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Multi-drug resistance pattern of bacterial isolates from urinary tract infection

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Abstract: In the community and among hospitalized patients, urinary tract infections (UTIs) rank as the most common bacterial infections. The researchers processed urine samples obtained from affiliated hospitals of Peshawar Medical College. The samples were examined under a microscope to assess the presence of bacteria, pus cells and red blood cells. Following this, the samples were inoculated on MacConkey and blood agar and subsequent antibiotic susceptibility testing was conducted. The findings revealed that 35.9% of hospitalized patients and 16.9% of outpatients were diagnosed with UTIs. Furthermore, 82.2% of the identified UTIs were found to be multidrug-resistant (MDR), with MDR Escherichia coli accounting for 77% of cases. Trimethoprim sulfamethazine (26.8%), penicillin (0%), cefepime (27.8%), cefotaxime (23.7%), aztreonam (2.1%), meropenem (86.6%), ciprofloxacin (51.5%), amoxicillin/clavulanic acid (37.1%), nitrofurantoin (70.1%), gentamycin (73%), ceftazidime (19.5%), levofloxacin (51.5%) and ceftriaxone (25.77%) were subjected to antibiotic susceptibility testing. It is concerning that among the 13 antibiotics examined, solely nitrofurantoin displayed oral efficacy as an effective treatment choice for UTIs.

Keywords: Analytical profile index, antibiotic susceptibility, multidrug-resistant organisms, nitrofurantoin, urinary tract infection.

INTRODUCTION

Urinary tract infections (UTIs) rank among the most prevalent bacterial infections in both community and hospital settings, as documented by Mancini *et al*. (2020). This particular type of infection stands as a leading cause of hospital admissions and is associated with significant mortality, morbidity and economic expenses. UTIs impact a staggering number of individuals every year, with an estimated 150 million people affected annually, resulting in a global economic burden exceeding 6 billion US dollars, as indicated by Öztürk and Murt (2020) and Zeng *et al*. (2022). While UTIs can occur in individuals of all age groups and genders, Erdem *et al*. (2018) note that they are more commonly observed in females compared to males.

The causative agents of UTIs are predominantly bacterial, with more than 95% of cases attributed to bacterial infections. The majority of these bacteria fall under the Gram-negative category, specifically within the family Enterobacteriaceae. Among these bacteria, Escherichia coli (*E. coli*) is the most commonly encountered, accounting for over 80% of UTIs. Klebsiella spp. and Enterobacter spp. are also frequently implicated. While less common, other Gram-negative organisms, such as Pseudomonas aeruginosa, may also play a role in UTI infections.

The treatment of UTIs is becoming a challenge due to the emergence and spread of MDR bacterial strains resulting in severely limited therapeutic alternatives for clinicians (Ramírez-Castillo *et al*., 2018; Gajdács *et al*., 2020). It is especially a matter of concern if the patients have some underlying conditions (Gajdács and Urbán, 2019). An unreasonable degree of resistance against commonly prescribed antibiotics has been seen in Gram-negative bacteria in regions where no restrictions were implemented to their use in the community which has led to treatment failure (Jamal *et al*., 2018).

According to a survey, approximately 700,000 deaths occur each year as a result of antimicrobial resistance (AMR). If appropriate monitoring and preventive measures are not implemented to address the improper use of antibiotics, AMR could become a leading cause of mortality among hospitalized and non-hospitalized patients in both developing and industrialized countries (Assar *et al*., 2020; Gandra *et al*., 2020).

Given the empirical nature of UTI treatment, it is vital to possess prior insights into the prevalence of causative agents and their susceptibility to antimicrobials within a particular region. However, it should be noted that the distribution of UTI causative agents and their antibiotic susceptibility profiles may exhibit regional variations. Consequently, it becomes crucial to conduct an assessment of the local etiology and antimicrobial susceptibility profiles in order to establish the optimal empirical therapy approach.

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MATERIALS AND METHODS

Study design
The study was conducted using a comparative cross-sectional prospective design.

Inclusion criteria
The inclusion criteria involved collecting urine samples from both outpatients and inpatients who exhibited symptoms of UTI, as well as inpatients who had an indwelling urinary catheter for a minimum of 48 hours. These samples were obtained from affiliated hospitals of Peshawar Medical College.

Study setting
The samples utilized in this study were collected from affiliated hospitals of Peshawar Medical College and subsequently processed at the Microbiology Laboratory located at Peshawar Medical College in Peshawar.

Sample size calculation
The sample size was determined using OpenEpi info sample calculation, considering a 95% confidence level. Based on a prevalence rate of 11.6% of UTI in symptomatic patients within our population, a margin of error of 5% and an absolute precision of 0.05%, the calculated sample size was determined to be 158 individuals (Ullah *et al*., 2018).

Sampling technique
A non-probability convenience sampling technique was employed for participant selection.

Collection of samples
Sterile containers were used to collect a volume of 10-15 mL of midstream urine from 158 patients between November 2021 and March 2022. These patients were sourced from affiliated hospitals of Peshawar Medical College and the collected samples were subsequently processed at the Microbiology Laboratory.

Isolation and identification of microorganisms
Microscopic examination of the urine involved observing bacteria, pus cells and red blood cells using the high-power field after centrifugation. Inoculation on MacConkey and blood agar was performed using the standard loop technique. The incubation of plates took place at 37°C for 24 hours. A colony counts equal to or ≥105 colony-forming units per milliliter (CFU/mL) was considered significant. Gram staining was conducted on the colonies and the identification of bacteria was carried out using biochemical tests with API (Analytical Profile Index) 10 S.

Antibiotic susceptibility
Antibiotic susceptibility testing, using the Kirby-Bauer disc diffusion method, was carried out on Mueller-Hinton Agar (MHA). According to the clinical and laboratory standards institute (CLSI) 2020 manual and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) protocols, the following antibiotics were utilized for determining antibiotic susceptibility: cefepime, ciprofloxacin, nitrofurantoin, ceftazidime, penicillin, trimethoprim sulfamethazine, gentamycin, levofloxacin, ceftriaxone and meropenem.

Ethical approval
Ethical approval was taken from the Institutional Review Board of the Prime Foundation Pakistan with approval number “Prime/IRB/2021-385” dated 8th November 2021.

STATISTICAL ANALYSIS

Statistical analysis was performed and p-value 0.05 was used as level of significance for statistical analysis.

RESULTS

Out of the 158 UTI patients included in the study, 53 (34%) were male, with a mean age of 46.9±16.5, while 105 (66%) were female, with a mean age of 42.4±13.8 (fig. 1). A total number of 135 UTI patients (85.5%) had growth out of which 64 (90.1%) were inpatient and 71 (81%) were outpatient and 23 (14.5%) had no growth out of which 7 (9.9%) were inpatient and 16 (19%) were outpatient. Out of fifty-two catheterized patients, 45 (86%) had growth and 7 (14%) had no growth. Out of one hundred and six non-catheterized patients, 90 (85%) had growth and 16 (15%) had no growth (table 1). Isolated organisms from cultures were evaluated for the relationships with respect to non-MDROs vs multi-drug resistant organisms (MDROs). Out of 135 positive cultures, *E. coli* 97 (71.9%) and 23.00% non-MDRO and 77% MDRO, Enterobacter 4 (3%) and 100% MDRO, *Klebsiella oxytoca* 15 (11.1%) and 100% MDRO, *Klebsiella pneumoniae* 7% non-MDRO and 93% MDRO, P. aeruginosa 9 (6.7%), 100% MDRO, *Serratia marcescens* 2 (1.5%) and 100% MDRO *Serratia odorifera* 1 (0.5%) and 100% non-MDRO were reported (table 2). Antibiotic susceptibility in isolated organisms was shown in table 3.

DISCUSSION

The present study revealed that the occurrence of urinary tract infections (UTIs) was higher among female patients, accounting for 66% of the cases, which is nearly double compared to male patients at 34% (fig. 1). This finding is consistent with previous reports from Iran and other countries. In a study conducted in Colombia, the prevalence of acute UTIs among women and men was reported as 23.3% and 6.8%, respectively, while the prevalence of recurrent UTIs was 54.2% among women and 15.7% among men. These results further support our findings, indicating a greater prevalence of UTIs among females compared to males (Medina and Castillo-Pino, 2019).

In the present study, it was determined that *E. coli* was responsible for 71.9% of the urinary tract infections (UTIs) analyzed (table 2). A Colombian study with a sample size of 1959 individuals reported a UTI prevalence of 31%, wherein *E. coli* accounted for 69% of the cases and Klebsiella sp. for 8% (Medina and Castillo-Pino, 2019). In our study, MDRO (multidrug-resistant organism) *E. coli* was found in 77% of the cases (table 2), while extended-spectrum beta-lactamase (ESBL) positive *E. coli* was present in 25% (table 2). The escalating global occurrence of highly virulent ESBL-producing uropathogenic *E. coli* (UPEC) strains, which are also resistant to multiple drugs, has resulted in the aggravation of urinary tract infection (UTI) cases. This, in turn, has led to a diminished efficacy of commonly prescribed first-line antibiotics, leading to increased medical expenses, higher morbidity rates and an elevated risk of mortality.

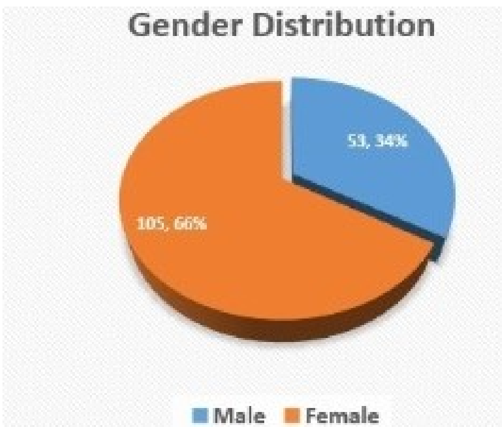

Fig. 1: Demographic representation of UTI patients.

AMR varies by region, making accurate worldwide estimates of these issues challenging. Unfortunately, our analysis revealed a large number of MDR *E. coli* isolates. This finding could be related to our region's ease of availability of common antibacterial medications without a prescription. This critical public health issue could severely limit the antibiotic options for treating *E. coli*-related UTIs.

In related investigations conducted in Mexico, Western Saudi Arabia and Mongolia, notable prevalence of multidrug-resistant (MDR) *E. coli* was also observed, with rates of 100%, 96.9% and 93.9%, respectively (Paniagua-Contreras *et al*., 2017; Yasir *et al*., 2018). The variation in the rate of MDR isolates among different countries can be attributed to distinct policies and prescription patterns implemented across various regions. Notably, a study from Mexico reported the presence of MDR *E. coli* in 63% of the cases analyzed (Ramírez-Castillo *et al*., 2018). Similarly, research conducted in the Iranian province of Kerman identified MDR isolates in 55.6% of UPECs from outpatients (Hashemizadeh *et al*., 2018). These aforementioned studies strongly support and validate our own findings.

In our study, UTI inpatients (hospital-acquired) were 71/158 (44.9%) while outpatients (community-acquired) were 87/158 (55.1%) (table 1). A small Argentinian study (n = 87) examined HAUTIs (48% of participants) and community-acquired UTIs (52% of participants) (Medina and Castillo-Pino, 2019), the results of this study are comparable to our study.

Within the scope of this study, Enterobacteriaceae comprised 91.1% of all isolates and *E. coli* representing 71.9%, K. pneumoniae accounting for 11.1%, K. oxytoca for 5.2% and Enterobacter for 3% (table 2). In a similar investigation conducted in Morocco, Enterobacteriaceae constituted 71% of all isolates and *E. coli* (68%) being the most prevalent species.

With a significant prevalence of 23 percent, K. pneumoniae was also involved in these UTIs (Hamamouchi *et al*., 2021). This finding is consistent with other scientific citations that have varying rates (Larramendy *et al*., 2020; Ndzime *et al*., 2021). The prevalence of these gram-negative bacilli is clearly explained by their uropathogenic nature and the ascending pathophysiology of UTI from the urethral flora (colonization of the perineum by enterobacteria of digestive origin) (Ziółkowski *et al*., 2020) and these investigations back up our findings.

Regarding our study, nitrofurantoin was found to be the most effective oral antibiotic, with a sensitivity rate of 70% (table 3). Resistance to nitrofurantoin was observed in 30% of cases. Other investigations conducted worldwide have reported a nitrofurantoin sensitivity rate of 90% among *E. coli* isolates from community-acquired UTIs (Derakhshan *et al*., 2018; Lee *et al*., 2018). Based on these findings, nitrofurantoin is recommended as a first-line treatment for UTIs by esteemed organizations such as the European Association of Urology (EAU) and the Infectious Diseases Society of America (IDSA), particularly in regions where the prevalence of resistance to this antibiotic is below 20% (Lee *et al*., 2018). Similar recommendations have been made in studies conducted in Iran, suggesting nitrofurantoin as a preferred first-line therapy for UTIs (Derakhshan *et al*., 2018). However, our findings indicate a recent increase in nitrofurantoin resistance, possibly attributed to the growing empirical use of this antibiotic for UTI treatment in our region, contrasting with the outcomes of previous research.

The rates of antimicrobial resistance (AMR) observed in this study were notably high, with 82.2% (111/135) of the tested drugs exhibiting resistance (table 2). Notably, all isolates (100%) demonstrated resistance to penicillin (table 3), while aminoglycosides displayed the lowest resistance frequency (28.9% of all isolates resistant to gentamicin, 39/135). Specifically, 27% (26/97) of *E. coli* isolates were found to be resistant to gentamicin. The findings align with

Table 1: Culture results of urine samples in different categories of patients

Categories of patients		Growth	No growth
Hospitalization Status	In patients n=71	64 (90.1%)	7 (9.9%)
	Outpatients n=87	71 (81%)	16 (19%)
Catheterization	Catheterized n=52	45 (86%)	7 (14%)
	Non-Catheterized n=106	90 (85%)	16 (15%)
Total	n=158	135 (85.5%)	23 (14.5%)

Table 2: Isolated organism and relationship with respect to non-MDRO vs MDRO

Isolated organisms	*Non-MDRO		*MDRO	
	Number	Percentage	Number	Percentage
E. coli (n=97)	22	23.00%	75	77.00%
*Enterobacter (n=4)	0	0.00%	4	100.00%
**K. oxytoca* (n=7)	0	0.00%	7	100.00%
K. pneumoniae (n=15)	1	7.00%	14	93.00%
**P. aeruginosa* (n=9)	0	0.00%	9	100.00%
**S. marcescens* (n=2)	0	0.00%	2	100.00%
**S. odorifera* (n=1)	1	100.00%	0	0.00%
Total=135	24	17.8%	111	82.2%

*Enterobacter, *K. oxytoca*, *P. aeruginosa* and *S. marcescens* exhibited significant results and *S. odorifera* showed non-significant result in terms of MDRO

Table 3: Antibiotic susceptibility in isolated organisms

DRUGS	*E. coli* n=97	Enterobacter n=4	*K. oxytoca* n=7	*K. pneumoniae* n=15	*S. marcescens* n=2	*S. odorifera* n=1	*P. aeruginosa* n=9
Nitrofurantoin	68 (70.1%)	2 (50%)	2 (28.6%)	9 (60%)	1 (50%)	1 (100%)	-
Trimethoprim sulfamethazine	26 (26.8%)	0 (0%)	1 (14.3%)	1 (6.7%)	0 (0%)	1 (100%)	-
Ciprofloxacin	50 (51.5%)	3 (75%)	5 (71.4%)	7 (46.7%)	2 (100%)	1 (100%)	6 (66.7%)
Levofloxacin	50 (51.5%)	3 (75%)	5 (71.4%)	7 (46.7%)	2 (100%)	1 (100%)	6 (66.7%)
Ceftriaxone	25 (25.77%)	0 (0%)	0 (0%)	1 (6.7%)	0 (0%)	1 (100%)	-
Cefotaxime	23 (23.7%)	0 (0%)	0 (0%)	1 (6.7%)	0 (0%)	1 (100%)	-
Ceftazidime	19 (19.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (11.2%)
Cefepime	27 (27.8%)	0 (0%)	0 (0%)	1 (6.7%)	0 (0%)	1 (100%)	5 (55.6%)
Aztreonam	2 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Meropenem	84 (86.6%)	2 (50%)	4 (57.1%)	13 (86.7%)	1 (50%)	1 (100%)	7 (77.8%)
Amoxicillin/clavulanic acid	36 (37.1%)	2 (50%)	2 (28.6%)	1 (6.7%)	0 (0%)	1 (100%)	-
Gentamycin	71 (73%)	3 (75%)	4 (57.1%)	9 (60%)	2 (100%)	1 (100%)	6 (66.7%)
Penicillin	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a previous study conducted in Mexico (Paniagua-Contreras *et al*., 2017), which reported penicillin resistance in 97.4% of *E. coli* isolates, with the lowest resistance observed for gentamicin (14.4%). Similarly, research conducted in Western Saudi Arabia indicated a penicillin resistance rate of 99.5% in *E. coli* isolates, with gentamicin resistance being the lowest (Yasir *et al*., 2018). Given the increasing prevalence of penicillin resistance, this antibiotic is no longer recommended for empirical treatment of UTIs.

In our study, it was found that the majority (73.2%) of the UPECs analyzed exhibited resistance to trimethoprim-sulfamethoxazole, which is a commonly used and effective antibiotic for treating urinary tract infections (UTIs) (table 3). Similar findings were reported by Ali *et al*. who identified a significant prevalence of trimethoprim-sulfamethoxazole resistance among UPEC isolates in Pakistan (82%) (Naziri *et al*., 2020). Moreover, a Mexican investigation revealed that over 70% of UPECs showed resistance to trimethoprim-sulfamethoxazole (Ramírez-Castillo *et al*., 2018). Another study conducted in Mexico reported a frequency of 66% for this resistance (Paniagua-Contreras *et al*., 2017). Additionally, there has been a substantial increase in the rate of trimethoprim-sulfamethoxazole resistance among urine *E. coli* isolates in US outpatients from 2000 to 2010, which raises concerns about the limited efficacy of this antibiotic in UTI treatment (Naziri *et al*., 2020; Caskurlu *et al*., 2020).

Considering that quinolones are commonly recommended for treating uncomplicated pyelonephritis and complicated UTIs, it is crucial to assess the resistance of UPECs to these antibiotics. In our study, approximately 48.5% of the isolates analyzed were found to be resistant to quinolones (table 3). These results align with a study conducted in Mexico (Ramírez-Castillo *et al*., 2018). Another study observed that 23.9% of *E. coli* strains exhibited resistance to ciprofloxacin, while resistance rates of 54.1% were reported for other strains of the same species (Kotov *et al*., 2021). The growing resistance to quinolones may be attributed to their excessive use.

In our investigation of UPECs, it was determined that the average resistance rates against tested cephalosporins were approximately 75% (table 3). Comparable or different rates of antimicrobial resistance (AMR) in UPEC isolates have been reported in various regions of Iran, as well as in countries such as Pakistan, Turkey, Mexico, Saudi Arabia, Brazil, Mongolia and others. Consequently, the use of cephalosporins as empirical medications for UTI treatment should be approached cautiously, taking into account the antimicrobial susceptibilities of infecting *E. coli* on a regional or even case-by-case basis (Naziri *et al*., 2020).

Antibiotic resistance in *E. coli* strains, the bacillus most commonly associated with UTIs in hospitals and the community, has revealed variable and high rates of resistance to the antibiotics employed, particularly the primary antibiotics given to treat these infections. Indeed, our study has detected the resistance as 77% *E. coil*, 93% *K. pneumoniae* and 100 % *K. oxytoca* (table 2). Antibiotic resistance gained by bacteria has become a worldwide fact, according to another analysis. It was 34.1 percent against *E. coli* and 32.7 percent against *K. pneumoniae*, respectively. There have also been significant and variable rates reported in the literature (Karlowsky *et al*., 2019).

In conclusion, the current study highlights the alarming prevalence of multidrug-resistant organisms (MDROs) in urinary tract infections (UTIs). This poses a significant public health concern as these MDROs contribute to the widespread antimicrobial resistance (AMR) within the community, rendering many commonly used UTI treatments ineffective. Notably, among the 13 antibiotics tested, only nitrofurantoin showed acceptable efficacy as an oral treatment for UTIs. These findings underscore the urgent need for regular antibiotic susceptibility testing to guide appropriate antibiotic selection and inform the development of new therapeutic approaches for UTIs. This is particularly crucial in developing countries where variations in the characteristics of *E. coli* strains across different geographic regions and their evolution over time necessitate tailored treatment strategies.

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