Nitrofurantoin and Fosfomycin, effective oral empirical treatment options against multidrug resistant Escherichia coli

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Author's Contribution

[1,6] Conception of study
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Abstract

Objective: The present study is designed to monitor the antibiotic susceptibility pattern of *Escherichia coli* to assist in forecasting empirical therapy of urinary tract infection.

Materials and Methods: It is a retrospective cross-sectional study. It was carried out at Dow Diagnostic Research and Reference Laboratory for a period of 3 months from February 2017 to April 2017. Data of a total of 5000 urine culture and sensitivity test reports were taken from the medical record. The data were analyzed by SPSS version 16.

Results: Out of 5000 urine samples processed, 1565 showed significant bacterial growth. *Escherichia coli* was the most common pathogen isolated. Meropenem, Amikacin, Fosfomycin, and Nitrofurantoin respectively were found to be the most effective antibiotics against *Escherichia coli*.

Conclusion: Fosfomycin and Nitrofurantoin are effective oral antibiotics against *Escherichia coli* causing urinary tract infection. The present study may help clinicians in making a rational choice of empirical treatment of the patients.

Keywords: Antibiotic resistance, Antibiotic susceptibility, Bacteria, *Escherichia coli*, Urinary tract infection.

Introduction

Urinary tract infection (UTI) is among the most common bacterial infections affecting all age groups.[1] It has been estimated that UTIs cause around 8.1 million visits to health care personnel annually presenting as one of the major reasons for global economic burden.[2] Prevalence of UTI is affected by multiple factors such as old age, poor personal hygiene, pregnancy, urinary catheterization, genitourinary tract abnormalities, and co-morbidities like diabetes, HIV infection.[3] UTIs affect both genders but it is more common in the female population. It has been assessed that more than 50% of all women experience at least one UTI during their lifetime, with 20–30% presenting with recurrent UTI due to their anatomy and reproductive physiology.[4] Clinically UTI may present as asymptomatic, acute, chronic, complicated, or uncomplicated depending upon the type of infectious agent, part of urinary tract involved, and patient's immune response.[5] Most UTIs are treated empirically based on the culture and sensitivity pattern generated by regional microbiology laboratories. The spectrum of antimicrobial susceptibility of UTI pathogens varies from time to time and in different geographic areas. Therefore regular monitoring of the antibiotic susceptibility pattern of uropathogens is very important. However, due to the indiscriminate use of antibiotics, there is high emergence of antibiotic resistance among urinary pathogens making it a major public health problem.[6]

At present, new antibiotics that have been approved, are mostly for parental use, so for oral empirical treatment, we have very limited options. Literature search shows that multidrug-resistant *Escherichia coli* (*E. coli*) still retains susceptibility to two oral antibiotics are Nitrofurantoin and Fosfomycin. Both maintain high urinary concentration and minimal toxicity in comparison to newer antibiotics and have been considered as safe and effective drugs for the treatment of uncomplicated urinary tract infection in women.[7]

With this background, a study is designed to determine the antibiotic susceptibility pattern of *E. coli* which may help in prescribing effective empirical treatment of urinary tract infection.

Materials and Methods

This retrospective cross-sectional study was conducted in the Microbiology section of DDRRL. Urine culture and sensitivity reports were collected from medical records of the Microbiology section of DDRRL after taking approval from Institutional Review Board (IRB) having Reference No. IRB-1794/DUHS/Approval/2021. This retrospective data record is maintained by the database of LIS (Laboratory Information System) under the supervision of Director DDRRL. The data contains information about the patient's age, gender, isolated organism, and antibiotic susceptibility pattern. The culture reports included samples from both inpatient and outpatient departments during a period from February 2017 to April 2017. A sample size of 5000 subjects was taken which achieved 98% power to detect a difference of 3.9% between two diagnostic tests (Fosfomycin & Nitrofurantoin) whose sensitivities were 95.8% and 91.9% respectively. This procedure used PASS version 15 software, a two-sided McNemar test with a 95% confidence interval. The prevalence of disease in the population was 73.2%. The proportion of discordant pairs was 35.1%.

All samples having information regarding the patient's age, gender, and isolated organism were included in the study. However antibiotic susceptibility of antibiotics against only *E. coli* is included in the study. Samples having a lack of the above-mentioned information were excluded from the study as well as antibiotic susceptibility against organisms other than *E. coli* is excluded from the study. Urine culture samples were processed as per standard microbiological procedures and antibiotic susceptibility testing by Disk Diffusion method was performed according to CLSI guidelines 2021.[8] The antibiotic discs used for susceptibility testing against *E. coli* included Amoxicillin / Clavulanic acid 30μg, Ampicillin 10μg, Amikacin 30μg, Meropenem 10μg, Piperacillin / Tazobactam 110μg, Gentamicin 10μg, Ceftriaxone 30μg, Cefuroxime 30μg, Ciprofloxacin 5μg, Cotrimaxazole 25μg, Cefixime 5μg, Nitrofurantoin 300μg and Fosfomycin 200μg. The data was entered in SPSS version 16 and statistical analysis was done. Descriptive statistics were measured in percentages.

Results

In the present study, a total of 5000 urine culture and sensitivity test report data was taken from medical records for a period of 3 months from Feb 2017 to April 2017. Out of them, 1565 (31.3%) urine samples were found positive for bacterial growth. Amongst these, 3303 (66%) samples were of female patients and 1697 (34%) samples were of male patients. The

frequency of significant bacterial growth was much greater in the patients between 51-60 years of age followed by 21-30 years of age as compared to other age groups. (Figure 1)

Among the isolated microorganisms, Gram-negative bacteria 1282 (81%) were more than Gram-positive bacteria 283 (18%). Of the gram-negative bacteria, the most frequent isolate was *E. coli* 938 (73%). (Table 1) *E. coli* was found highly sensitive to Meropenem, Amikacin, Fosfomycin, and Nitrofurantoin respectively. (Table 1)

Age wise distribution of uropathogens %
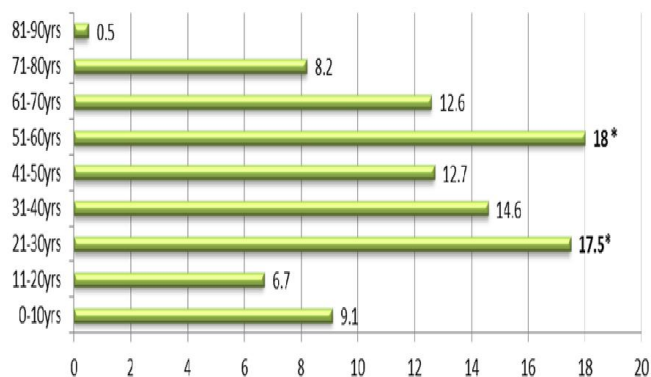
* Showing a high percentage of uropathogens in age groups

Figure 1: Age-wise distribution of uropathogens in %

Table I: Bacteria isolated from urine samples

Total Bacterial growth	1565		
Gram Negative Bacteria	n=1282 (81.9%)	**Gram Positive Bacteria**	n=283 (18.1%)
Name of Bacteria	**Frequency**	**Name of Bacteria**	**Frequency**
Escherichia coli	938 (73.2%)	*Enterococcus*	158 (56%)
Klebsiella species	160 (12.5%)	*Streptococcus D*	57 (20.1%)
Pseudomonas aeuroginosa	47(3.7%)		
Citrobacter species	42 (3.3%)	*Staphylococcus species*	28 (9.9%)
Enterobacter species	35 (2.7%)		
Proteus mirabilis	19 (1.5%)	*Streptococcus species*	28 (9.9%)
Acinetobacter species	16 (1.3%)		
Pseudomonas species	10 (1%)	*Staphylococcus aureus*	12 (4.2%)
Proteus vulgaris	10 (1%)		

Table 2: Resistant pattern of E. coli in %

Antibiotics	Escherichia coli N=938
Ampicillin	806 (86%)
Amoxicillin/clavulanic acid	445 (47.5%)
Piperacillin/tazobactam	140 (15%)
Ceftriaxone	684 (73%)
Cefixime	684 (73%)
Cefuroxime	684 (73%)
Meropenem	28 (3%)*
Gentamicin	318 (34%)
Amikacin	48 (5.2%)*
Ciprofloxacin	590 (63%)
Cotrimoxazole	647 (69%)
Fosfomycin	39 (4.2%)*
Nitrofurantoin	75 (8.1%)*

*Microorganisms showing significant sensitivity to antibiotics.

Discussion

This study has emphasized on antimicrobial susceptibility pattern of *E. coli*. This may help physicians in the appropriate selection of antibiotics for empirical treatment of patients suffering from UTI. The prevalence of UTI in our study was found to be 31.3% which is similar to the results of the study done in Rawalpindi by Khan MI.[9] Out of positive bacterial growth samples, 38% were females and 24% were males. Increased prevalence of UTI in females was also found in a research study done by Ullah A. in Kohat Teaching Hospital.[10]

Moreover, patients of age group 51-60 years (18%) and 21-30 years (17.5%) were the most commonly affected age group which was consistent with data presented by Bitew A. in 2017.[11]

In the present study, out of 1565 (14 species), bacterial isolates were recovered, Gram-negative bacteria constituted (81%) major portion as compared to Gram-

positive bacteria (18%). This is in accordance with the study findings by Yadav M.[12]

The most prevalent isolated bacteria were found to be *E. coli* (73.2%), also reported in a study conducted by Khan MI.[9] In the present study, *E. coli* was found to be highly sensitive to Meropenem, Amikacin, Fosfomycin, and Nitrofurantoin consistent with the results published in studies by Khan IU., Al-Zahrani J. and Pouladfar G.[13-15] However it was found resistant to Ampicillin 86%, Cephalosporin 73%, Ciprofloxacin 63% and Cotrimoxazole 69%. A similar pattern was documented in many studies.[9,16,17]

Literature shows that Nitrofurantoin is an active drug against *E. coli*, the most common pathogen of urinary tract infection and overall resistance to it is uncommon and many multidrug-resistant pathogens are still found susceptible to it. Therefore Nitrofurantoin can be prescribed as a first-line antimicrobial option for the empirical therapy of suspected acute uncomplicated cystitis.[18]

Susceptibility of Fosfomycin was also found highly effective in multidrug-resistant *E. coli* in UTI in comparison to other available antibiotics. Similar results were found in many related studies[19,20] which have shown that Fosfomycin is can an effective antibacterial drug for empirical treatment of UTI patients.[21]

The Carbapenem group of antibiotics is still a reliable option for parental treatment of urinary tract infection as low resistance has also been observed in other studies.[16,22] Moreover, our study displayed low resistance against Amikacin, compatible findings are noted in other studies as well done in India and Turkey.[12,16] Therefore it can also be preferred as a parental drug for empirical therapy of UTI.

As most physicians prefer broad-spectrum antibiotics for the treatment of outpatient UTIs therefore Ciprofloxacin had remained one of the most frequently prescribed antibiotics for UTI treatment.[23] However, a significant increase in antimicrobial resistance to ciprofloxacin has been noticed over a time period.[24] In our study, *E. coli* showed 63% resistance to ciprofloxacin. Similarly, high Cephalosporin resistance has been recorded in multiple studies due to its unchecked prescription practices.[17] They should be used with caution for empirical treatment in hospitalized patients due to their high resistance rates. Furthermore, high resistance rates of Ampicillin have also been noticed in other related studies by Bitew A. and Demir M.[11,16] Therefore, it is not appropriate to use it as a single agent in empirical treatment.

Cotrimoxazole resistance was also found high in our study which is in agreement with the studies done in 2019 and 2020 respectively.[16,25] Hence, it should not be considered a suitable option for empirical treatment in UTI.

The high emergence of antibiotic resistance is mainly due to unchecked doctor practices, self-medication, and non-compliance of the patients.[26]

The limitation of the study is that the data was retrospective therefore it was not known whether the patient was symptomatic, asymptomatic, or critically ill. Likewise, the source of the urine samples could not also be identified whether it was midstream urine or taken from a urine bag or catheter. Similarly, the data did not sort out inpatients and outpatients separately. Moreover, patients submitting more than one sample with complaints of recurrent UTI or colonization could not be identified.

Conclusion

The present study revealed that Fosfomycin and Nitrofurantoin are very effective oral antibiotic options for empirical treatment against *E. coli* causing urinary tract infection. They should be prescribed cautiously by the physicians to avoid the emergence of antibiotic resistance.

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