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Approach To Combat Multidrug Resistance Urinary Tract Infections: Evaluating Alternative Therapies Amidst Limited Antibiotic Options

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ABSTRACT

Introduction – Urinary tract infection (UTI) is the significant public health concern, affecting millions world wide and leading to substantial prescription. The primary pathogen responsible for UTI is Escherichia coli (E. coli) which accounts for nearly 70% cases[1]. Irrational use of antibiotics leads to emergence of multidrug resistance which poses a challenge to clinicians especially regarding the carbapenems group of antibiotics. With few new antibiotics expected in the next five to ten years, we need to use current antibiotics wisely and reconsider older ones like nitrofurantoin and Fosfomycin to combat resistance.

Methodology – The study was carried out in the Department of Microbiology, Bengaluru at our tertiary care hospital. The aim was to conduct a retrospective analysis comparing multidrug-resistant (MDR) and non-MDR isolates with respect to their susceptibility to Fosfomycin and Nitrofurantoin. The isolates were obtained from positive urine culture showing significant growth ($\geq 10^5$ CFU/mL). Isolates were classified as multidrug-resistant if they exhibited resistance to at least one antibiotic in three or more different classes of antibiotics. The efficacy of Fosfomycin and Nitrofurantoin were evaluated against these resistant strains, which is crucial for guiding treatment decisions in clinical practice, particularly for urinary tract infections. This also highlights the ongoing challenge of antibiotic resistance in healthcare settings, emphasizing the need for effective antibiotic stewardship programs to manage and mitigate the spread of resistant pathogens.

Results – *E.coli* was the most common Enterobacteriaceae to be isolated (71.59%) followed by Klebsiella pneumoniae (10.27%) and Pseudomonas aeruginosa(6.25%). High susceptibility was noted to fosfomycin and Nitrofurantoin, with only 3% and 19.3% of the isolates shows resistance pattern respectively. Highest resistance was noted against ampicillin with 1119 (86.4%) being resistant followed by Ciprofloxacin (68.2%), Cefotaxime (65.2%), Ceftriaxone (63.1%). Approximately 51.3% of the *E.coli* isolates were found

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to be multi-drug resistant. There was no significant difference in the resistance rates to fosfomycin among the MDR (3.77%) and non-MDR isolates (2.22%, p>0.05), while 20.46% of the MDR isolates and 8.24% of non-MDR isolates were resistant to Nitrofurantoin (p<0.001)

Conclusions – This study demonstrates the effectiveness of fosfomycin against both MDR and non-MDR urinary *E. coli* isolates, with resistance rates remaining as low as 4% regardless of MDR status. While nitrofurantoin showed good overall activity, its effectiveness was notably reduced against MDR strains (20.46% resistance) compared to non-MDR strains (8.24% resistance). These findings support the use of fosfomycin as a reliable first-line treatment option for uncomplicated UTIs, even in settings with high MDR prevalence. The study reinforces the value of reconsidering older antibiotics as viable treatment options in the era of increasing antimicrobial resistance.

Key Words – Escherichia coli, Nitrofurantoin, Fosfomycin, Drug resistance, urinary tract Infection

INTRODUCTION – Urinary tract infections (UTIs) pose a significant global health challenge which affects millions of individuals placing significant strain on global healthcare system worldwide. *Escherichia coli* (*E. coli*) emerges as the predominant pathogen, responsible for approximately 70% of all UTI cases, making it the primary target for clinical intervention[1]. The rising threat of antimicrobial resistance has transformed UTI from a relatively manageable condition to a complex clinical challenge. A recent study from Karnataka, India reported fluoroquinolones resistance surpassing 65% and ampicillin resistance surpassing 85%.[2] This compels the health care workers for a much better strategic approach to curb the irrational use of antibiotics.

The diminishing pipelines for novel antibiotics, with new medications not expected to enter the market for the next five years, along with the increasing compromise of traditionally used treatment protocols, compel medical professionals to re-evaluate therapeutic strategies. This urgency is driven by the rising trend of multidrug resistance (MDR), particularly within the carbapenem group of antibiotics[3]. Consequently, there is a critical need to explore and develop innovative solutions to address the growing challenge of antibiotic resistance and ensure effective patient care.

Nitrofurantoin and Fosfomycin have emerged as promising alternatives, particularly for lower urinary tract infections. These medications offer potential advantages in combating resistant bacterial strains while providing targeted treatment[3,4]. Infection prevention and control plays a crucial role in the

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management of UTI which includes improved hygiene, increased doctor-nurse-patient education, rational use of antibiotics, in house antibiotic policy and robust surveillance methods[4].

Urinary tract infections remain as one of the most common reason to look for medical attention which may be presented as complicated UTI and uncomplicated UTI. The latter occurs in healthy woman who are sexually active or after menopause. In contrast, complicated UTIs are associated with factors such as urinary obstruction (e.g., kidney stones, prostate enlargement), catheterization, impaired voiding, metabolic disorders, or immunocompromised states, such as renal transplantation[5]. There are number of etiological agents are responsible for causing the UTI, the commonest being the *E. coli*, specially Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* which is increasingly reported in both hospital and community settings causing menace to healthcare workers. The rise of multidrug-resistant and carbapenem-resistant strains further complicates treatment. Other microbial agents include *Klebsiella* spp., *Proteus* spp., *S.saprophyticus*, *Enterococcus* spp. And *P.aeruginosa* etc

According to the data released by Indian Council of Medical Research – Antimicrobial Resistance Surveillance Network (ICMR – AMRSN), 2018, resistance rates for commonly used oral antibiotics are alarmingly high with levofloxacin (73.4%), ciprofloxacin (72.1%), and cotrimoxazole (60.6%). However, older antibiotics such as nitrofurantoin (14% resistance) and fosfomycin (11.9% resistance) remain relatively effective[4]. The ICMR Treatment Guidelines for Antimicrobial Use in Common Syndromes 2019 recommends nitrofurantoin or Fosfomycin as first-line options for acute cystitis, with cotrimoxazole, ertapenem, or amikacin as alternatives[5]. In cases of suspected pyelonephritis or prostatitis, these drugs should be avoided in favor of piperacillin-tazobactam or ertapenem, with imipenem, meropenem, or amikacin as alternatives. The resistance pattern varies based on various factors like patient demographics, location, prior antibiotic exposure, hospital associated or community acquired etc[5].

The prudent use of antibiotics and reconsideration of older options like nitrofurantoin and Fosfomycin are vital to combating further resistance, as there is a rapid emergence of antimicrobial resistance and the limited development of new antibiotics, optimizing current treatments is crucial. This study aims to assess the antimicrobial susceptibility of *E. coli* from urine samples, with a specific focus on resistance to these key oral antibiotics.

MATERIALS AND METHODS – After obtaining the approval from the institutional ethical committee, a retrospective study was conducted in department of Microbiology, MVJ Medical College and Research

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Hospital from March 2021 - April 2022. The study included all the urine samples that were received in the laboratory and processed according to standard microbiological techniques. Significant bacteriuria was defined as $\geq 10^5$ CFU/mL of a single organism. Bacterial identification was performed using the VITEK® 2 COMPACT system (bioMérieux, France) following manufacturer's guidelines and quality control procedures. Antimicrobial susceptibility testing was performed using the VITEK® 2 system, and results were interpreted according to Clinical and Laboratory Standards Institute CLSI 2021 guidelines[6]. Quality control was performed using E. coli ATCC 25922 strains The data were retrieved from hospital records which include information like patient age, sex, clinical history and symptoms, bacterial isolates identified, antibiotic susceptibility pattern etc.

E.coli isolates resistance to Ampicillin, Amoxicillin-Clavulanic acid, Ciprofloxacin, Norfloxacin, Cotrimoxazole, Fosfomycin and Nitrofurantoin etc. were taken into consideration. The organism which was resistance to at least three classes of antibiotics including Penicillin's, beta-lactam/beta-lactamase inhibitors, fluoroquinolones, and trimethoprim-sulphonamides combinations[7,8]. The susceptibility of MDR and non-MDR isolates to Fosfomycin and Nitrofurantoin to *E.coli* was compared. Data were systematically entered into google spread sheet analysed using SPSS version 25.0. Chi-square test was used to compare resistance patterns between MDR and non-MDR isolates. P-values <0.05 were considered statistically significant.

Inclusion criteria:

a. All urine samples processed in the microbiology laboratory
b. Patients of all ages and genders with positive urine cultures
c. Isolates identified as E. coli

Exclusion criteria:

a. Samples with mixed bacterial growth or contaminants
b. Urine cultures showing no significant bacterial growth
c. Patients with incomplete clinical or microbiological records

RESULTS – The microbiology laboratory received 6678 urine samples for culture and sensitivity over a period of 14 months from March 2021 to April 2022. Out of the total samples received, 1295 (19.39%, 95% CI : 18.4-20.4) samples yield positive growth, while 113 (8.72%) samples had 2 or more organisms, 75.1% or the samples (n = 5012) yield no growth and 371(5.5%) samples had mixed flora. The number of

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females patients' samples received is 738 (56.98%) while the males is 557 (43.01%). *Escherichia coli* (71.59%) was the most common Enterobacteriaceae to be isolated, followed by *Klebsiella pneumoniae* (11.43%) and *Pseudomonas aeruginosa* (6.25%). The other species of microbial agents responsible for causing UTI which were isolated in our laboratory are shown in Table 1

Table 1 – List of Microorganisms isolated from Urine culture

Name of the Isolate	Number of Isolates	Percentage (95% CI)
Escherichia coli	927	71.59 (69.1-74.0)
Klebsiella pneumoniae	133	10.27 (8.7 -12.0)
Klebsiella oxytoca	15	1.16 (0.7-1.9)
Pseudomonas aeruginosa	81	6.25 (5.0 -7.7)
Enterococcus faecalis	39	3.01 (2.2 - 4.1)
Enterococcus faecium	15	1.16 (0.7 - 1.9)
Enterobacter aerogenes	23	1.78 (1.2 - 2.6)
Enterobacter cloacae	13	1.00 (0.6 - 1.7)
Citrobacter koseri	4	0.31 (0.1 - 0.8)
Citrobacter freundii	9	0.69 (0.4 - 1.3)
Proteus mirabilis	18	1.39 (0.9 - 2.2)
Morganella morganii	5	0.39 (0.2 - 0.9)
Acinetobacter baumannii	9	0.69 (0.4 - 1.3)
Staphylococcus saprophyticus	4	0.31 (0.1 - 0.8)
Total	**1295**	**100**

Among E. coli isolates, resistance was highest for Ampicillin (86.4%) followed by Ciprofloxacin (68.2%), Cefotaxime (65.2%), Ceftriaxone (63.1%), Ceftazidime (61.7%) were observed. Fosfomycin resistance low at 3% whereas the resistance to Nitrofurantoin increased up to 19.35%. The details of Antibiotic susceptibility pattern are mentioned in table 2

Table 2 – Antibiotic susceptibility pattern for E. coli isolated from urine samples

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Antibiotic	**Sensitive**		**Intermediate**		**Resistance**	
	Number	(%) age	Number	(%) age	Number	(%) age
Ampicillin	109	8.4 %	67	5.2 %	1119	86.4 %
Ciprofloxacin	290	22.4 %	122	9.4 %	883	68.2 %
Amoxicillin Clavulanic acid	443	34.2 %	97	7.5 %	755	58.3 %
Cotrimoxazole	528	40.7 %	89	6.9 %	678	52.4 %
Ceftriaxone	371	28.6 %	107	8.3 %	817	63.1 %
Ceftazidime	391	30.2 %	105	8.1 %	799	61.7 %
Cefepime	512	39.5 %	133	10.3 %	650	50.2 %
Cefotaxime	349	26.9 %	102	7.9 %	844	65.2 %
Meropenem	1097	84.7 %	75	5.8 %	123	9.5 %
Imipenem	1113	85.9 %	80	6.2 %	102	7.9 %
Gentamicin	671	51.8 %	83	6.4 %	541	41.8 %
Amikacin	1125	86.8 %	63	4.9 %	107	8.3 %
Fosfomycin	1194	92.2 %	62	4.8 %	39	3 %
Nitrofurantoin	948	73.1 %	97	7.5 %	250	19.3%
Colistin	269	98.0 %	10	0.8 %	16	1.2 %

Among the 1,295 Escherichia coli isolates, 51.3% were multidrug-resistant (MDR). A very high susceptibility was noted for fosfomycin and nitrofurantoin, with only 3% and 19.3% of the isolates being resistant, respectively. The highest resistance was observed against ampicillin (86.4%), followed by ciprofloxacin (68.2%), cefotaxime (65.2%), ceftriaxone (63.1%), ceftazidime (61.7%), and amoxicillin-clavulanic acid (58.3%). Carbapenems remained highly effective, with meropenem (84.7% susceptible) and imipenem (85.9%) susceptible showing minimal resistance (9.5% and 7.9%) respectively excluding Fosfomycin and Nitrofurantoin.

Table 3 – Comparative analysis of Fosfomycin vs Nitrofurantoin against *E.coli*

Antibiotic	**Category**	**MDR *E. coli* (n = 664)**	**Non-MDR *E. coli* (n = 631)**
Fosfomycin	Sensitive (%)	620 (93.37%)	607 (96.20%)

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	Intermediate (%)	19 (2.86%)	10 (1.58%)
	Resistant (%)	25 (3.77%)	14 (2.22%)
Nitrofurantoin	Sensitive (%)	397 (59.79%)	539 (85.42%)
	Intermediate (%)	78 (11.75%)	40 (6.34%)
	Resistant (%)	136 (20.46%)	52 (8.24%)

The table 3 compares the effectiveness of two antibiotics, Fosfomycin and Nitrofurantoin, against Multidrug-Resistant (MDR) and Non- Multidrug-Resistant (non MDR) E. coli strains. Most of the E. coli strain including MDR and Non MDR are sensitive to Fosfomycin. In contrast, for Nitrofurantoin, 59.79% of MDR E. coli and 85.42% of Non-MDR E. coli strains are sensitive, 11.75% and 6.34% show intermediate sensitivity, and 20.46% and 8.24% are resistant, respectively. Overall, Fosfomycin shows higher effectiveness against both MDR and Non-MDR E. coli strains compared to Nitrofurantoin, which is less effective particularly against MDR E. coli strains.

DISCUSSION – Most common organism to be isolated from patients who have urinary tract infection is *E. coli* accounting for two third of all urinary isolates[3,9]. Antimicrobial resistance has emerged due irrational and wide spread use of antibiotics. The bacteria uptake the resistance gene by various genetic transfer viz transformation, transduction, conjugation etc. These mutated bacteria are capable of producing penicillinases, cephalosporinases, and extended-spectrum β-lactamases (ESBLs) and more recently, the production of carbapenemases which has led to resistance against carbapenems such as imipenem, meropenem, ertapenem, and doripenem. These carbapenems were previously considered the drugs of choice for treating ESBL-producing organisms but with rise of frequent MDR strains, it is causing menace to the health care system[7-10]. With the rapid rise in antibiotic resistance and a limited pipeline of new antimicrobial agents, there is a renewed interest in re-evaluating older, underutilized antibiotics like Fosfomycin and nitrofurantoin as potential alternatives to combat resistant bacterial infections. Fosfomycin, originally discovered in Spain in 1969, its oral formulation, fosfomycin trometamol, became available in 1995[10,11]. Introduced into clinical practice in 1952, nitrofurantoin remains a highly effective treatment for UTIs, both fosfomycin and nitrofurantoin have significant advantages, including high urinary concentrations, minimal impact on gastrointestinal flora, and a low potential for resistance development, making them valuable choices for the management of uncomplicated UTIs.

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In the present study, we analyzed the in vitro susceptibility of *E.coli* to commonly prescribed antibiotics like Ampicillin, Amoxicillin-Clavulanic acid, Ciprofloxacin, Norfloxacin Nitrofurantoin and Fosfomycin etc. Our study indicates high resistance rates to Ampicillin (86.4%) followed by Ciprofloxacin (68.2%), Cefotaxime (65.2%), Ceftriaxone (63.1%), Ceftazidime (61.7%), Amoxicillin Clavulanic acid (58.3%) which correlates with various other studies in India. In a study conducted in Puducherry, Niranjan V et al reported high levels of resistance to ampicillin (88.4%), norfloxacin (74.2) and co-trimoxazole (64.2%)[12]. Similar observations were reported in yet another study by Kothari et al. with highest resistance to amoxicillin (82.3%), followed by co-trimoxazole (70%), ciprofloxacin (64.2%) and Amoxycillin/Clavulanate (58.4%).[13] A study from Puducherry, reported higher rates of resistance to Norfloxacin and cotrimoxazole of 77.6% and 73.4 % respectively among urinary isolates of *E.coli*.[14] The result of yet another study from southern part of India by Sabharwal et al., which almost coincides to our findings reported 2.8% of *E.coli* isolated from urine samples were resistant to Fosfomycin and high resistance is noted against Amoxycillin/Clavulanate, Norfloxacin, Ciprofloxacin and Cotrimoxazole[15]. High resistance rates to these oral antibiotics may be due to irrational and uncontrolled use of these antibiotics over the past decade. Low resistance (1.86%) to Fosfomycin among urinary *E.coli* was also reported by Banerjee S et al. from eastern part of India, while a study from northern part of India found all the *E.coli* isolates tested were susceptible to fosfomycin.[16,17] Over 85% of our isolates were susceptible to Nitrofurantoin which correlates with several other studies from India and worldwide.[10,12,14,18] The high susceptibility of Escherichia coli to Nitrofurantoin may be due to limited use of the antibiotic because of its narrow spectrum of activity, limited indication, narrow tissue distribution and limited contact with bacteria outside the urinary tract[19]. Multi drug resistance *E.coli* not only increases the cost of treatment and morbidity but also mortality in severe cases.[2]

In our study 51.3% were MDR isolates and a study conducted in a tertiary care hospital in North eastern Karnataka found 43% of their isolates to be MDR which correlates with the result of our study.[2] Similar findings were also reported by Das B et al from northern part of India.[20] Our study also found that the resistance to Fosfomycin remains low even among the MDR isolates while resistance to Nitrofurantoin is more among MDR isolates when compared to non-MDR isolates. This corelates with the findings of the study by Gopichand et al who reported that fosfomycin retained the inhibitory effect on MDR isolates as

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well and Sultan A et al who reported that MDR Escherichia coli exhibited a decreased susceptibility to Nitrofurantoin.[21,22]

CONCLUSIONS – The study shows that Fosfomycin is efficacious and maintains high susceptibility against strains that are MDR (93.37%) and non-MDR (96.20%). This difference suggests Fosfomycin unique mechanism which prevents bacteria to develop resistance. While nitrofurantoin also showed good overall activity, its effectiveness was more significantly impacted by MDR status, with resistance rates of 20.46% in MDR strains compared to 8.24% in non-MDR strains. Fosfomycin emerges as a reliable first-line treatment option for uncomplicated UTIs, regardless of suspected MDR status whereas Nitrofurantoin remains a viable alternative, particularly for non-MDR infections, but should be used with caution in settings with high MDR prevalence. To conclude this study provides strong evidence supporting continued use of fosfmycin and nitrofurantoin in treatment of urinary tract infections

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