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Original Research Article

Nitrofurantoin and Fosfomycin for the CRE and MDR uropathogens: are the choices still same?

Nusrat Perween[1], Asfia Sultan[1]*, Anees Akhtar[1], Fatima Khan[1], Meher Rizvi[1], Haris M. Khan[1], Manzoor Ahmad[2]

[1]Department of Microbiology, J. N. Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India
[2]Department of Surgery, J. N. Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

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***Correspondence:**
Dr. Asfia Sultan,
E-mail: drasfia@gmail.com

ABSTRACT

Background: Urinary tract infection (UTI) is one of the most common bacterial infections, affecting 150 million people each year worldwide with substantial clinical and financial burden. With upcoming multi drug resistance (MDR) and carbepenem resistance among uropathogens there is urgent need to explore other new or old treatment options like nitrofurantoin and fosfomycin trometamol.
Methods: This is a cross-sectional (descriptive study) conducted over 6 month's period from October 2019 to March 2020. Out of 9045 urine samples, 1788 (19.8%) were positive (1721 samples with single organism and 67 samples with 2 organisms). Total 1855 isolates were identified and antimicrobial susceptibility was performed by Kirby-Bauer method and VITEK 2 system. Methicillin‑resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE), multi drug resistance (MDR) and metallo‑beta‑lactamases (MBL) production was detected.
Results: *E. coli* 41.8% was found commonest followed by enterococcus species (21.6%). Methicillin resistance was 66% while 1.8% were VRE. 429 (34.5%) were CRE (carbapenem resistant enterobacteriales) out of which, 154 (36%) were MBL while 188 (44%) were detected as serine carbapenemase producers via modified carbapenem inactivation method (mCIM) and EDTA-modified carbapenem inactivation method (eCIM) testing. Among 742 (40%) MDR, fosfomycin was effective in 611 (82.3%) while 331 (77.1%) of the CRE isolates were susceptible to fosfomycin.
Conclusions: Fosfomycin should be reserved for MDR and nitrofurantoin should be used cautiously otherwise resistance will increase to these drugs in the coming days.

Keywords: MDR, Uropathogens, Fosfomycin, Nitrofurantoin

INTRODUCTION

Antibiotic resistance among bacteria causing common infections is increasing in all regions of the world.[1] It is interesting that pattern of resistance observed varies from hospital to community, large hospital to small hospital, state to state, and even vary from country to country.[2] Emergence of resistance to antibiotics illustrates importance of using evidence-based strategies for treatment.[3] In urinary tract infection (UTI) cases, antibiotic treatment is often started empirically before the results of urine culture and susceptibility testing are available. Hence, it becomes important to regularly monitor the resistance or susceptibility patterns of uropathogens, so that the guidelines for empirical therapy can be improved to include antibiotics with low resistance, aiding clinicians in proper management of UTIs with minimal therapeutic failures.[4,5]

The common UTI causing organisms are all known to harbor multiple drug resistance (MDR) mechanisms, both inherited or transmissible and chromosomal or extrachromosomal against the commonly used oral antimicrobial agents for UTI i.e., fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, and second and third-generation cephalosporins.[6] With rampant overuse and abuse of these drugs, particularly in the developing countries like India with availability of over the counter drugs, UTI causing organisms have become overwhelmingly resistant to all or most of these agents, making outpatient oral therapy increasingly difficult. Fosfomycin is an old broad-spectrum bactericidal antibiotic agent that inhibits the synthesis of the bacterial cell. Its pharmacokinetic profile encourages its use for UTIs; the mean peak urinary concentration of an oral single dose of 3 g fosfomycin occurs within 4 hours, while concentrations sufficient to inhibit the majority of the urinary pathogens are maintained for 1 to 2 days.[7]

Taking all these into consideration a need was felt for a study to know causative agents of UTI and their antimicrobial susceptibility patterns, in a referral hospital in Aligarh, Uttar Pradesh, Northern India. This study can help us take a step towards evidence-based medicine and help us keep track of antimicrobial susceptibility trends if still fosfomycin is effective for the MDR UTI isolates.

METHODS

A cross-sectional (descriptive study) was conducted from October 2019 to March 2020 in a 1207 bedded tertiary care hospital in Aligarh, Northern India. With informed consent, urine samples were taken from the patients who had clinical features suggestive of UTI from the inpatients and outpatients departments. Freshly collected mid-stream clean-catch urine samples were taken from the non-catheterized, alert, conscious, adult patients with indications for urine culture as assessed by the clinicians from the various departments.[8] In catheterized patients, urine samples were collected from the catheter with needle and syringe in sterile manner as described in erstwhile standard technique guidelines.[9]

The urine samples were processed immediately within 1 hour of collection. Direct microscopy of the un-centrifuged urine sample was done, and pus cells and bacteria were noted. The urine samples were plated by semi-quantitative method with standard loop (0.01 ml) technique on cystine lactose electrolyte deficient (CLED) agar incubated at 37 degrees Celsius overnight. The growth of organisms (single or double) based on colony count (=>104 CFU/ml) were considered significant.[10]

Inclusion criteria

Either one or two abundant isolates obtained from the samples with significant bacteriuria with background of relevant supportive clinical features of UTI and/or the presence of significant pus cells on direct microscopy, as described in the standard guidelines of ICMR with some modifications, were included in the study.

Exclusion criteria

Purely sterile specimens/ samples with high probability of contamination having more than 2 isolates/ samples with insignificant bacterinuria/ samples with no pus cells in direct smear and no any clinical history suggestive of UTI were excluded from the study.

Sample size was calculated using the following formula.[11]

Sample size=$Z_{(1-\alpha/2)^2}p(1-p)/d^2$

$Z_{(1-\alpha/2)}$ =Standard normal variate (at 5% type 1 error ($p<0.05$) it is 1.96 and at type 1 error ($p<0.01$) it is 2.58. As in our study p is considered significant below 0.05 hence 1.96 value is used in this study.

p= Expected proportion in population based on previous studies or pilot studies.

d= Absolute error or precision

Sample size was calculated using the absolute or precision error of 5% and at type I error of 5% (Table 1).

Table 1: Calculation of sample size.

z	Expected proportion	d	z square	p (1-p)	d square	Sample size
Fosfomycin						
1.96	0.059	0.05	3.8416	0.055519	0.0025	85.31271616
Nitrofurantoin						
1.96	0.723	0.05	3.8416	0.200271	0.0025	307.7444294

Since the prevalence of previously reported resistance to various antibiotics is different, in the present study we calculated the required sample size for detecting fosfomycin and nitrofurantoin resistance (our main objective of this study), then chose the largest sample size thus obtained to ensure adequate power. Nevertheless the number of samples in the present study far exceeds the calculated sample size. No further statistics was used in our study.

Antibiotic susceptibility testing

Antimicrobial susceptibility testing of all isolates was performed on Mueller Hinton agar by Kirby-Bauer disk

diffusion method. Along with these, the susceptibility to the following antimicrobial agents was also performed as per clinical laboratory standards institute guidelines.[12] All the disc were obtained from Hi-Media Laboratories, Mumbai, India.

Enterobacterales isolates

Cotrimoxazole (1.25/23.75 µg), amikacin (30 µg), ceftriaxone (30 µg), ceftriaxone-sulbactam (75 µg,1:1), cefixime (5 µg), amoxicillin-clavulanic acid (20 µg/10 µg), fosfomycin (200 µg), nitrofurantoin (300 µg), norfloxacin (10 µg) and meropenem (10 µg) as the first line drugs. Pathogens resistant to these drugs were considered multi drug resistant (MDR) and were tested against second line drugs, piperacillin-tazobactam (100:10 µg), tobramycin (10 µg), imipenem (10 µg), polymyxin B (300 µg) and colistin (10 µg).

Pseudomonas species

Piperacillin-tazobactam (100:10 µg), meropenem (10 µg), colistin (10 µg), amikacin (30 µg), aztreonam (30 µg), cefepime (30 µg), nitrofurantoin (300 µg), gentamycin (10 µg), levofloxacin (5 µg) and ceftazidime (30 µg).

Staphylococcus isolates

Amikacin (30 µg), amoxicillin (20 µg), azithromycin (15 µg), vancomycin (30 µg), cefoxitin (30 µg), cotrimoxazole (1.25/23.75 µg), fosfomycin (200 µg), nitrofurantoin (300 µg) and norfloxacin (10 µg).

Enterococcus species

Ampicillin (10 µg), azithromycin (15 µg), doxycycline (30 µg), fosfomycin (200 µg), high content gentamycin (120 µg), high content streptomycin (300 µg), vancomycin (30 µg), nitrofurantoin (300 µg) and norfloxacin (10 µg).

Detection of metallo-beta-actamases

Imipenem/meropenem resistant isolates were tested phenotypically for metallo-beta-lactamases (MBL) via MCIM (modified carbapenemase inhibition method) and ECIM (EDTA carbapenemase inhibition method).[12]

Screening for methicillin resistance in Staphylococcus species

Test was performed on Muller Hilton agar with 4% NaCl using cefoxitin (30 µg) disc. Isolates showing a reduction in zone size <22 mm for *Staphylococcus aureus* and <25 mm for Other *Staphylococcus* species are considered resistant.[12]

Screening for high-level aminoglycoside resistance and vancomycin resistance in enterococci. In case of enterococci, high-level aminoglycoside resistance (HLAR) was detected using high content gentamycin (120 µg) and streptomycin (300 µg). Zone size ≥10 mm is considered as sensitive and zone size <6 mm (no zone) is considered to be resistant (HLAR).[12] and for the detection of VRE, 30 µg disc of vancomycin disc is used along with the routine susceptibility testing and zone of inhibition ≤14 are considered as VRE. Those with intermediate zones are confirmed by MIC methods.[12]

Definition of MDRs

MDR (Multi drug resistant) organisms are those which are resistant to any three different classes of antibiotics as defined by the previous guidelines.[13] In our study, it includes resistance to any three of the following groups-cephalosporins, fluoroquinolones, aminoglycosides, folate pathway inhibitors (trimethoprim-sulfamethoxazole) and nitrofurantoin.

RESULTS

Out of 9045 samples collected from outpatient department (OPD) and inpatient department (IPD) in 6 months of study period, 1788 (19.8%) samples were found positive with available sensitivity reports and were included in the data analysis. Overall, 1855 uropathogens were isolated from the positive samples (1721 samples were with single organism and 67 samples with 2 organisms). Maximum of the samples were of female patients 5909 (79.9%) with a female predominance of 3.9:1 among which most of them were of 21-40 years of age group as shown in Figure 1.

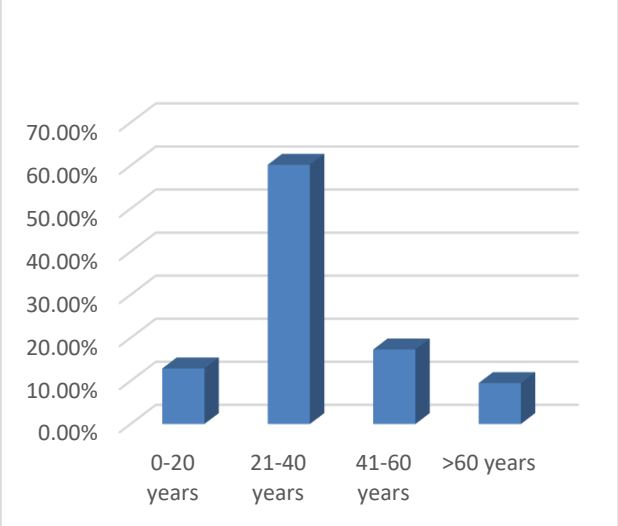

Figure 1: Age distribution in the study population.

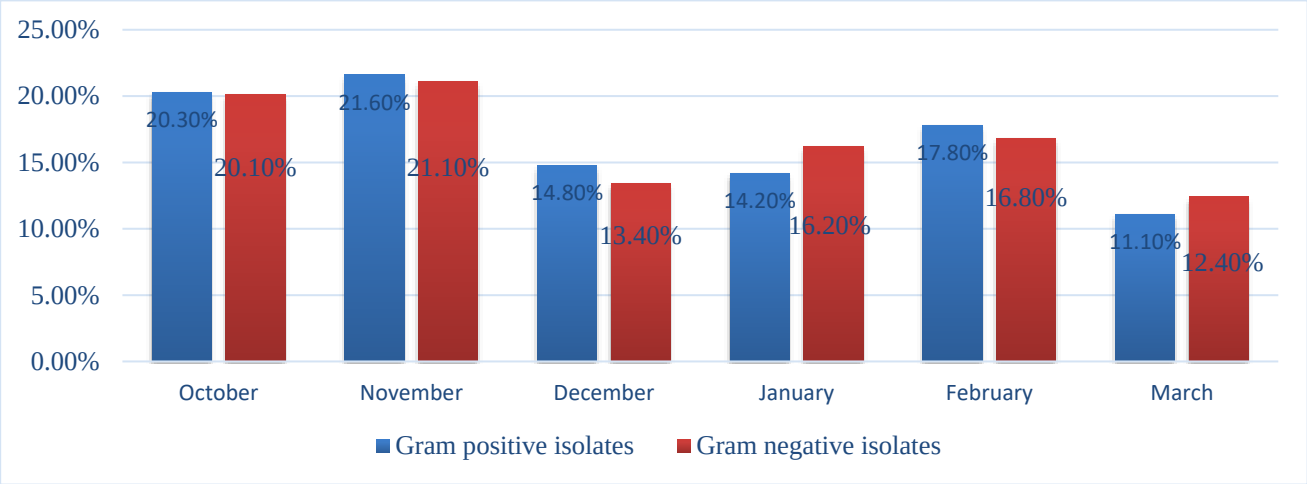

Figure 2: Month wise distribution of gram positive and gram negative isolates.

Out of 1855 urinary isolates, *E.coli* has been found to be the major pathogen which account for 775 (1.8%) followed by enterococcus species 400 (21.6%), *Klebsiella* species 232 (12.5%), *Citrobacter* species 109 (5.9%), *Staphylococcus aureus* 95 (5.1%), other *Staphylococcus* species 88 (4.7%), *Pseudomonas* species 73 (3.9%), *Proteus* 48 (2.6%), *Streptococcus* species 28 (1.5%) and *Acinetobacter* species 7 (0.4%). In present study, the gram negative bacilli contribute to 67.1% of the total bacterial isolates while gram positive cocci constituted 32.9%.

Antibiotic susceptibility patterns of most frequent uropathogens to different antibiotics are shown in Table 2 and 3. 63.2% of *Staphylococcus aureus* isolates were found to be methicillin resistant (MRSA) and 69.3% of other *Staphylococcus* species were also found to be as methicillin resistant (MRSS). Fortunately no VRSA was detected. Approximately, 31.3% of the enterococci were found to possess high level aminoglycoside resistance (HLAR) while 1.8% were VRE (vancomycin resistant enterococcus). Among the 1244 gram negative isolates, 429 (34.5%) were found to be as CRE (carbapenem resistant *Enterobacteriales*) out of which, 154 (36%) were detected as MBL (metallo beta lactamase producers), 188 (44%) were detected as serine carbapenemase producers via mCIM and eCIM testing and remaining had indeterminate results (not included in this study).

Among the injectable drugs tested, the gram negative isolates showed maximum resistance to cephalosporins (63.9%) then to amikacin (49%) and to meropenem (34.5%). But the gram positive isolates were mostly sensitive to vancomycin, the only injectable drug tested for it, showing just 1.1% resistance.

Among the oral drugs tested, gram negative isolates showed 92.4%, 66.7%, 54.7% and 29.7% resistance to amoxiclav, norfloxacin, cotrimoxazole and nitofurantoin respectively while just 7.8% resistance to fosfomycin. Although, tribe proteae is intrinsically resistant to nitrofurantoin but only showed 60.4% in vitro resistance to it. Furthermore, around 83.3% isolates were fortunately susceptible to fosfomycin which can be given as the oral antibiotic in the UTI caused by the tribe proteae. Nearly, 90% of the gram positive isolates were found resistant to azithromycin and norfloxacin but were just 12.6% and 5.5% resistance to nitrofurantoin and fosfomycin respectively.

Pseudomonas isolates showed 84.9% resistance to cefepime, 42.6% to ceftazidime, 41% to aztreonam, 32.8% to piperacillin-tazobatum, 24.6% to gentamycin, and 27.4% to levofoxacin. However, colistin was resistant in just 9.6% of these isolates. Thus, leaving behind colistin as the only option for treating the UTI caused by MDR *Pseudomonas* isolates.

Out of 1855 uropathogen isolated, 742 (40%) were multidrug resistant (MDR) and fosfomycin was the only drug showing susceptibility of 611 (82.3%) in those MDR isolates. Among the 429 CRE, 331 (77.1%) of the CRE isolates were susceptible to fosfomycin.

Table 2: Distribution of urinary pathogens in this study (n=1855).

Species	Number	Percentage (%)
Escherichia coli	775	41.8
***Enterococcus* species**	400	21.6
***Klebsiella* species**	232	12.5
***Citrobacter* species**	109	5.9
Staphylococcus aureus	95	5.1
Other *Staphylococcus* species	88	4.7
***Pseudomonas* species**	73	3.9
***Proteus* species**	48	2.6
***Streptococcus* species**	28	1.5
***Acinetobacter* species**	7	0.4
Total	1855	100

Table 3: Resistance pattern of the gram positive isolates in this study.

Antibiotics	*Staphylococcus aureus* (n=95)	Other *Staphylococcus* species (CONS) (n= 88)	*Enterococcus* species (n=400)	*Streptococcus* species (n=28)
	Resistance (%)	Resistance (%)	Resistance (%)	Resistance (%)
Ampicillin	-	-	253 (63.3)	13 (46.4)
Amikacin	18 (18.9)	7 (7.9)	-	
Cotrimoxazole	53 (55.8)	55 (62.5)	-	
Amoxicillin	57 (60.0)	55 (62.5)	-	
Azithromycin	74 (77.9)	71 (80.7)	376 (94.0)	24 (85.7)
Cefoxitin	60 (63.2)[MRSA]	61 (69.3)[MRSS]	-	
Doxycycline	-	-	309 (77.3)	17 (60.7)
Norfloxacin	75 (78.9)	72 (81.8)	363 (90.8)	21 (75.0)
High content gentamycin	-	-	*125 (31.3)	-
High content streptomycin	-	-	155 (38.8)	-
Vancomycin	0 (0.0)	0 (0.0)	7 (1.8)[VRE]	0 (0.0)
Nitrofurantoin	9 (9.5)	9 (10.2)	55 (13.8)	4 (14.3)
Fosfomycin	7 (7.4)	4 (4.5)	22 (5.5)	0 (0.0)

*In *Enterococcus* species, 125 (31.3%) of isolates are HLAR and 7 (1.8%) are VRE.

Table 4: Resistance pattern of the gram negative isolates in this study.

Organ-isms	Ak (%)	Am-c (%)	Cf-m (%)	Ctr (%)	Cot (%)	Nx (%)	Mr-p (%)	Nit (%)	Fo (%)	At (%)	Cp-m (%)	Ca-z (%)	Ge-n (%)	Pit (%)	Le (%)	Cl (%)
***E. coli* (n=775)**	409 (52.8)	759 (97.9)	555 (71.6)	550 (70.9)	473 (61.0)	587 (75.7)	281 (36.3)	176 (22.7)	46 (5.9)	-	-	-	-	-	-	-
***K. pneu-monia* (n=232)**	105 (45.3)	230 (99.1)	134 (57.8)	131 (56.5)	115 (49.6)	141 (60.8)	77 (33.2)	118 (50.9)	30 (12.9)	-	-	-	-	-	-	-
***Citro-bacter species* (n=109)**	45 (41.3)	109 (100)	75 (68.8)	80 (73.4)	60 (55.0)	73 (66.9)	36 (33.0)	44 (40.4)	14 (12.8)	-	-	-	-	-	-	-
***Proteus species* (n=48)**	30 (62.5)	45 (93.8)	28 (58.3)	30 (62.5)	31 (64.6)	27 (56.3)	14 (29.2)	29 (60.4)	8 (16.7)	-	-	-	-	-	-	-
***Acinet-obacter species* (n=7)**	2 (28.6)	7 (100)	4 (57.1)	4 (57.1)	1 (14.3)	2 (28.6)	2 (28.6)	3 (42.9)	0 (0)	-	-	-	-	-	-	-
***Pseudo-monas* (n=73)**	19 (26.0)	-	-	-	-	-	19 (26.0)	56 (76.7)	-	30 (41.1)	62 (84.9)	31 (42.5)	18 (24.7)	24 (32.9)	20 (27.4)	7 (9.6)

Abreviation: Ak- amikacin, Amc- amoxicillin + clavulanic acid, Cfm- cefixime, Ctr- ceftriaxone, Cot- cotrimoxazole, Nx- norfloxacin, Mrp- meropenem, Nit- nitrofurantoin, Fo-fosfomycin, At- aztreonam, Cpm- cefepime, Caz- ceftazidime, Gen- gentamycin, Pit- piperacillin + tazobactum, Le- levofloxacin, Cl- colistin

DISCUSSION

This study was conducted to evaluate the potential of certain older antibiotics in the treatment of UTIs, especially against MDR pathogens. Our study showed a high prevalence of UTI in females (79.9%) than in males (20.1%) which correlate with findings from other studies.[14-16] The reason behind this high prevalence of UTI in females is due to close proximity of the urethral meatus to the anus, shorter urethra, sexual intercourse, incontinence, and bad toilet.[14] Higher incidence was observed in middle age females, i.e. in reproductive age group (21-40 years). Similar observation has been reported by Devanand et al.[14] In our study, *E. coli* (41.8%) was the most common pathogen which is consistent with the other previous reports.[17,18] However, enterococcus species

(21.6%) as the second common uropathogen has also been reported by Patel et al in their study.[19] The gram negative bacilli contribute to 67.1% of the total bacterial isolates while gram positive cocci constituted 32.9%. Higher incidence of gram negative bacteria, in causing UTI has many factors which are responsible for their attachment to the uroepithelium such as they are able to colonize in the urogenital mucosa with adhesins, pili, fimbriae, and P-1 blood group phenotype receptor.[14]

Prevalence of MDR in our study was 742 (40%) which is similar to the findings of Banergee et al who found 42.7% of MDRE isolates in his study.[20] The prevalence of CRE was higher (36.3%) in our study which is consistent with the study of Patel et al.[18] But, other authors have found just 3.8% and 11.1% of CRE in their studies.[20,21] Among the 429 CREs, 154 (36%) were detected as MBL via mCIM and eCIM testing. As per our knowledge, no other report has been found on uropathogens depicting such findings till date. Among the gram-positive bacteria, a high percentage of methicillin resistant Staphylococcus species (63.2%) which is much lower than that reported by Sofia Maraki et al in their study.[22] The prevalence of HLAR was 31.3% in this study was found higher than reported in 2011 from same institute but is consistent with the findings of 2015 study, pointing towards exonerable increase in drug resistance.[23,24] However, the prevalence of VRE is fortunately low (1.8%) this time as compared to reports of other studies.[18,22,23]

The antimicrobial resistance pattern of *E. coli* (the most common uropathogen of this study) is comparatively discussed with the pattern of resistance in *E.coli* in the studies in and outside India in Table 5. Most of the results are comparable with others and somewhat higher resistance in amoxiclav and meropenem may be because of the prolonged antibiotic usage as most patients in our tertiary care centre are referred ones who had already taken antibiotics before.[24-26]

The current study demonstrated considerable resistance to oral antibiotics like cotrimoxazole (61%) and norfloxacin (75.7%), which concur with reports of other studies.[27,28] The other two oral antibiotics, which were tested in this study were nitrofurantoin and fosfomycin. Overall, in the gram negative isolates (1244), nitrofurantoin was found to be susceptible in 874 (70.3%) of the isolates and fosfomycin was susceptible in 1146 (92.2%) of them. Among the gram positive isolates (611), nitrofurantoin was still sensitive in 534 (87.4%) of the isolates and fosfomycin was found sensitive in 578 (94.6%) of them. This susceptibility pattern gives us an impact that although, resistance to nitrofurantoin has increased in recent years as compared to our previous report but it was still found effective in significant number of gram positive and negative isolates (except MDRs).[23]

Among the most common gram negative isolates, 94.1% of the *E.coli* isolates were susceptible to fosfomycin, 87.1% of *Klebsiella* species were susceptible to fosfomycin. These findings are very similar to the studies of Rajenderan et al and Sahni et al.[29,30] Among the gram positive isolates, 94.5% of Enterococcus species were susceptible to fosfomycin. Similarly, Patel et al found 97.2% of their enterococcus isolates to be susceptible to fosfomycin.[19]

Among the total 742 MDR isolates, 611(82.3%) were susceptible to fosfomycin which is consistent with the findings of other authors.[20] Also, 88.3% of MRSA and 82.4% of the HLAR were susceptible to fosfomycin. These findings corroborate to that of Maraki et al, who found Fosfomycin to be effective in 100% of MRSA and HLAR.[22] Our previous study of 2015 also had the similar susceptibility results of fosfomycin on MRSA and HLAR.[23] Out of 429 CREs, 331(77.2%) were susceptible to fosfomycin. Similarly, Banergee et al found 89.1% of CREs to be susceptible to fosfomycin.[20] Despite of these reports of high percentage of in vitro susceptibility of Fosfomycin, it is an underrated agent for complicated UTI cases though urinary concentration and safety profile is way above many other commonly prescribed antibiotics for the MDRE and CRE pathogens.[31]

Table 5: Comparative findings of the resistance pattern of *E. coli* (most common uropathogen) with the studies within and outside India.

Author	Country	Sample size	Cot	Nx	Mrp	Nit	Fo	Amc
Present study, 2019-2020	India	1788	61%	75.7%	34.5%	22.7%	5.9%	97.9%
Patel et al[17], 2019-2020	India	1401	32.0%	-	91.9%	72.3%	-	-
Pardeshi et al[20], 2018	India	584	46.2%	71.7%	3.8%	20.4%	-	48.4%
Banergee et al[19], 2017	India	345	51.8%	-	11.1%	21.3%	1.9%	67.6%
Zahrani et al[24], 2016	Saudi Arabia	179	72.2%	-	0%	30.5%	-	45.8%
Pouladfar et al[25], 2016	Iran	202	86.5%		1.9%	67.3%	-	-

CONCLUSION

Fosfomycin and nitrofurantoin are antimicrobial agents which are still found effective. The extraordinary antimicrobial activity of fosfomycin, against MDR strains, makes it an effective and safe drug in the treatment of UTIs in which previous antibiotics (cotrimoxazole, nitrofurantoin) have failed to cure the infection or when the patients are intolerant to the first‑line treatment agents.

As the resistance is increasing day by day, fosfomycin should be reserved for the UTI caused by MDR isolates (MBL, CRE, HLAR, MRSA and VRE). For empirical treatment drugs like cotrimoxazole, norfloxacin and nitrofurantoin should be preferred depending on the prevailing susceptibility pattern of uropathogens. Imprudent empirical use of fosfomycin should be contained because this injudicious use can further lead to the development of high resistance for fosfomycin in the coming days.

This study provides important data regarding the role of nitrofurantoin and fosfomycin in uropathogens. Susceptibility of nitrofurantoin has somewhat reduced but fosfomycin is still working in the MDR isolates. So, justifiable use of antimicrobial agents is need of the hour.

Limitations

This study was done for the evaluation of in vitro activity of fosfomycin and not a clinical evaluation of efficacy. There were very few enterobacteriaceae isolates other than *E. coli* and *K. pneumoniae* found in the study. Resistance of fosfomycin needs to be confirmed by molecular methods.

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