Original Article

ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF COMMON BACTERIAL UROPATHOGENS, A COMPREHENSIVE STUDY AT TERTIARY CARE HOSPITAL OF BALOCHISTAN

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ABSTRACT

Objective: To assess the frequency of the bacterial agents responsible for UTIs and their antibiotic susceptibility patterns in a tertiary care hospital.

Material and Methods: This Laboratory- based cross- sectional study was conducted at The Microbiology Department, Combined Military Hospital, Quetta in time duration of one year from April 2022 to March 2023. This study encompassed 512 bacterial isolates that were cultured positive from a collection of 1282 urine samples obtained from patients receiving care both in indoor and outdoor settings. The specimens were inoculated on CLED agar. Identification of isolated colonies was done by standard microbiological techniques and the Kirby Bauer disc diffusion method was used for antibiotic susceptibility testing. Quality control was ensured by using reference strains, and antibiotics were tested according to the CLSI 2022 recommendations.

Results: Bacterial uropathogens were identified in urine samples of 33.5% of male and 44.7% of female patients, with an overall infection rate of 39.93%. Of the 512 bacterial isolates, 91.79% were Gram-negative and 8.21% were Gram-positive. *Escherichia coli* was the most common isolate (69.53%), followed by *Klebsiella pneumoniae* (12.1%), *Enterococci* (7.6%), *Pseudomonas* (2.92%), among other bacterial species. The gram-negative isolates were sensitive to Nitrofurantoin (96%), Fosfomycin (93%), Amikacin (79%), Imipenem (75%), and Meropenem (74%), while gram positive isolates were highly sensitive to Linezolid (100%), Vancomycin (95%) and Nitrofurantoin (90%).

Conclusion: *E. coli* was the most common cause of UTIs at our hospital, followed by *Klebsiella pneumonia* with Nitrofurantoin and Fosfomycin being effective treatment options.

Keywords: *E coli,* Nitrofurantoin, Uropathogens.

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INTRODUCTION

Urinary tract infections (UTIs) are a widespread and increasingly significant issue in global health [1]. UTIs can occur in any part of the urinary tract, including the kidneys, bladder, ureters, and urethra. Symptoms of UTIs may include pain or burning during urination, frequent urination, urgency to urinate, cloudy or bloody urine, and lower abdominal pain or discomfort [2].

Women are more susceptible to UTIs than men because they have a shorter urethra, which allows bacteria to reach the bladder more easily [3]. Some studies indicate that up to 60% of women will experience a UTI at least once in their lifetime. There are several risk factors that can increase a woman's likelihood of developing a UTI, including sexual activity, pregnancy, menopause, certain types of birth control, urinary tract abnormalities, and a weakened immune system [3,4].

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The most common uropathogens (bacteria that cause urinary tract infections) vary depending on a person's age, sex, and other factors, but some of the most commonly identified organisms include *Escherichia coli (E. coli), Klebsiella pneumoniae, Proteus mirabilis,* and *Enterococcus faecalis. E. coli* is by far the most common cause of UTIs, accounting for approximately 80-90% of all cases [4,5]. Other less common uropathogens that can cause UTIs include *Staphylococcus saprophyticus, Pseudomonas aeruginosa,* and *Enterobacter spp.*

The emergence of antibiotic-resistant uropathogens is a growing public health concern, as it can make UTIs more difficult to treat and lead to longer hospital stays, higher healthcare costs, and increased mortality rates. To combat this issue, healthcare providers must be judicious in their use of antibiotics, using them only when they are necessary and appropriate. Additionally, researchers are working on developing new antibiotics and alternative treatments for UTIs, such as vaccines and probiotics, to reduce the reliance on traditional antibiotics.

The results of this study will provide valuable information on the antimicrobial susceptibility patterns

of common bacterial uropathogens in our region, which can help guide the empirical treatment of UTIs and contribute to the development of effective antimicrobial stewardship programs. This study will also help in identifying the emerging trends in antimicrobial resistance patterns and provide insights into the appropriate use of antimicrobial agents for the treatment of UTIs.

MATERIAL AND METHODS

A laboratory- based cross-sectional study was carried out in Combined Military Hospital, Quetta in time duration of one year from April 2022 to March 2023.The sample size of this study was calculated by using WHO calculator version 2.1, taking prevalence rate of 39.63% [6] with a 5% margin of error and 95% level of confidence, which gave the value of 368. Non-probability consecutive sampling technique was used to include 1282 number of samples in our study, which were received in the specified time period, after getting ethical permission, CMH QTA-IERB/02/2023.

The study population included both indoor and outdoor patients who had signs or symptoms of urinary tract infection such as dysuria, burning micturition, urgency of urine or flank pain. Patients having congenital renal disease and tumors of the genitourinary tract and having a history of antibiotic use in previous 48 hrs, samples taken from a bag or taken from a catheter without following the proper sterilized procedure were excluded from study. The urine samples were processed within 2 hours of collection.

The collected samples were inoculated by using a calibrated wire loop (0.001ml) on cysteine lactose electrolyte deficient agar (CLED). The inoculated plates were incubated overnight at 37^{o}C. The plates having no growth were incubated for 48 hrs time, and then observed for the growth. The single colony counts more than 10^5 CFU/ml were considered significant. The pure isolated colonies were then identified according to standard microbiological techniques such as colony morphology, gram stain and biochemical tests. For further identification of the species, Analytical Profile Index (API) was used by using standard guidelines. Identification of gram- positive bacteria was done using catalase and coagulase tests.

The methodology used for antibiotic susceptibility testing was the Kirby Bauer disc diffusion method. The testing was performed on both Müller-Hinton agar and blood agar, using a variety of antibiotics and concentrations as specified by the CLSI 2022 guidelines [7]. Quality control was ensured by using reference strains of S. aureus (ATCC 25923), *E. coli (*ATCC 25922), and *P. aeruginosa* (ATCC 27853). The zone of inhibition of antibiotics was measured and interpreted according to the CLSI 2022 guidelines. The antibiotics tested included Penicillin (10), Amikacin (30), Amoxicillin clavulanic acid (30), Cefepime (30), Ceftazidime (30), Ciprofloxacin (5), Cotrimoxazole: Trimethoprim-sulphamethoxazole (25), Imipenem (30), Meropenem (30), Nitrofurantoin (30), Pipercillin-tazobactam (40), Ampicillin (10), Ceftriaxone (30), Linezolid (10), Vancomycin (30), Cefoxitin (30), Fosfomycin (50), and Tetracycline (30)[7]. The data obtained was initially recorded in Microsoft Excel 2010, and subsequently analyzed using Statistical Package for the Social Sciences (SPSS) version 26:00 for evaluation using descriptive statistics. Categorical variables were presented as frequencies with corresponding percentages, while numerical variables were expressed as mean ± standard deviation.

RESULTS

A total of 1282 urine samples were collected and analyzed at our laboratory within a one-year timeframe, out of which 728 were female and 554 were male. The significant growth of bacterial uropathogens were seen in 33.5% of the male population while 44.7% of the female population. In total population, 39.93% patients were having infection by bacterial pathogens (Table-I).

According to the result, out of the total 1282 urine specimens analyzed, 512 (39.93%) had significant bacteriuria (≥ 10^5 CFU/mL). Moreover, the age range of 12 to 40 years showed the highest occurrence of significant bacteriuria, with 253 cases (49.41%) being identified. Among the male population, the highest bacteriuria, 109 (58.60%), was observed in the age group of 40-70 years, while among the female population, the highest bacteriuria, 187 (57.36%), was observed in the age group of 12-40 years (Table-II).

Out of the 512 bacterial isolates obtained, the majority (91.79%) were identified as Gram-negative while the remaining 8.21% were Gram-positive bacteria. Among all the isolates, *Escherichia coli* was found to be the most common, accounting for 69.53% of the total isolates, followed by *Klebsiella pneumoniae* (12.1%), *Enterococci* (7.6%), *Pseudomonas* (2.92%), and other bacterial species. Table III provides a breakdown of the distribution of isolated uropathogens in both genders based on their frequency.

The susceptibility pattern of the gram-negative isolates which was observed in our study, showed high rate of sensitivity to Nitrofurantoin (96%), Fosfomycin (93%), Amikacin (79%), Imipenem (75%), and Meropenem (74%), while low rates of sensitivity was observed for Ceftazidime (50%), Pipercillin Tazobactum (39%), Co-trimoxazole (36%), Cefepime and Ceftriaxone (29%), Amoxicillin-clavulanic acid (21%), Ciprofloxacin (11%) and Ampicillin (8%) (Table-IV).

Among the antibiotics that were tested, the Gram-positive bacterial isolates exhibited varying degrees of sensitivity. Linezolid showed a sensitivity rate of 100%, while Vancomycin and Nitrofurantoin were sensitive in 95% and 90% cases respectively. Other drugs with their sensitivity rates were Fosfomycin (79%), Cotrimoxazole (67%), Amoxicillin-Clavulanic acid (57%), Ampicillin (55%), Tetracycline (54%), Penicillin (29%) and Ciprofloxacin (7%). The sensitivity rates of antibiotics in gram positive bacteria are shown in Table-V.

Table-I: Distribution of uropathogenic bacteria in urine culture according to gender.

Gender	Positive n (%)	Negative n (%)	Total n (%)	p value
Male	186 (33.57)	368 (66.43)	554 (43.21)	
Female	326 (44.78)	402 (55.22)	728 (56.79)	.0024
Total	**512 (39.93)**	**770 (60.07)**	**1282 (100)**	

Table-II: Distribution of isolated uropathogenic bacteria according to age.

Age in years	Male n (%)	Female n (%)	Total n (%)	p value
0 -12	11 (5.91)	49 (15.03)	60 (11.71)	
12- 40	66 (35.48)	187 (57.36)	253 (49.41)	< 0.00001
40 -70	109 (58.60)	90 (27.60)	199 (38.86)	
Total	**186**	**326**	**512**	

Table-III: Distribution of isolated uropathogenic bacteria in both genders according to their frequency.

Uropathogens	Male (n=186)	Female (n=326)	Total (512)
E coli	125 (67.20%)	231 (70.85%)	356 (69.53%)
Klebsiella pneumonie	26 (13.97%)	36 (11.04%)	62 (12.1%)
Enterococci	12 (6.45%)	27 (8.28%)	39 (7.6%)
Psuedomonas	7 (3.76%)	8 (2.45%)	15 (2.92%)
Proteus	5 (2.68%)	9 (2.76%)	14 (2.73%)
Serratia	3 (1.61%)	6 (1.84%)	9 (1.75%)
Acinetobacter	2 (1.07%)	3 (0.92%)	5 (0.97%)
Citrobacter	1 (0.53%)	3 (0.92%)	4 (0.78%)
Burkholderia	2 (1.07%)	1 (0.31%)	3 (0.58%)
Staphylococcus	1 (0.53%)	2 (0.61%)	3 (0.58%)
Stenotrophomonas	2 (1.07%)	0 (0%)	2 (0.39%)

Table-IV: Sensitivity rates of antibiotics in Gram negative bacteria.

	***E. coli* (356) N (%)**	***K. pnemoniae* (62) N (%)**	***P. aurignosa* (15) N (%)**	***P. mirabilis* (14) N (%)**	***S. marcesense (9) N (%)***	***A. baumanii* (5) N (%)**	***Citrobacter freundii* (4) N (%)**	***Burkholderia-cepacia* (3) N (%)**	***Stenotrop-hmonas maltophila* (2) N (%)**	**Total N (%)**
Ampicllin	28 (8)	IR	IR	1 (7)	IR	IR	IR	IR	IR	29 (8)
Amoxicillin clavulanic acid	82 (23)	5 (8)	IR	5 (36)	IR	IR	IR	IR	IR	92 (21)
Cefepime	103 (29)	16 (26)	5 (33)	6 (43)	4 (44)	0(0)	1 (25)	NT	NT	135 (29)
Ceftriaxone	103 (29)	16 (26)	IR	5 (36)	4 (44)	0(0)	1 (25)	NT	IR	129 (29)
Ceftazidime	NT	NT	5 (33)	NT	NT	NT	NT	3 (100)	2 (100)	10 (50)
Piperacillin-Tazobactam	146 (41)	17 (27)	4 (27)	6 (43)	6 (67)	1(20)	2 (50)	NT	IR	182 (39)
Imipenem	288 (81)	38 (61)	6 (40)	7 (50)	5 (56)	2(40)	3 (75)	NT	IR	349 (75)
Meropenem	281 (79)	37 (60)	5 (33)	8 (57)	5 (56)	2(40)	3 (75)	3 (100)	IR	344 (74)
Ciprofloxacin	39 (11)	7 (11)	2 (13)	3 (21)	1 (11)	0(0)	0 (0)	1 (33)	0(0)	53 (11)

Cotrimoxazole	121 (34)	24 (39)	IR	5 (36)	4 (44)	1(20)	2 (50)	3 (100)	2 (100)	162 (36)
Amikacin	288 (81)	49 (79)	10 (67)	9 (64)	6 (67)	1(20)	3 (75)	IR	IR	366 (79)
Nitrofurantoin	349 (98)	56 (90)	NT	IR	IR	3(60)	0 (0)	NT	NT	408 (96)
Fosfomycin	342 (96)	55 (89)	NT	8 (57)	7 (78)	IR	3 (75)	IR	IR	415 (93)

Table-V: Sensitivity rates of antibiotics in gram positive bacteria isolated.

Antibiotics	*Enterococcus spp* (39) n (%)	*Staphyloccocus saprophyticus* (3) n (%)	Total n (%)
Penicillin	12 (31)	0 (0)	12 (29)
Ampicillin	23 (59)	0(0)	23 (55)
Ciprofloxacin	1 (3)	2(67)	3 (7)
Amoxicillin clavulanic acid	NT	1 (33) *	24 (57)
Tetracycline	21 (54)	NT	21 (54)
Co-trimoxazole	IR	2(67)	2 (67)
Vancomycin	37 (95)	3 (100)	39 (95)
Linezolid	39 (100)	3 (100)	42 (100)
Nitrofuratoin	35 (90)	3 (100)	39 (90)
Fosfomycin	30 (77)	3 (100)	33 (79)

*Reported on the basis of Cefoxitin disc (a surrogate marker for methicillin resistance)

DISCUSSION

Urinary tract infections (UTIs) are a common health issue affecting different age groups in different geographic locations. The appropriate treatment of UTIs requires the information about their statistical data of prevalence of uropathogens and their antibiogram. Additionally, the data can provide information on the emergence of antibiotic resistance and guide public health interventions aimed at reducing the spread of resistant bacteria.

During the specified timeframe, our laboratory received and analyzed 1282 urine samples from patients exhibiting symptoms of UTI, with 56.79% (728) collected from females and 43.21% (554) from males. Among the entire study population, 39.93% (512) of patients were found to have a bacterial infection.

This finding is similar to a previous study conducted in AFIP Rawalpindi in 2012, which reported a 39.63% prevalence of significant bacteriuria [7]. Additionally, our results are comparable to the prevalence rates reported in other studies, which range from 31% to 36.1% in patients with UTIs. [8,1,9,10] In contrast, lower prevalence rates were observed in some studies, such as 24.54% in a study conducted in Nepal[11] and 21.1% and 16.71% in studies done in Ethiopia and Iraq [12,13]. One study conducted in Iran reported a very low prevalence rate of 6.52% [14].

The results show that among patients with significant bacteriuria, a higher proportion of females (63.67%) than males (36.33%) had UTIs caused by bacterial pathogens. This finding is consistent with previous studies, including one conducted in Peshawar [15] where 63.90% of uropathogens were found in female patients and another in Italy [10] where 60% of patients with bacteriuria were female. However, there are some studies where the percentage of females with UTIs was lower, such as 57%, 50.7% [16,8] and in contrast, one study in Iraq found a much higher prevalence of 72.3% [9].

Additionally, in our research, it was found that 44.7% of females had a significant growth of bacterial uropathogens, while only 33.5% of males showed a similar growth. Notably, these figures are higher than those reported in a study conducted in Nepal, where only 28% of females and 17% of males had bacterial uropathogens in their urine culture [11].

Based on our study, the age range of 12-40 years had the highest incidence of significant bacteriuria, with 253 cases (49.41%) reported, possibly due to the reproductive age group and pregnancy-related urinary tract infections. In contrast, an Italian study found that the maximum bacteriuria rate of 45.5% occurred in the age group of more than 61 years [10].

Out of the 512 bacterial isolates that were cultured, the majority (91.79%) were identified as Gram-negative bacteria, while the remaining 8.21% were Gram-positive bacteria. This finding coincide with a study done in Rawalpindi, which reported a Gram-negative prevalence of 94% and a Gram-positive prevalence of 6% [7]. Similarly, another study conducted in India found that 95% of the total isolates were Gram-negative [17]. In contrast, a study conducted in Italy reported a lower percentage of Gram-negative bacteria at 78.5% [10]. In Iraq, one study suggested that 85% of the total isolates were Gram-negative bacteria [18].

Escherichia coli was the most commonly found isolate, accounting for 69.53% of all isolates, which is a higher percentage compared to some studies where *E. coli* constituted only 40.5% [9], 48.6% [12], 53.5%[10], 61.3% [7], and 68.9%[8] of the total isolates. In another study, the prevalence of *E. coli* was higher at 82.1% of all isolates [19].

Klebsiella pneumoniae was the second most commonly found isolate in our study, accounting for 12.1% of all isolates, followed by *Enterococci* (7.6%), *Pseudomonas* (2.92%), and other bacterial species. In contrast, another study found that the spectrum of uropathogens consisted mainly of *E. coli* (72.16%), followed by *K. pneumoniae* (10.3%) and *S. agalactiae* (5.7%) [14].

Variations in the occurrence and type of bacterial uropathogens have been recorded in different geographic locations and depending on how patients' urinary tract infections are classified [18,19,20].

The sensitivity and resistance patterns of antimicrobial agents can differ among communities and hospitals. One reason for this variation is the emergence of antibiotic-resistant strains, which can result from the inappropriate use of antibiotics. Our study investigated the sensitivity pattern of uropathogens, and the following results were observed. Overall, the gram negative isolates were found to be highly sensitive to Nitrofurantoin (96%), Fosfomycin (93%), Amikacin (79%), Imipenem (75%), and Meropenem (74%). Observations in our study indicated an increase in resistance of Gram-negative bacteria against beta-lactams, quinolones, and trimethoprim/sulfamethoxazole antibiotics, which may be a result of prolonged and selective usage of these antibiotics in our region. A similar trend was also reported in a study conducted in Karachi [21].

The empirical treatment choice for UTI is influenced by the susceptibility pattern of *E. coli,* given that it is the most commonly isolated pathogen of urinary tract infections (69.53% in our study). Among all isolates of *E coli*, 98 % and 96% cases were sensitive to Nitrofurantoin and Fosfomycin. So these drugs are the best choice for treatment as per results of our study , these results are comparable to study done in North West India by Singhal *et al* showing 90.6% cases sensitive to Nitrofuratoin.[20] Similarly in another study, 100% cases were sensitive to Nitrofurantoin [22]. While a recent study done in Karachi by Mubashir, *et al* shows lower sensitivity of Nitrofurantoin and Fosfomycin, 74% and 91% respectively [19]. According to a study conducted in Peshawar [8], it was found that Imipenem, Meropenem, and Fosfomycin have sensitivity rates of 60%, 50%, and 40%, respectively, for *E. coli* isolates. However, Nitrofuratoin was only sensitive in 20% of cases.

Our study found that Imipenem (81%), Amikacin (81%), and Meropenem (79%) were highly effective against *E. coli*. However, Piperacillin Tazobactam and Cotrimoxazole showed sensitivity rates of only 41% and 34%, respectively. The least effective drugs were Ampicillin (8%) and Ciprofloxacin (11%). The Ciprofloxacin sensitivity rate was quite high 77.8% in a study done in Ethiopia [23]. Interestingly, despite Cotrimoxazole being commonly prescribed for UTIs, our study suggests that its efficacy is relatively low (34%). Our study's findings are consistent with a previous study conducted in Lahore, [24] which reported susceptibility rates of 79% for Nitrofurantoin, 76% for Fosfomycin, and 71% for Meropenem, respectively. The study reported a mere 11% susceptibility rate of E. coli isolates to Cotrimoxazole.

The gram positive bacteria isolated in our study were *Enterococcus spp* (7.6%) and *Staphyloccocus saprophyticus* (0.58%). Linezolid is the only drug which was sensitive in 100% cases of all gram positive bacteria. Vancomycin (95%), Nitrofurantoin (90%), and Fosfomycin (77%) were found to be effective against *Enterococcus spp*, aside from Linezolid. *Enterococcus spp* were highly resistant to Penicillin (31%) and Ciprofloxacin (3%). These results are comparable with study done in Rawalpindi having 100% sensitivity for Vancomycin and Linezolid [7]. Our study shows a relatively low percentage of resistance among gram-positive bacteria, especially when compared to the findings from a study conducted in Peshawar [8]. In case of *Staphylococcus saprophyticus*, Vancomycin, Linezolid, Nitrofurantoin and Fosfomycin all are 100% sensitive, while Penicillin and Ampicillin were 100% resistant. According to Mollick *et al*, Vancomycin and Linezolid were identified as the most efficient drugs for treating UTIs caused by gram-positive bacteria [25].

In tertiary care hospitals, patients are often more susceptible to infections due to various medical conditions, such as underlying diseases or invasive medical procedures. This makes it necessary to monitor the prevalence of UTIs and their susceptibility patterns in these settings. Based on our comprehensive findings, we suggest using nitrofurantoin and fosfomycin for both uncomplicated and complicated urinary tract infections (UTIs). For hospitalized patients, we recommend the initial use of Meropenem, either alone or in combination with

Amikacin, and then adjusting the treatment as per the results of the culture report. This approach can help to minimize the development of antibiotic resistance and ensure optimal treatment outcomes for UTIs. It is essential to correlate symptomatic bacteriuria with culture reports, especially in elderly patients who may have poor hygiene or can be bedridden, pregnant women with increased urine stasis, and individuals with benign prostatic hyperplasia. In such cases, positive culture reports may not necessarily indicate an infection, but rather the presence of asymptomatic bacteriuria. Though in some cases asymptomatic bacteriuria should be treated as well but treating every case with antibiotics can result in the development of antibiotic-resistant strains, and therefore caution should be exercised before prescribing antibiotics.

CONCLUSIONS

The most frequently isolated pathogens responsible for UTIs among our studied populace was *E. coli*, followed by *Klebsiella pneumoniae*. Nitrofurantoin and Fosfomycin were identified as effective treatments which limit the use of commonly prescribed oral antimicrobials for UTI treatment. Given the ongoing evolution of drug resistance among bacterial pathogens, it is essential to conduct regular surveillance and monitoring studies in various regions to equip physicians with up-to-date knowledge for empirically treating UTIs in their respective areas.

CONFLICT OF INTEREST

None

AUTHORS CONTRIBUTION

Iqra Sadiq: Manuscript writing, literature review, acquisition and interpretation of data and its review

Fatima Sana: Conception of the work, literature review, manuscript review, data collection and its review

Nadia Tayyab, Umer Shujaat: Acquisition and manuscript review, literature review

Hamid Iqbal, Javaria Ahsan: The ultimate endorsement of the version intended for publication

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