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Prevalence of Multi-drug Resistance Pattern of *Escherichia coli* in Different Ages and Gender of Urinary Tract Infected Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Author RS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors PCS and JK managed the analyses of the study. Author SD managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To find out the prevalence of multi-drug resistance pattern of *Escherichia coli* in urinary tract infected patients in Dhaka, Bangladesh.
Study Design: The study was influenced by recurrent urinary tract infections (UTIs) and presence of high multi-drug resistant (MDR) *E. coli*.
Place and Duration of Study: Department of Microbiology, Primeasia University, Institute of Laser Surgery and Hospital, Millennium Heart & General Hospital, between January to December 2017.
Methodology: Total 605 patients (age range <1-80 years) were included as sample populations. Followed by overnight enrichment of urine samples in LB medium at 37ºC, isolates were confirmed as uropathogenic *E. coli* (UPEC) by using selective media and biochemically through oxidase, indole and citrate test. All the isolates were examined for antibiotic susceptibility to fifteen commonly used antimicrobial agents by disk diffusion assay on Mueller Hinton agar results were interpreted by

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following the guideline of Clinical and Laboratory Standards Institute (CLSI).
Result: About 38% (230 out of 605) UPEC have been screened out. Prevalence of *E. coli* was observed high (58%) in female patients and the most vulnerable age group was (50-80) which showed approximately 63% presence of UPEC. Almost 100% isolates have become considered as multi-drug resistant (>5 drugs). All the isolates showed 100% resistance against rifamicin, while no resistance was observed against colistin. Statistically, antibiotic resistance of UPEC against meropenem and amikacin was significant within male and female. Most alarming resistance have been observed against commonly prescribed antibiotic, 4th generation cephalosporin (cefipime) and ciprofloxacin were 95% and 74% respectively, 3rd generation cephalosporin (ceftriaxone 97%, cefixime 90%, ceftazidime 83%). At the same time 94% isolates showed resistance to vancomycin, 89% to piperacillin, 91% to azithromycin, 87% to gentamicin, 66% to nitrofurantoin, 59% to amikacin, 47% to meropenem and 45% to imipenem.
Conclusion: This finding is useful for the determination of appropriate antimicrobial treatment in UTI patients.

Keywords: Urinary tract infection (UTI); multi-drug resistance (MDR); uropathogenic Escherichia coli (UPEC); anti-microbial agent.

1. INTRODUCTION

Urinary tract infections (UTI) are one of the most common bacterial infections in the human urinarysystem which causes serious health problem, affecting 150 millions of individuals worldwide, especially in many developing countries, including Bangladesh [1]. It occurs when a significant number of microorganisms (>105 cfu/ml) is present in urine [2]. When UTI affects the lower urinary tract it causes bladder infection and when it leads to enlarged prostate gland (in men) or a kidney stone may cause kidney damage to different ages of people. Different factors such as age, sex, vaginal delivery, obstetric trauma, menopausal status, food habit, improper sanitation system greatly influence the incidence of urinary tract infections [3].

There are different pathogens that cause UTI, more specifically *E. coli* (over 80% infections) [4], *Klebsiella* species, *Pseudomonas aeruginosa*, and *Enterococcus* species were the most common bacterial pathogens isolated from the urinary tracts of infected patients [5]. Alarming antimicrobial resistance has been observed among the common bacterial agents of UTI over the last decade. In this context, previously preferred drug as front-line agent of empiric therapy of UTI can no longer be used confidently. Presently, antibiotic resistance is becoming a major problem both in hospital acquired complicated UTIs and in uncomplicated community-acquired cases which makes UTI treatment more intricate.

Microorganisms considered as multidrug-resistant (MDR) when it showed resistance to at least three antibiotics [6]. There has been remarkable increase of antibiotic resistance pattern among the *E. coli* isolates from UTI because of improper prescribing policy of antibiotic [7]. The rate of MDR among UTI isolates vary within different geographic regions such as, the prevalence of MDR UPEC was reported to be 92% in India [8] 72% in Bangladesh [9] whereas the prevalence in the United States and Slovenia were 7.1% and 42%, respectively [10,11].

Updated knowledge on the diverse etiology of UTIs and the resistance of the causative organisms against antibiotics is important to clinicians when treating such patients. This retrospective study was conducted to investigate multi-drug *E. coli* prevalence in urinary tract infection of chronic kidney diseased patient in south Dhaka, Bangladesh. This study is clinically significant in order to formulate antibiotic prescription policies in case of UTI patients.

2. EXPERIMENTAL DETAILS

2.1 Study Population

The study included about six hundred and five UTI patients of different ages (<1 year to 80 years) with details history and clinical examinations. A prospective analysis of the predominant isolate was conducted in the Department of Clinical Pathology and Microbiology, Institute of Laser Surgery and Hospital; Department of Clinical Pathology and Microbiology, Millennium Heart & General Hospital; Department of Microbiology, Primeasia University, Banani, Dhaka.

2.2 Sample Collection

Urine samples were collected from UTI patients irrespective of their age and sex during one year period (1st January, 2017 to 31st December, 2017). According to Sonnenwirth and Jerett, about (10- 20) ml individual midstream urine have been collected in air-tight sterile container in order to prevent contamination [12]. These collected samples have been processed immediately, in case of delay, samples have been kept at 4ºC in the refrigerator until processing.

2.3 Isolation and Identification of *E. coli* from Urine Sample

About 230 *E. coli* isolates have been screened out from 605 samples of urine. Urine samples were inoculated in LB broth (Yeast extract .5%, Trypton 1%, NaCl 1%) followed by overnight incubation at 37ºC for enrichment. Bacterial cultures were grown on Mac CONKEY agar (OXOID, UK) and then further sub cultured on nutrient agar (UNIPATH, UK) for pure culture. Isolates as *E. coli* have been confirmed by using selective media Eosine Methylene Blue (EMB) agar (OXOID, UK) and biochemically confirmed by methyl-red test, oxidase test, indole test, citrate test. All the isolates of *E. coli* were harvested and stored in trypticase soya broth (OXOID, UK) containing 30% glycerol at -80ºC for further analysis.

2.4 Determination of Antimicrobial Resistance of the *E. coli* Strains

Antibiotic susceptibility of all the two hundred and thirty (230) isolates was examined according to Kirby-Bauer disk diffusion assay [13] on Mueller-Hinton agar (UNIPATH, UK). Briefly, an individual colony of each isolate (revived from stock solution) was introduced into 2 ml of Mueller- Hinton broth (OXOID,UK), incubated for 4 hours, and the culture turbidity was then adjusted to a 0.5 McFarland standard. Sterile cotton swabs were dipped into the suspensions and were streak evenly over the entire agar surface. Antibiotic-impregnated disks (OXOID Limited, UK); azithromycin (AZM) 15 µg, amikacin (AMC) 30 µg, ceftriaxone (CI) 30 µg, ceftazidime (CAZ) 30 µg, cefepime (FEP) 30 µg, cefixime (CFM) 5 µg, ciprofloxacin (CIP) 5 µg, colistin (CT) 10µg, gentamycin (CN) 10 µg, imipenem (IP) 10µg, meropenem (MRP) 10 µg, nitrofurantoin (NIT) 300 µg, piperacilin (PIT) 75 µg, rifampicin (RA) 30 µg, vancomycin (VA) 30 µg were then applied onto the surface of the inoculated plates. After incubation, strains were characterized as susceptible or resistant to antibiotics based on the inhibition zone size according to interpretive criteria of the guideline of Clinical and Laboratory Standards Institute (CLSI). *E. coli* 25922 was used as positive control in this experiment.

2.5 Statistical Analysis

Chi square test was performed to test the significant difference among resistance pattern of the antimicrobial agent between male and female patient. The difference was considered as significant if probability that chance would explain the result was reduced to less than 5% ($p \leq 0.05$). The normality and homogeneity was also checked.

3. RESULTS AND DISCUSSION

3.1 Prevalence of *E. coli* Isolates in Different Ages and Gender

The study investigated urine sample about six hundred and five patients. UTI prevalence is common in Asia as well as Bangladesh and it has been predominant in all age groups and sex [14]. About 38% (230 out of 605) positive samples have been found within the age range 1> to 80. In this study, about 63% (145 out of 230) isolates have been found within 50-80 age group as shown in Table 1. Prevalence of isolates in the observed male and female ratios was 1:1.4(9/133). The frequency of UPEC have been found from female patient comparatively more than male patients because of their anatomy irrespective of other causes [15].

Table 1. Prevalence of *E. coli* isolates by age category of patient

Age	Male	Female
>1-19	15	15
20-49	20	35
50-80	62	83

3.2 Antibiotic Susceptibility Testing Of *E. coli* Isolates

The antibiotic susceptibility test was performed against wide range of antibiotics shown in Fig. 1. The resistance pattern of antimicrobials varies

from country to country [16]. Highest resistance (100%) was demonstrated against rifampicin whether no resistance was found less than 45% except colistin (0%).

Considering high resistance rate of different antimicrobial drugs such as ampicillin, co-trimoxazole throughout different parts of the world, floroquinolone (ciprofloxacin),early cephalosporin, nitrofurantoin have been as front line agent of UTI treatment all over the world [17,18]. Nonetheless, their widespread use has made *E. coli* resistant to these drugs. The present study showed 74% resistance against ciprofloxacin which correlated with the result of different studies [19]. Usually third-generation cephalosporin has been prescribed to treat gram-negative bacterial infections of various body sites, the current study showed high levels of resistance to third generation cephalosporin (ceftriaxone 97%, ceftazidime 83%, cefixime 90%). Nitrofurantoin has been used for a long time in UTI treatment, but in different studies, it did show low level of resistance [20,21] which can be explained due to its exclusive pharmacodynamics properties and specificity [22]. In this study, *E. coli* showed 66% resistance against nitrofurantoin.

All of the *E. coli* isolates from this study showed high level of resistance against second line of antibiotics such as amikacin, 4th generation cephalosporin. About 90% resistance was observed against 4th generation cephalosporin, cefixime. These might have become resistant due to the presence of ESBL in these strains [23]. In this study, *E. coli* isolates showed 59% resistance to amikacin, 87% to gentamicin. Organisms have become 74% resistant against ciprofloxacin (quinolone) which is the commonly prescribed antibiotic against urinary tract infection. Ciprofloxacin which has also been widely recommended for the urinary tract infections has also become resistant due to inappropriate use of floroquinolone for humans [24].

Different studies showed that the resistance property against carbapenem group (imipenem, meropenem) still was not developed within *E. coli* [19,25]. This present study showed 47% resistance against meropenem and 45% resistance against imipenem.

Strikingly, no resistance property was observed against colistin (polymixin). This result correlated with the study of antimicrobial resistance in rural Kerala [21]. The effectiveness of colistin mainly depends on the daily dose and the infection site, so it cannot develop resistance [26]. Colistin was old drug but its use has been banned for safety and availability of safer drug, but now it has been recommended with the combination of other drug in the treatment of gram-negative bacterial infection [27]. In case 94% isolates showed resistance to vancomycin (glycopeptide group), 66% to nitrofurantoin, 89% to piperacilin, and 91% to azithromycin (macrolide group).

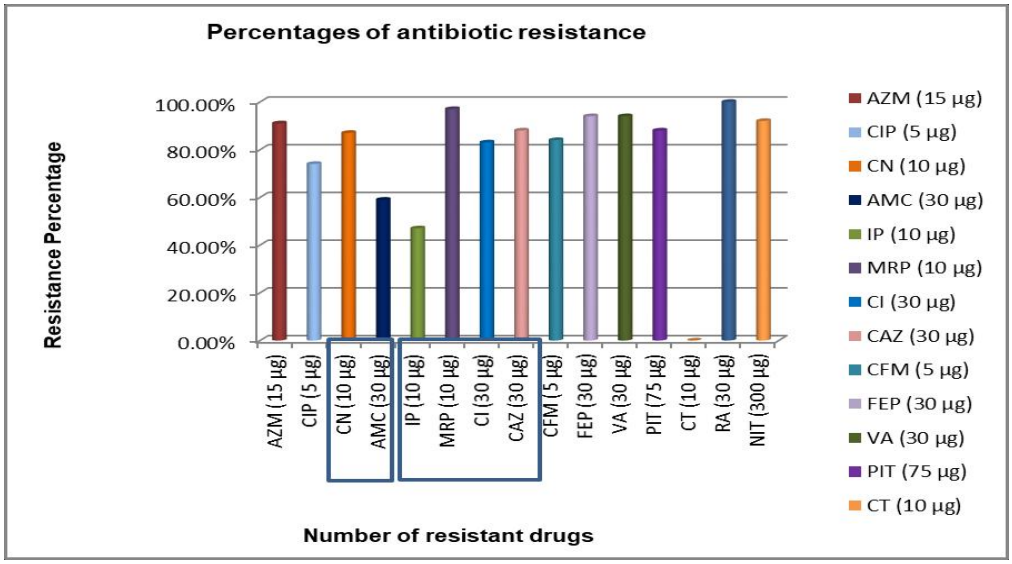


Fig. 1. Different groups of antibiotics are represented by X-axis and y-axis showed resistance percentage of each antibiotic

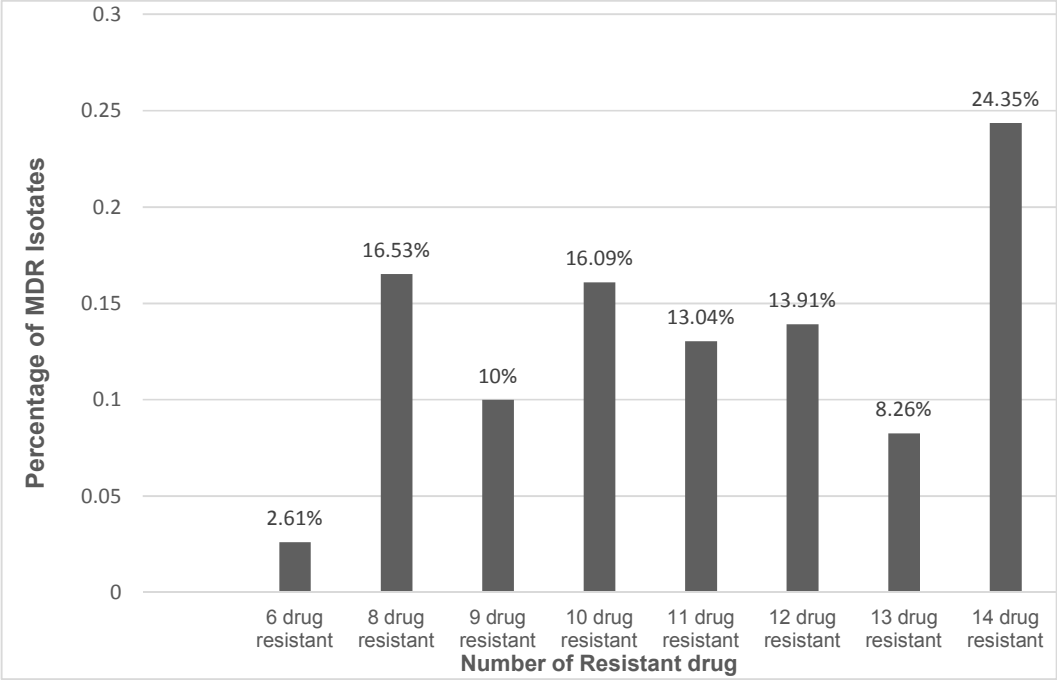
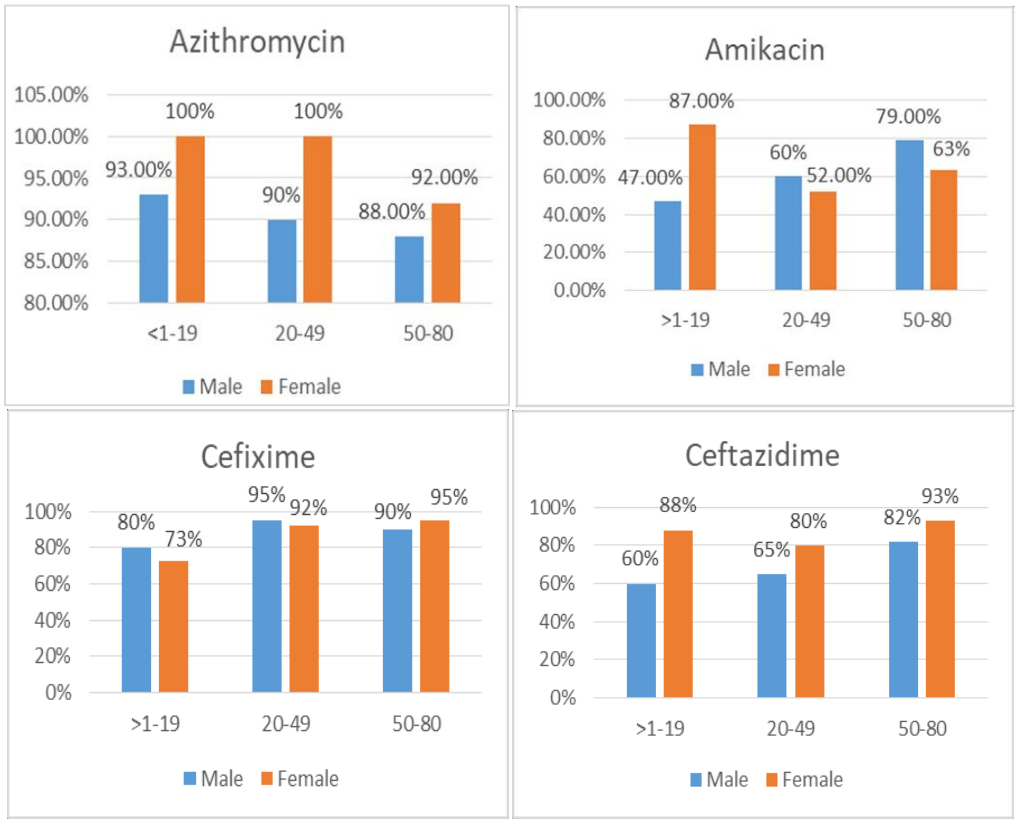
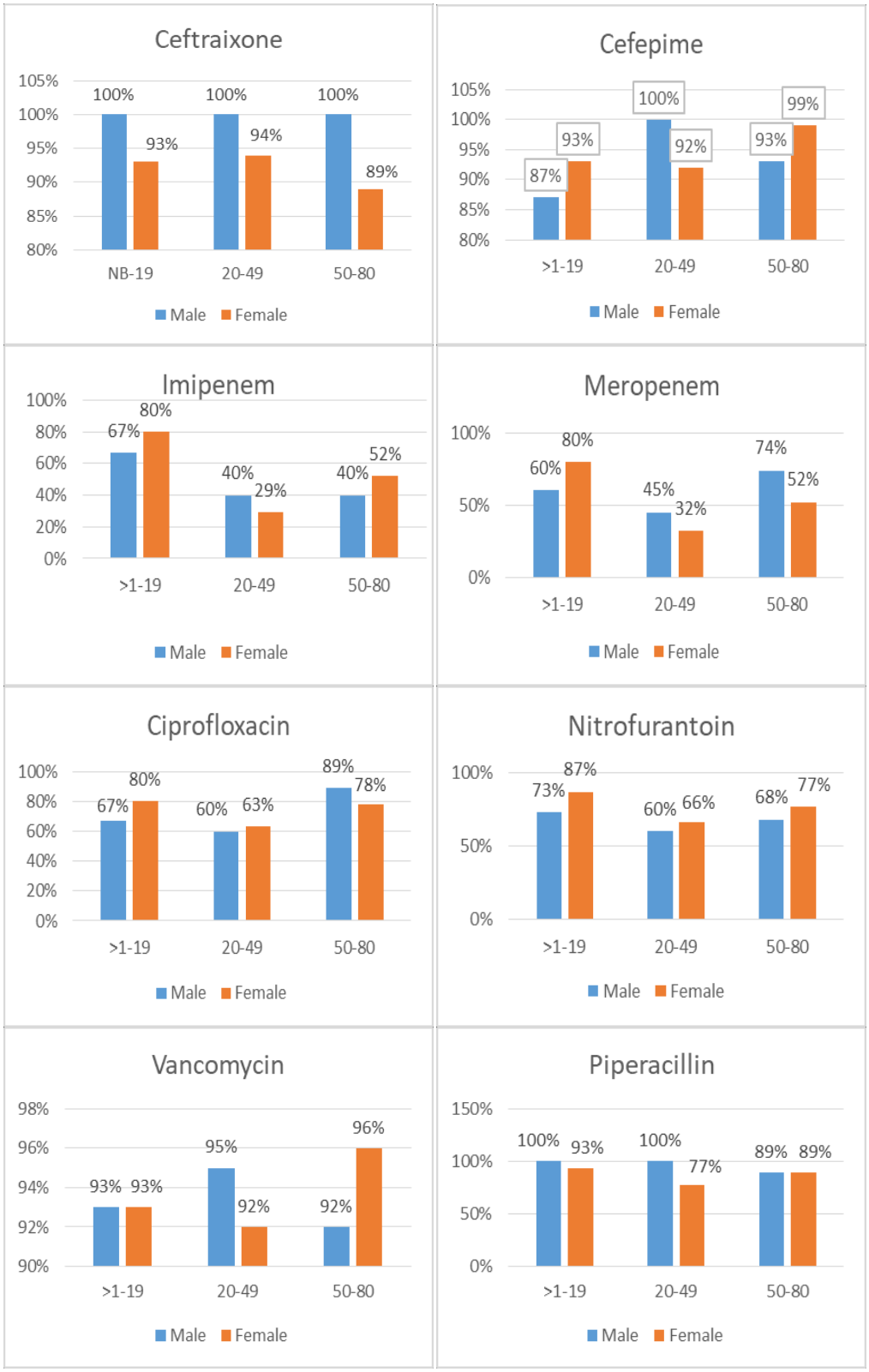


Fig. 2. Multi-drug resistance pattern of UPEC; x-axis showed the number of resistant drug and y-axis showed the percentage of MDR isolates of *E. coli*




Ceftraixone
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90%
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80%
100%
93%
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94%
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Male
Female
Cefepime
105%
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95%
90%
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100%
92%
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99%
>1-19
20-49
50-80
Male
Female
Imipenem
100%
80%
60%
40%
20%
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67%
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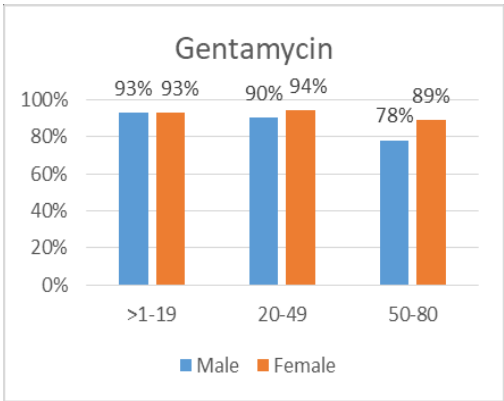

Fig. 3. Antibiotic resistance patterns for the drugs tested in the present study. The name of each antibiotic is given at the top of each graph. The y-axis shows the resistance (%) to the relevant antibiotic. The x-axis showed the age distribution of male and female

Table 2. Statistical analysis of the resistance pattern of individual antimicrobial agent

Drug	Gender	<1-19	20-49	50-80	*P* value
Azithromycin	Male	93%	90%	88%	.96
	Female	100%	100%	92%	
Amikacin	Male	47%	60%	79%	.001
	Female	87%	52%	63%	
Cefepime	Male	87%	100%	93%	.70
	Female	93%	92%	99%	
Cefixime	Male	80%	95%	90%	.80
	Female	73%	92%	95%	
Ciprofloxacin	Male	67%	60%	89%	.38
	Female	80%	63%	78%	
Imipenem	Male	67%	40%	40%	.14
	Female	80%	29%	52%	
Meropenem	Male	60%	45%	74%	.009
	Female	80%	29%	52%	
Nitrofurantoin	Male	73%	60%	68%	.94
	Female	87%	66%	77%	
Ceftazidime	Male	60%	65%	82%	.96
	Female	88%	80%	93%	
Gentamycin	Male	93%	90%	78%	.82
	Female	93%	94%	89%	
Vancomycin	Male	93%	95%	92%	.93
	Female	93%	92%	96%	
Piperacillin	Male	100%	100%	89%	.42
	Female	93%	77%	89%	
Ceftriaxone	Male	100%	100%	100%	.96
	Female	93%	94%	89%	

P≤.05 significant value,P<.01 significant value*

3.3 Multi-drug Resistance Pattern of UPEC

Distribution of *E. coli* strains accordingly used antibiotics to which they were resistant showed that about 24% isolates become resistant to fourteen drugs out of fifteen drugs in Fig. 2. Almost about 100% isolates have become resistant to more than five drugs. Based on the result of the present study this can be claimed that they were all multi-drug resistant *E. coli*. The result of this study has been correlated with different studies of multi-drug resistant *E. coli* [28,29 and 30]. This multidrug resistance

property might evolve due to an inevitable genetic response to the strong selective pressure imposed by antimicrobial chemotherapy through the transfer of plasmid containing resistant gene among other bacterial cells and species [30].

3.4 Age and Gender Affecting Antibiotic Resistance Pattern

It has been observed that the resistance of antimicrobial agents varies according to age and gender distribution. The resistance percentages of all isolates are graphically represented in the Fig. 3 which correlated with Lee et al. [31].

According to statistical analysis, a significant difference (p-value ≤.05) was observed against meropenem and amikacin within male and female in Table 2.

4. CONCLUSION

Imipenem and colistin might be prescribed in the treatment of urinary tract infection provided that other drugs fail to give protection. Increasing resistant pattern of antimicrobials has given warning to the most used antibiotic and threaten the global health problem which led to the invention of a novel antibiotic. High co-relation between antibiotic misuse and resistance leads to formulate a new antibiotic intake policy that should be strictly followed by the concerned authorities for the effective control of antibiotic resistance.

CONSENT AND ETHICAL APPROVAL

With the permission of the hospital authority and institutional ethical review committee, informed consent was obtained from each participant. In the case of young patients (<20 years), consent was obtained from parents/legal guardians.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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