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Revisiting fosfomycin to treat urinary tract infections in the era of rising carbapenem resistance

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ABSTRACT

Background: Most of the studies on antibiotic resistance are pre-judiced over the use of last-resort antibiotics for Multidrug resistant organisms (MDRO) and fail to acknowledge the effectiveness of older antibiotics. There is a dearth of information regarding the susceptibility of fosfomycin and nitrofurantoin, which are oral alternatives for such infections. **Aims and Objectives:** To study the antibiotic susceptibility profile of uropathogenic *Escherichia coli* and infer whether fosfomycin can be used as an efficient oral option for the management of uncomplicated urinary tract infection (UTI), especially in carbapenem-resistant cases. **Materials and Methods:** Clean catch midstream urine samples from cases clinically suspected of UTI received for culture were processed using standard guidelines for microbiological procedures. Antimicrobial sensitivity was performed through the Kirby Bauer disc diffusion method. Discrepant results were confirmed with VITEK 2. **Results:** This study reports antimicrobial susceptibility pattern of 100 *E. coli* isolated from urine samples of patients with signs and symptoms suggestive of UTI. There was a female predominance in the study population and the most affected age group was 20–40 years (52%). Most specimens were received from the obstetrics and gynecology department (32%) followed by General medicine (28%). Higher sensitivity was observed for fosfomycin (97%), amikacin (80%), and meropenem (79%). **Conclusion:** Fosfomycin is an oral, safe, and efficient antibiotic for UTI. It is a valuable alternative for outpatient treatment of MDROs causing UTI. Thus, decreasing hospitalization and consequently reducing the financial burden of treatment for the patients.

Key words: Multidrug resistance; Urinary tract infection; Antimicrobial drug resistance; Carbapenems; Uropathogenic *Escherichia coli*

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INTRODUCTION

Urinary tract infection (UTI) is among the most common bacterial infections impacting more than 150 million people and an economic strain of more than $6 billion worldwide each year. It is the major reason of outpatient visits among adult women with a lifetime incidence of 50–60% in females and 12% in males.[1,2] UTIs can be either uncomplicated affecting healthy individuals with no structural or neurological urinary tract abnormalities, while complications arise due to compromised urinary tract or host defenses. *Escherichia coli* prevails as the leading cause of UTI, accounting for around 90% of community-reported and 50% of hospital-acquired cases.[3]

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Although the prevalence of UTI among children and pregnant women remains updated due to their susceptibility to secondary complications. However, data regarding UTI prevalence in the general population is scarcely available due to the focus being fixated on pathogens with pandemic potential. Moreover, if overlooked for long such common infections with emerging drug-resistant strains, such as carbapenem-resistant *E. coli* (CREC) may become unmanageable without regular monitoring of the burden and rationalized policies for treatment. Carbapenem being a preferred choice in cases of multidrug-resistant organisms (MDROs), its resistance poses an urgent threat, with no major contender antibiotic in the future pipeline. Most of the drugs among the exiguous options for CREC management are administered by intravenous route mandating the need for hospitalization. Fosfomycin, a broad-spectrum oral antibiotic that has high drug concentration in the urinary tract for an extended duration acts as an alternative for treatment of MDROs or CREC. Furthermore, it reduces the burden of hospitalization minimizing the financial and physical suffering endured by the patients.[4,5]

There is a dearth of information regarding the susceptibility of fosfomycin, which is an oral alternative for the treatment of UTI. In the present study, the antibiotic resistance of various antimicrobials used for the treatment of UTI has been studied on CREC and carbapenem sensitive *E. coli* (CSEC) isolated from clinically suspected cases of UTI in rural community with a focus on sensitivity of fosfomycin.

Aims and objectives

To study the antibiotic susceptibility profile of UPEC and infer whether fosfomycin can be used as an efficient oral option for the management of uncomplicated lower UTI, especially in CREC patients.

MATERIALS AND METHODS

This was a prospective observational study conducted from a multispecialty hospital serving rural community from March 2020 to September 2020. All the tests were performed according to standard guidelines in the Microbiology laboratory which participates regularly in the EQAS program and is NABL accredited for the procedures performed in the study.

Inclusion criteria

All consecutive non-duplicate *E. coli* strains (100) isolated in the Microbiology department from clean catch midstream (CCMS) urine specimens of clinically suspected UTI patients from both Outpatient Department (OPD) and inpatient Department during the study period were included in this study.

Exclusion criteria

All specimens other than CCMS urine and isolates other than *E. coli* from CCMS urine were excluded from the study.

Procedure

One microliter of CCMS urine specimen was streaked on cystine lactose electrolyte deficient (CLED) agar. The culture was performed by a semi-quantitative method using the calibrated loop. The inoculated culture plates were aerobically incubated for 18–48 h at 37 °C. The plates were observed for significant growth of microorganisms. The colony counts were considered significant based on criteria in Table 1.[6,7] The significant growth was then processed for Gram's staining and biochemical analysis based on colony characteristics on CLED agar. The isolated colonies were subjected to biochemical tests, such as indole test, citrate utilization, urease test, nitrate reduction, sugar fermentation tests (glucose, lactose, and maltose), decarboxylase test (lysine), triple sugar iron agar, methyl red and Voges-Proskauer test to confirm the diagnosis of *E. coli*. The biochemical reactions shown by *E. coli* have been elaborated in Table 2.

Antimicrobial susceptibility testing was performed on Mueller Hinton agar (MHA) by disc diffusion using Kirby Bauer method. The antibiotics tested with their potency were; ampicillin (10 μg), co-trimoxazole (25 μg), piperacillin-tazobactam (10 μg), levofloxacin (5 μg), nitrofurantoin (300 μg), amikacin (30 μg), cefixime (5 μg), ceftriaxone (30 μg), fosfomycin (200 μg), nalidixic acid (NA) (30 μg), gentamicin (10 μg), and meropenem

Table 1: Criteria for significant colony count[5,6]

S. No.	Category	Criteria	
		Clinical	Significant colony count
1.	Acute uncomplicated UTI in females/Acute urethral syndrome	Dysuria, urgency, frequency, suprapubic pain with pyuria (no such episode in last four weeks)	≥10^3 CFU/ml (single pathogen)
2.	Acute uncomplicated UTI in males	Dysuria, urgency, frequency, suprapubic pain with pyuria (no such episode in last four weeks)	≥10^5 CFU/ml (single pathogen)
3.	Acute uncomplicated pyelonephritis	Fever, chills, flank pain with exclusion of other site infection or clinical evidence of urinary tract abnormalities	>10^4 CFU/ml
4.	Asymptomatic	No urinary symptoms	10^5 CFU in two urine cultures >24 hours apart

Pus cell count in UTI should be>10 WBC/mm3 with the above colony count to be significant. UTI- Urinary tract infection, CFU- Colony forming unit.

Table 2: Biochemical characteristics of *Escherichia coli*

Organism/biochemical reactions	Indole production	Citrate utilization	Urease test	Nitrate reduction	Triple sugar iron agar	Methyl red	Voges-Proskauer	Lysine decarboxylase	Sugar fermentation		
									Glucose	Maltose	Lactose
Escherichia coli	+	–	–	+	A/A with gas	+	–	+	+	+	+

+Means positive reaction shown in the test, –Means negative reaction shown in the test. A/A with gas: Acid slant and acid butt with gas production

(10 μg). The zone sizes on MHA were interpreted as per clinical and Laboratory Standards Institute guidelines recommended for *Enterobacteriaceae*.[8] The test results of identification as well as antimicrobial sensitivity were confirmed using automated system, VITEK-2 for bacterial identification.

Multidrug-resistance criteria were defined as resistance to one or more antibiotics belonging to three or more classes.[8] CREC was defined as *E. coli* showing decreased susceptibility to any of the carbapenems.[1,9] Quality control was done using ATCC strains, *E. coli* 25922 (CSEC control), and *E. coli* ATCC BAA 2340 (CREC control). All antibiotic susceptibility tests were independently performed in duplicative experiments.

Statistical analysis

Data were entered and recorded in Microsoft Excel 2010. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 20 software and results were presented through suitable tables and graphs. Comparison of categorical variables, such as percentage of resistance based on gender, adults, or children (below 18 years of age) was done by Chi-square test, while the continuous variables, such as age was done by student's T test. $P<0.05$ were considered statistically significant for confidence interval of 95%.

Ethics statement

Ethical approvals have been obtained from the Institutional ethical committee for exemption of consent from patient and patient information sheet since the isolates will be anonymized, coded by randomization, and will be delinked from any identity of the patients.[10]

Compliance with ethical standards

The study was approved by the Institute's Ethical Committee and Departmental Research Committee (SGTU/FMHS/IEC/2020/45). The Declaration of Helsinki has been followed as per recommendations.

RESULTS

A total of 100 *E. coli* isolates from urine samples of suspected UTI patients were included in this study. The median age of the study population was 30 years (IQR-24.5), the mean being 34.65 years with the most common age group affected was 20–40 years. The median age of the CREC affected patients was 23 years (IQR-16), mean being 26.76 years. There was female predominance 55% in the study population as well as in the CREC affected 66.7%. Most of the patient specimens were received from obstetrics and gynecology (32%) followed by general medicine (28%) (Table 3).

Out of the 100 isolates, most resistant antibiotics were ampicillin with susceptibility of 20% and cephalosporins (cephazolin then third generation cephalosporins) while fosfomycin (97%), aminoglycosides (amikacin-80% and gentamicin-77%), and carbapenems (79%) showed good activity against UPEC (Figure 1). The proportion of MDR *E. coli* accounted for 37% and 21% were CREC.

On comparison of the sensitivity of various antimicrobials among CREC and CSEC, it was seen that most of them showed statistically significant differences in their sensitivity in these two categories as shown in Table 2. The difference in sensitivity of piperacillin-tazobactam (73.4% and 62%) and fosfomycin (98.7%, 90.4%) in CSEC and CREC categories, respectively, was not statistically significant (Table 4).

Co-resistance to the combination of antibiotics in CREC isolates was observed in between three antibiotics NA, fosfomycin and nitrofurantoin as they are most common agents used for treatment of UTI. Resistance to all three together was found to be in 9.5%. However, susceptibility of antibiotic combinations with NA and nitrofurantoin was 28.5%, fosfomycin either nitrofurantoin or NA was 9.5% (Table 5).

DISCUSSION

The management of bacterial infections has become cumbersome due to the spread of MDR pathogens and the paucity of new antimicrobials that are active against such infections. The practice of dispensing carbapenem as broad-spectrum coverage for empirical therapy has led to the emergence of carbapenem resistance among community-acquired infections, which are usually susceptible to lower classes of antibiotics. As a result, attention has been drawn to antibiotics not commonly preferred due to high level of toxicity, such as polymyxins,

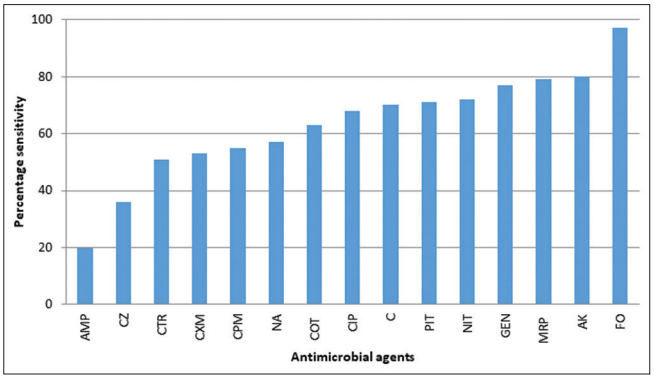

Figure 1: Antimicrobial sensitivity pattern among *Escherichia coli* isolates (n=100). AMP-Ampicillin, CZ-Cephazolin, CTR-Ceftriaxone, CXM-Cefixime, CPM-Cefepime, NA-Nalidixic acid, COT-Cotrimoxazole, CIP-Ciprofloxacin, C-Chloramphenicol, PIT-Piperacillin-Tazobactam, NIT-Nitrofurantoin, GEN-Gentamicin, MRP-Meropenem, AK-Amikacin, FO-Fosfomycin

Table 3: Demographic profile of study population

Demography	Overall (%) (n=100)	CREC (%) (n=21)
Gender		
Male	45	33.3
Female	55	66.7
Age (years)		
0–20	15	28.6
21–40	52	57
41–60	11	4.7
>61	22	9.4
Location		
Obstetrics and gynecology	32	47.6
General medicine	28	28.5
Pediatrics	11	23.8
Surgery	13	0
Others*	16	0

CREC: Carbapenem resistant *Escherichia coli*. *Other includes: Dermatology, orthopedic, ENT, pulmonary medicine

Table 4: Comparative susceptibility pattern of various antimicrobials for carbapenem sensitive *Escherichia coli* (CSEC) and carbapenem resistant *Escherichia coli* (CREC) isolates

Antibiotics	Sensitivity (%)		Statistical analysis
	CREC (n=21) (%)	CSEC (n=79) (%)	(P-value)
Ampicillin	0 (0)	20 (25.3)	0.001
Cefazolin	1 (4.8)	35 (44.3)	0.001
Ceftriaxone	2 (9.5)	49 (62)	0.001
Cefepime	3 (14.3)	52 (65.8)	0.001
Piperacillin-Tazobactam	13 (62)	58 (73.4)	0.484
Cotrimoxazole	9 (43)	54 (68.3)	0.0328
Nitrofurantoin	11 (52)	63 (79.7)	0.01
Nalidixic acid	5 (24)	52 (66)	0.001
Ciprofloxacin	9 (43)	59 (74.7)	0.036
Amikacin	11 (52)	69 (87)	0.034
Gentamicin	10 (47.6)	67 (84.8)	0.021
Fosfomycin	19 (90.4)	78 (98.7)	0.671

Table 5: Co-resistance to combination of antibiotics

CREC isolates	Co-resistance pattern			
n=21	Three antibiotics (%)	Two antibiotics (%)		
	NA, FO, NIT	NA, FO	FO, NIT	NA, NIT
	2 (9.5)	2 (9.5)	2 (9.5)	6 (28.5)

CREC: Carbapanem resistant *Escherichia coli*, NA: Nalidixic acid: NIT-Nitrofurantoin: FO: Fosfomycin

tetracyclines, and aminoglycosides. Lately, to keep these last resort agents from developing resistance and in cases where they cannot be used due to toxicity, older oral antimicrobial agents have gained attention, as they remain active against MDR bacteria and can be used for uncomplicated infections. In spite of good activity, limited studies have been documented on fosfomycin sensitivity patterns in the community, especially in the peri-urban population.

In this study out of the 100 cases included in the study, the prevalence of UTI was higher among females (55%) which correlates with findings of many other epidemiological studies done on UTI.[11,12] The reasons of high rates of urinary infection in females are close proximity of the urethral meatus to the anus, sexual intercourse, frequent incontinence, shorter urethra, use of contraceptives, and behavioral factors, such as the habit of holding urination when in social places. Such conditions aid the colonization and proliferation of coliform bacteria. Etiology in older post-menopausal women is determined by their health condition, age, residential status, presence of co-morbidities, such as diabetes mellitus, and history of catheterization and antibiotic intake. While males have anatomical and physiological advantages due to longer urethra and antimicrobial activity of prostatic fluid, but in old age when prostatic activity declines the chances of getting UTI increases. In the present study, the most commonly affected age group was 21–40 years which pertains to years of maximum sexual activity.[13]

Enterobacteriaceae members are the common agents causing UTI with UPEC being the most frequent microorganism causing uncomplicated UTI (70–90%).[14] Rising trends of resistance among uropathogens especially *E. coli* have been reported globally since the past two decades. Risk factors for this trend include recent broad-spectrum antimicrobial use, indwelling devices allowing biofilm formation, previous treatment for severe illness with antibiotics of last resort, nosocomial origin, and travel to parts of the world where MDRO are prevalent.[14,15] Regional causes of such alarming trends are lack of antimicrobial susceptibility testing for UTI, inaction on sensitivity reports, over the counter availability of antibiotics and antibiotic usage without professional prescription or supervision.

The treatment strategy for uncomplicated UTI has seen a major shift over the years from cotrimoxazole being replaced by fluoroquinolones or nitrofurantoin and then to higher antibiotics, such as carbapenems. Such transitions have been due to resistance seeping in resulting in constant failure of UTI treatment.[15-20] In the present study, 37% of *E. coli* isolated were found to be MDR strains while 21% were found to be CREC. Various studies from India have reported more or less similar trends. Kumarasamy et al., found 23.7% prevalence rate of CRE in Haryana while Wattal et al., observed 51% of CREC resistance in New Delhi.[21] Nair and Vaz from Mumbai found CRE to be around 12.26% whereas Datta et al., observed in Northern India CREC range 17–22%.[22,23] International studies have also shown rising trend of antimicrobial resistant among UPEC. Somashekara et al., from Southern part of India found that UPEC isolates showed less resistance to imipenem (8%), amikacin (16%), and were highly resistant to ampicillin (86%) and co-trimoxazole (69%).[24] Similar high resistance rates have been shown by studies from all parts of India over the years.[17-21]

In the present study, susceptibility rates in CREC isolates were found to be highest for fosfomycin followed by nitrofurantoin and piperacillin/tazobactam. Co-resistance to the combination of antibiotics in CREC isolates was observed in between common antibiotics used against UTI, that is, NA, fosfomycin, and nitrofurantoin. Maximum co-resistance was found with the NA and nitrofurantoin combination. Sabharwal and Sharma reported that 94.4% of the uropathogens were susceptible to fosfomycin.[25] Banerjee et al., found 95.18% of the uropathogenic *Enterobacteriaceae* to be fosfomycin sensitive.[26] In our study, 97% isolates were susceptible to fosfomycin which is quite similar to the findings of previous literature. Reviews and meta-analysis have also shown effectiveness of fosfomycin for treatment of UTI. Effectiveness of fosfomycin UTI can be explained by the fact that it achieves high concentration of 2000 μg/mL in urine and maintains this level for over 24 h.[27] Hence, single-dose oral therapy with fosfomycin has been found to be effective in uncomplicated UTI. The low prevalence of fosfomycin resistance can be explained by the fact that the resistant strains have lowered fitness to colonize the urinary tract. Furthermore, the target site of fosfomycin is not altered by other antimicrobials. Hence, there appears to be little cross-resistance between fosfomycin and the other commonly used urinary antibiotics.

Fosfomycin is a potent antibacterial drug, but its prescription should be confined to curb the emergence of resistance. It has proven to be an efficacious preference for community-based management of UTI patients.

Limitations of the study

The limitations of this study are that it is a retrospective study from a single multispecialty center and it is laboratory-based. Molecular confirmation could provide helpful insights for the specification of carbapenemase type and the gene responsible for fosfomycin resistance.

CONCLUSION

UTI is an infection that accounts for major footfall in the hospital premises. However, it can be managed with antibiotics at the OPD level and the unnecessary burden on the healthcare system can be avoided by prescribing oral antimicrobials. The results of our study augment the burden of MDROs, especially CREC. Furthermore, the susceptibility patterns reveal that fosfomycin can be considered as a viable alternative to spare the high-end antibiotics. Nevertheless, this constitutes only part of the versatile retaliation strategy and the pursuit for newer antibiotics should be continued. The establishment of a robust testing strategy and implementation of a comprehensive antimicrobial stewardship program with rigorous infection control practices are the armamentarium to combat the spread of antimicrobial resistance.

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