gmail.com

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fluoroquinolones, and beta-lactam agents as second-line agents.^[7]

Fosfomycin trometamol is an appropriate choice of the agent as it has a broad spectrum of activity, minimal resistance (nearly 85–100% susceptibility), and minimal propensity for collateral damage.^[8] Most of the available literature on fosfomycin resistance is on *E. coli* as CLSI guidelines^[9] have fosfomycin zone diameter for Enterobacteriaceae and *Enterococcus spp* only. There are few studies^[10] that have studied fosfomycin resistance in all gram-positive and gram-negative isolates. One such study^[11] was done in our center analyzing the data of 2014–2016 which showed that more than 95% of the isolates were sensitive to fosfomycin. The current study was thus planned on a similar methodology to determine the increase in the level of resistance to oral antibiotics especially fosfomycin in the urinary isolates from patients of uncomplicated UTI visiting the OPDs of a 2300 bedded tertiary care center of India. Ethical clearance was obtained from the institute ethics committee for performing the study (IEC-560/02.08.2019).

Methodology

The study was conducted over a period of 4 years (April 2015 to March 2019) to include urine samples of patients visiting the various OPDs with uncomplicated UTI. Urine was cultured as per the standard protocol and isolates obtained were identified using conventional methods. Duplicate isolates of the same pathogen from the same patient isolated over 2 weeks’ period were excluded. The sensitivity of gram-negative isolates was performed for the following antibiotics: ampicillin, amoxicillin/clavulanate, cotrimoxazole, nitrofurantoin, fluoroquinolones (norfloxacin/levofloxacin/ciprofloxacin), and fosfomycin. The sensitivity of *Staphylococcus spp* was performed for fluoroquinolones (ciprofloxacin/levofloxacin), cotrimoxazole, linezolid, nitrofurantoin, and fosfomycin. The sensitivity of *Enterococcus spp* was performed to fluoroquinolones (ciprofloxacin/levofloxacin), fosfomycin, nitrofurantoin, and linezolid. The results were interpreted as per CLSI guidelines.^[9]

Results

A total of 22,546 urine samples were received from OPD patients over 4 years and of these, 7, 295 isolates were obtained from patients with uncomplicated UTI. The mean age of the patients was 45 years (6 months to 74 years) and the male: female ratio was 3.54. Around 82% of the isolates were gram-negative bacilli (GNBs). The most common isolate was *E. coli* 1023 (67.2%) followed by *Klebsiella spp* 254 (16.7%) and *Pseudomonas spp* 63 (4.1%). The profile of the pathogens causing uncomplicated UTI is shown in Figure 1. The resistance of the GNBs (*Enterobacteriaceae* and nil fermenters) and GPCs (*Staphylococcus spp* and *Enterococcus spp*) to the various antibiotics tested is shown in Table 1.

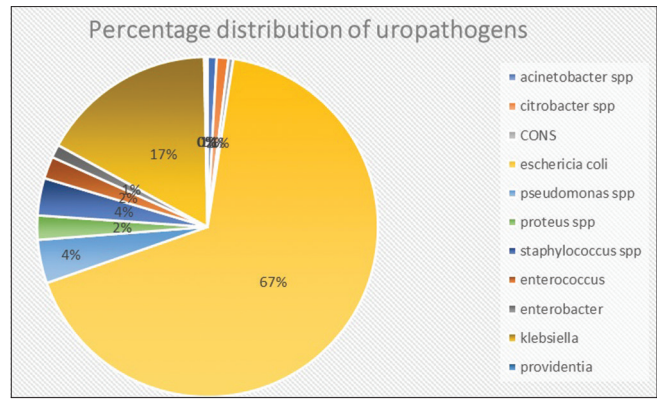


Figure 1: Percentage distribution of UTI causing pathogens

Table 1: Percentage antibiotic resistance to various antibiotics and P for the statistical significance of the trend of antibiotic resistance

Organism	Antibiotic	2015	2016	2017	2018	P
Enterobacteraceae	Ampicillin	58.7	62.8	79.4	98.3	0.000
	Amoxicillin clavulanate	48.2	56.8	75.4	93.2	0.000
	Cotrimoxazole	63.4	7.5	62.5	70.6	0.270
	Fluoroquinolones	51.4	59.2	67.3	69.5	0.000
	Nitrofurantoin	45.6	42.3	4.5	35.7	0.012
Nil fermenters	Fosfomycin	2.16	8.9	13.2	23.1	0.000
	Fluoroquinolones	43.2	45.9	48.3	41.9	0.979
	Nitrofurantoin	59.1	66.9	66.5	84.3	0.035
Staphylococcus spp	Fosfomycin	3.75	10.8	17.5	34.2	0.010
	Ampicillin	61.3	69.5	79.2	93.5	0.033
	Cotrimoxazole	44.3	50.2	66.8	78.3	0.032
	Fluoroquinolones	44.3	52.4	60.4	62.7	0.263
Enterococcus spp	Nitrofurantoin	3.4	2.8	1.7	3.1	0.239
	Fosfomycin	5.7	11.2	13.5	23.5	0.262
	Ampicillin	7.5	76.8	85.6	95.7	0.073
	Fluoroquinolones	66	65.4	75.6	82.3	0.415
Enterococcus spp	Nitrofurantoin	5.9	7.8	7.5	7.7	0.331
	Fosfomycin	1.9	7.9	10.3	17.2	0.378

In the year 2018, when all the antibiotics were tested, maximum sensitivity was found to fosfomycin followed by nitrofurantoin for all the isolates tested. Resistance amongst all the uropathogens for ampicillin and amoxicillin/clavulanate was more than 90% and for cotrimoxazole and fluoroquinolones was nearly 60–70%. Thus, our study suggests that fosfomycin should be preferred over fluoroquinolones for use in the treatment of UTIs. By preferring fosfomycin over fluoroquinolones, they can be spared for use in other infections such as tuberculosis. It can also be seen that nitrofurantoin should be preferred over cotrimoxazole as a first-line agent for the treatment of uncomplicated UTI.

Of the isolates tested for the various classes of oral antibiotics, there were no isolates belonging to the years 2015 and 2016, which were resistant to all the oral antibiotics. However, in the year 2017, a total of 7 *E. coli* isolates and 5 *K. pneumoniae* isolates were resistant to all the oral antibiotics including fosfomycin. In 2018, 17 *K. pneumoniae*, 6 *E. coli*, 2 *Proteus spp*, 1 *Pseudomonas spp*, and 1 *Acinetobacter baumannii* were resistant to all the oral antibiotics

including fosfomycin. None of the gram-positive isolates were resistant to linezolid.

Statistical analysis of the trend of antibiotic resistance over the years was performed using the Chi-square trend test. It showed that there was a statistically significant increase in the resistance pattern for almost all antibiotics tested in gram-negative bacteria (both Enterobacteriaceae and nil fermenters) whereas the increase in the resistance was not statistically significant in gram-positive cocci. The results of the *P* value are given in Table 1.

Discussion

It can be easily seen from the study that the level of antibiotic resistance has been constantly increasing even in the community population. Being the biggest tertiary care hospital in India, we receive the maximum number of referred patients and most of these patients would have already received antibiotics either from the community local practitioners or some may be patients visiting the outpatient department after surgery and so on. This is a big limitation of our study as not all of the data may be representative of the community scenario.

In our study, the most common uropathogen was *Escherichia coli* (67.2%) followed by *Klebsiella spp* (4.1%), and *Staphylococcus spp* (3.5%). This is similar to that observed by other authors.^[12-14] In our study, there has been a statistically significant increase in the level of antibiotic resistance amongst Enterobacteriaceae to ampicillin, amoxicillin/clavulanate, fluoroquinolones, nitrofurantoin, and fosfomycin. Amongst nil fermenters, the increase in the resistance to nitrofurantoin and fosfomycin was significant. This can be easily explained by the use of these antibiotics (ampicillin, amoxicillin/clavulanate, fluoroquinolones) for many other ailments such as upper respiratory tract infections or gastroenteritis. With the revival of fosfomycin, its usage for treatment of UTI has been increasing very rapidly due to its minimal side effects and easy single-dose usage. This increasing use is well-reflected by the increase in antibiotic resistance. Similar trends of increasing antibiotic resistance in uropathogens have also been seen across other countries as well such as by Gajdacs *et al.* in Hungary^[15] and Shin *et al.* in Korea.^[16] Despite the high level of resistance, the level of resistance to nitrofurantoin and fosfomycin, antibiotics specific for urine, is quite low in almost all the isolates. Thus, these two antibiotics can be used in the treatment of UTI in outpatients sparing the other antibiotic classes (like fluoroquinolones, amoxicillin/clavulanate) for use in other illnesses. The information generated by the study would be useful in drafting the antibiotic policy of our outpatients.

This study being a retrospective study, we could not keep the isolates resistant to fosfomycin and thus the PCR for the genes responsible for fosfomycin could not be determined. In addition, testing of fosfomycin resistance by disc diffusion is not a standardized method for *Staphylococcus spp* and nil fermenters.

But in our study, we have used the susceptibility breakpoints for Enterococcus and Enterobacteriaceae, respectively as done by various other authors.^[10,11]

Conclusion

Through our study, it can be easily concluded that the level of antibiotic resistance in the community is increasing rapidly with the constant use and misuse of antibiotics. However, fosfomycin still has a promising role in UTI as the level of resistance amongst uropathogens is still very low.

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Conflicts of interest

There are no conflicts of interest.

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