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ORIGINAL ARTICLE

Prevalence and Antibiotic Susceptibility Profiling of MDR *Pseudomonas aeruginosa* from UTI Patients of Southern Punjab, Pakistan

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ABSTRACT

Background: Urinary Tract Infections (UTIs) are of major concern in health care settings. An increasing percentage of organisms causing nosocomial infections have now become multidrug resistant. Hence, constant surveillance of etiology and antimicrobial susceptibility of uropathogens including *Pseudomonas aeruginosa* is compulsory.

Objective: Main purpose of this study was to assess the prevalence rate of various pathogens, and to evaluate the multidrug resistance pattern of *Pseudomonas aeruginosa* in UTI patients of Southern Punjab, Pakistan.

Methodology: A cross-sectional study was performed to obtain quantitative data of UTI patients, for which one hundred and fifty (150) urine samples were obtained from UTI patients admitted to Nishtar Hospital, Multan. Samples were processed for culture, bacterial isolation and identification. Antibiotic sensitivity of *P. aeruginosa* isolates was determined in agreement with Clinical Laboratory Standard Institute Guidelines.

Results: Prevalence of UTI was greater in females (59%) when compared to males (41%). Among 150 urine samples, uropathogens isolated were *Escherichia coli*-50(33.33%), followed by *Klebsiella pneumoniae*-27(18%), *Proteus* spp.-15(10), *Staphylococcus saprophyticus*-13(8.66%), *Staphylococcus aureus*-11(7.33%), *Pseudomonas aeruginosa*-10(6.66%), *Enterobacter* spp.-9(6%), *Candida albicans*-8(5.33%) and *Citrobacter* spp.-7(4.66%). Antibiotic sensitivity profiling of *Pseudomonas aeruginosa* revealed highest sensitivity to cefixime (80%), followed by gentamicin (70%), piperacillin/tazobactam (60%) and nitrofurantoin (40%). Conversely, maximum resistance was observed against amikacin (80%), followed by ciprofloxacin (60%), imipenem (50%) and amoxicillin (50%).

Conclusion: Knowledge of dynamic etiology and ever-changing drug resistance patterns is essential for appropriate management and treatment of UTIs necessitating their exploration on a regular basis.

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INTRODUCTION

Urinary Tract Infections (UTIs) have been reported as one of the most predominant microbial infections globally, that can be diagnosed both in the outdoor and in the clinics[1]. These infections are generally categorized into hospital and community-acquired infections[2]. Patients develop a high risk of acquiring hospital-borne UTIs when admitted to hospital for 48hrs or longer[3]. Calculated percentage of UTIs that are acquired from hospitals is 35% in admitted patients[4]. In UTI patients, microorganisms can affect any part of urinary system by weakening natural body defense mechanisms which can be diagnosed depending on the infection site as pyelonephritis (inflammation of kidneys), cystitis (inflammation of bladder), and urethritis (inflammation of urethra), respectively[5]. On average, 95% of UTI cases are reported because of the presence of single microbial species, while more than one specie is usually present in urine culture due to contamination[6]. Out of all, 80-85% of the UTI cases are attributed towards gram negative bacteria including *Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp. and *Pseudomonas aeruginosa*, however the most frequently encountered pathogen among these is *E. coli*[7].

Specifically, among catheterized patients, the major causative agent is *P. aeruginosa*, a gram-negative pathogen considered as superbug in numerous human infections[8]. Its opportunistic behavior and ubiquitous existence enable it to become associated with pathogenesis particularly in immunocompromised patients[9]. *P. aeruginosa* is held responsible for 11% of nosocomial infections and it produces a multitude of virulence factors that enable its attachment to host cell surface, facilitating entry into the host tissues and suppression of host immunity[10]. In addition to virulence factors, *P. aeruginosa* produces biofilms and chemical signals for quorum sensing on the surface of urinary catheters leading towards the development of infections[11].

Antimicrobial resistance is one of the most significant and challenging issues emerging with regard to hospital as well as community-acquired UTIs[12]. Continuously rising drug resistance rate is creating complications with reference to treatment, morbidity rate, duration of stay in hospital, etc.[13]. Rate of UTIs varies between developing and developed countries depending on random usage of antibiotics. Antibiotic resistance against common bacteria has become a huge trial for clinicians in our part of world in terms of devising therapeutic strategies against UTIs[14].

The leading cause of increasing resistance rate is mutation and resistance gene transfer among pathogens. Plasmids and transposons are the carriers of resistance genes making single type of organism resistant to several drugs precipitating in the emergence of Multiple Drug Resistant (MDR) pathogens[15]. Recently, continuous increase in antibiotic resistance has been observed particularly against ampicillin and trimethoprim which is adversely affecting the management and treatment of UTIs[16]. Furthermore, encountering pathogenic infections that are contagious on routine basis is aggravating the problems while pathogens are becoming resistant to first-line antimicrobial agents[17]. It is hereby critical for physicians to recommend appropriate treatment in accordance with the susceptibility pattern of causative agents of UTIs[18]. When infection is in a specific area, an organized empirical therapy plan is required to reduce spread of resistance among pathogens, for which knowledge of prevalence rate of particular pathogens and their most recent antimicrobial susceptibility profile is compulsory[19].

Keeping this in view, we aimed to isolate, purify, and identify *P. aeruginosa* which is the predominant cause of UTIs among catheterized patients. Furthermore, we evaluated the antibiotic susceptibility profile of *P. aeruginosa* isolates in order to estimate emerging sensitivity pattern in the local population of Southern Punjab, Pakistan where 10% of population is speculated to suffer from UTI at some stage of their life[20].

MATERIALS & METHODS

Sample Collection

One hundred and fifty (150) samples of midstream urine were collected in sterilized containers from the UTI patients bedded in Nishtar Hospital, Multan for this hospital-based study after gaining ethical approval from the Ethical Committee of Nishtar Hospital. The main inclusion criterion was referral and admission to nephrology, urology, gynecology, neurology, & medicine wards of Nishtar Hospital in addition to catheterization and non-catheterization as well as both genders. Further, inclusion was based on appearance of symptoms within two days of stay in the hospital and diagnosis by physicians. All those cases showing symptoms of infection prior to 48hrs stay in the hospital, and/or diagnosed with infections other than UTI were excluded from the study. Personal information including demography and geography as well as medical information encompassing symptoms of patients was documented on a pre-designed questionnaire proforma signed by patients to ascertain informed consent. The samples were processed in microbiology section, pathology department of Nishtar Medical University, Multan, under standardized procedures to reduce the chances of contamination.

Isolation and Identification of *P. aeruginosa*

For the purpose of microscopic examination, centrifugation of urine samples was performed at 5000rpm for 5mins and sediment was considered for standard operating procedures. Cases with considerable pus cells (≥10 WBCs/mm) were administered for further analysis. For isolating and identifying uropathogens, urine samples were streaked onto Cysteine Lactose Electrolyte Deficient (CLED) agar plates maintaining sterility and incubated at 37ºC for 18-24hrs under ventilated conditions as CLED media is strongly recommended for isolation, identification, and quantification of the uropathogens. Subsequent to incubation, colony characteristics were observed by using hand lens. *P. aeruginosa* colonies on CLED medium were light green with typical intertwined surface, while colonies of *E. coli* were yellow due to its ability to ferment lactose. Colonies of *Klebsiella* spp. were also yellow and enormously mucoid in terms of appearance. Colonies of *Proteus* spp. were radiant blue and those of *S. aureus* were deep yellow. Gram staining was done subsequently to observe gram-negative rods of *P. aeruginosa*. Various biochemical tests comprising of triple sugar iron, oxidase, motility, citrate utilization, methyl red / Voges-Proskauer and indole tests were performed for species identification.

Antimicrobial Susceptibility Profiling

Antimicrobial susceptibility pattern of *P. aeruginosa* isolates was determined by performing Kirby-Bauer method (disc diffusion assay) using Mueller Hinton (MH) agar. About 3-5 colonies from pure cultures of *P. aeruginosa* isolates were transferred to a sterilized test tube containing 5ml normal saline, with the help of sterile wire loop and this suspension of colonies was compared with 0.5 McFarland standard. With the help of sterile cotton swab dipped in microbial suspension, each MH agar plate was inoculated and antibiotic discs were applied to it at specific and appropriate distance. The plates were then incubated at 37ºC for 24hrs subsequent to which antibiotic sensitivity zones were measured in mm by ruler and recorded as sensitive, intermediate sensitive or resistant following the Clinical and Laboratory Standard Institute (CLSI) guidelines. Isolates were evaluated for their susceptibility or resistance towards amikacin (AK), ciprofloxacin (CIP), imipenem (IPM), amoxicillin (AMX), cefixime (CFM), gentamicin (CN), piperacillin/tazobactam (TZP), and nitrofurantoin (NF).

RESULTS

Baseline Characteristics of Study Population

Of the 150 urine samples of patients admitted to different wards of Nishtar hospital collected and investigated for the presence of uropathogens, 88 were females whereas 62 were males. Out of all the females, 58 were associated with catheter while 30 were not associated with catheter. Out of all the males, 35 were associated with catheter and 27 were not associated with catheter. Patients belonged to different regions of Multan and nearby localities (Fig. **1**).

This highlights the fact that patients from all over South Punjab become admitted to Nishtar Hospital, Multan, thereby making our sample population representative of entire Southern Punjab region. Symptomatic frequency was observed to be greater in females when compared to males as evidenced by the fact that frequency of urination, burning sensation during urination, flanking pain and dysuria were all more frequently experienced by females in comparison with males (Fig. **2**). Information regarding prevalence of various risk factors associated with UTI was also documented and it was observed that indwelling catheter was the major risk factor associated with UTIs followed by pregnancy, presence of stone, enlarged prostate, diabetes, injured spinal cord and presence of tumor in kidney, respectively (Fig. **3**).

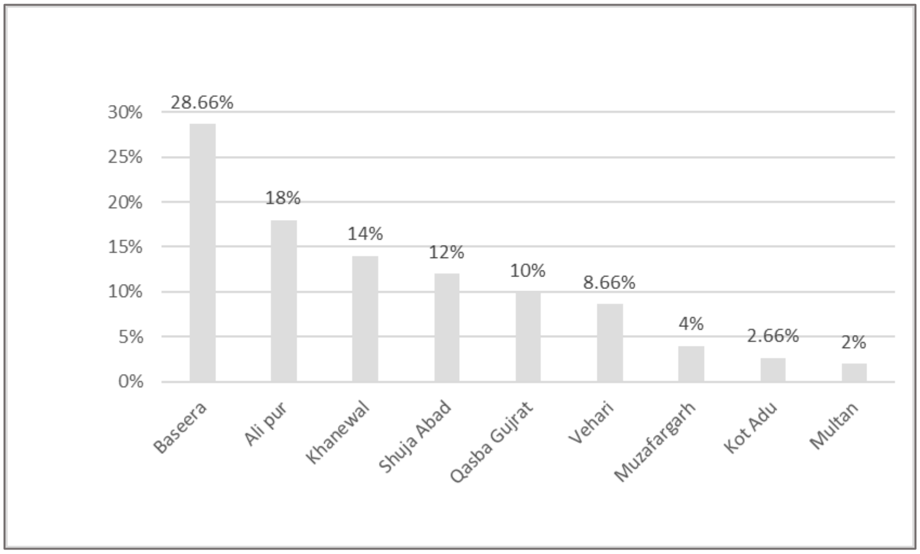

Figure 1. Geographical distribution of study population.

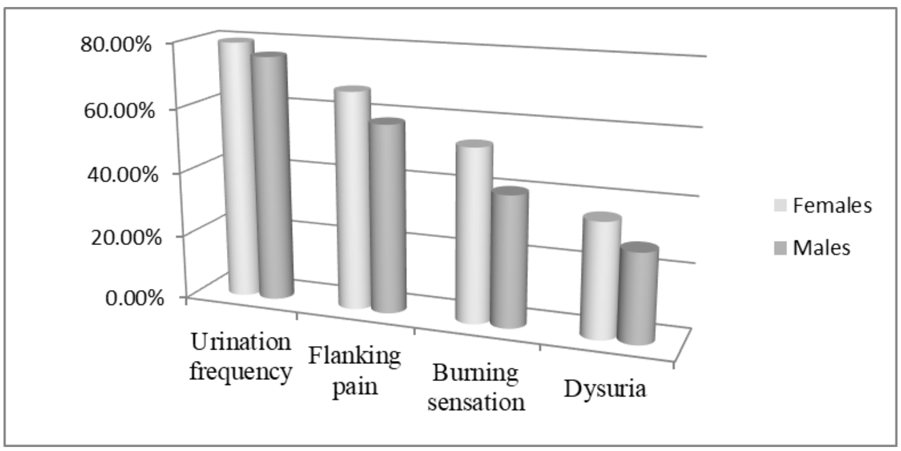

Figure 2. Gender-based prevalence of symptoms associated with UTI in study population.

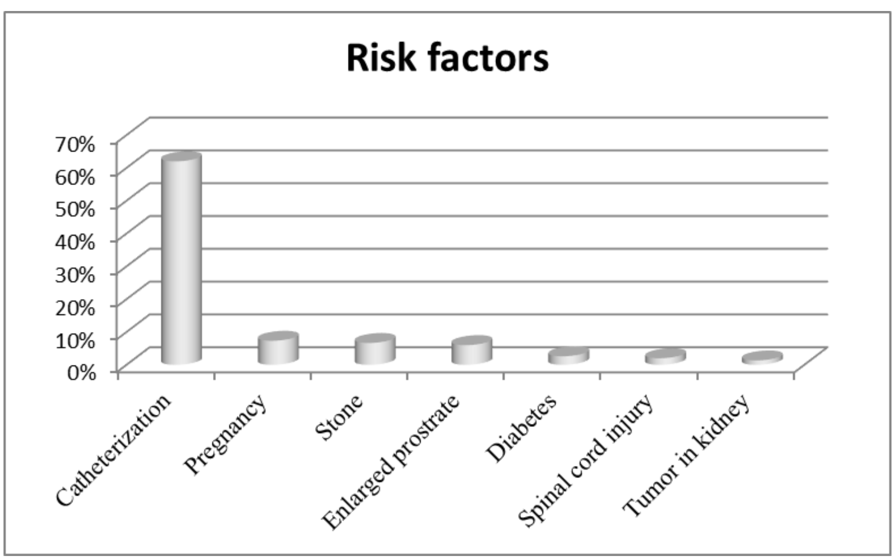

Figure 3. Prevalence of risk factors associated with UTI among study participants.

Age and Gender Based Prevalence of UTIs

UTIs were recorded as being more prevalent among females (59%) as compared to males (41%) in the study population highlighting the substantial gender-based differences in prevalence of UTI. Furthermore, UTI frequency was observed as being higher among younger females and males as compared to older males and females, in general (Table **1**). In both genders, UTIs were the most prevalent among individuals that were 20 to 30 years old, and its frequency constantly decreased while females grew older to 70 years and males grew older to 60 years. A slight increase in UTI frequency was observed among females older than 70 years and males older than 60 years.

Prevalence of Microbes in UTI Patients

Based on the urine cultures, it was confirmed that in all urine samples, at least one kind of urinary microbe was present. Isolates from various samples included *P. aeruginosa, E. coli, Enterobacter* spp*., Klebsiella* spp*., Proteus* spp*., S. aureus*, *S. saprophyticus, Candida albicans* and *Citrobacter* spp. It was observed that *E. coli* was the most predominant uropathogen among males as well as females followed by *K. pneumoniae, Proteus* spp., *S. saprophyticus*, *S. aureus*, *P. aeruginosa*, *Enterobacter* spp., *C. albicans* and *Citrobacter* spp*.,* respectively (Table **2**)*.*

Table 1. Age and Gender Based Prevalence of UTI in the Study Population.

Age in Years	Males (N=62)	Females (N=88)
20-30, N (%)	29 (46.77)	44 (50)
30-40, N (%)	12 (19.35)	20 (22.72)
40-50, N (%)	8 (12.90)	11 (12.50)
50-60, N (%)	3 (4.83)	3 (3.40)
60-70, N (%)	4 (6.45)	3 (3.40)
Above 70, N (%)	6 (9.67)	7 (7.95)

N = Number of individuals

Table 2. Gender Based Prevalence of Uropathogens Isolated from UTI Patients Included in the Study.

Uropathogen	Total (N=150)	Females (N=88)	Males (N=62)
E. coli, N (%)	50 (33.33)	31 (35.22)	19 (30.64)
K. pneumoniae, N (%)	27 (18)	17 (19.31)	10 (16.12)
Proteus spp., N (%)	15 (10)	8 (9.09)	7 (11.29)
S. saprophyticus, N (%)	13(8.66)	7 (7.95)	6 (9.67)
S. aureus, N (%)	11 (7.33)	6 (6.81)	5 (8.06)
P. aeruginosa, N (%)	10 (6.66)	6 (6.81)	4 (6.45)
Enterobacter spp., N (%)	9 (6)	5 (5.68)	4 (6.45)
Candida spp., N (%)	8 (5.33)	4 (4.54)	4 (6.45)
Citrobacter spp., N (%)	7 (4.66)	4 (4.54)	3 (4.83)

N = Number of individuals

Table 3. Antibiotics used against Isolates of *P. aeruginosa* with Their Mechanism of Action and Prevalence in Study Participants.

Antibiotic group	Antibiotic	Mechanism of action	Code	Prevalence (*S or*R)
Aminoglycoside	Amikacin	Inhibitor of protein synthesis	AK	80% (*R)
Fluoroquinolone	Ciprofloxacin	Inhibitor of nucleic acid synthesis	CIP	60% (*R)
Carbapenem (Beta-lectamase inhibitor)	Imipenem	Inhibitor of cell wall synthesis	IPM	50% (*R)
Beta-lactamase inhibitor	Amoxicillin	Inhibitor of cell wall synthesis	AMX	50% (*R)
Cephalosporin	Cefixime	Inhibitor of cell wall synthesis	CFM	80% (*S)
Aminoglycoside	Gentamicin	Inhibitor of protein synthesis	CN	70% (*S)
Beta-lactamase inhibitor	Piperacillin/ Tazobactam	Inhibitor of cell wall synthesis	TZP	60% (*S)
Urinary tract antiseptic	Nitrofurantoin	Inhibitor of cell wall and nucleic acid synthesis	NF	40% (*S)

*R=Resistant; S=Sensitive

Antibiotic Susceptibility Profile of *P. aeruginosa*

Antibiotic susceptibility pattern was determined specifically for *P. aeruginosa* isolates and the results have been summarized in Table **3**. Cefixime, which is a cephalosporin antibiotic, was demonstrated to be the most effective of all the drugs tested against *P. aeruginosa* isolates whereas amikacin, an aminoglycoside, was recorded as being the least effective drug in this regard. In terms of effectiveness against *P. aeruginosa* uropathogen, cefixime was followed by gentamicin, piperacillin/tazobactam and nitrofurantoin, respectively. With reference to ineffectiveness, amikacin was followed by ciprofloxacin, imipenem and amoxicillin, respectively. Furthermore, majority (90%) of the isolates had become resistant to two or more antibiotics classifying them as MDR pathogens.

DISCUSSION

P. aeruginosa was conferred for the first time in 1882 by Gessard when he isolated it from green pus[8]. Urinary tract is the most prevalent site of healthcare-associated infections, with *P. aeruginosa* accounting for 7-10% of UTIs diagnosed in patients admitted to hospitals[21]. Because of the dynamic nature and recent shift in the etiology and antimicrobial susceptibility pattern of UTIs, it has become essential for the clinicians to keep abreast of the etiological agents and their antimicrobial susceptibility profiles, so as to direct and improvise the preliminary empirical treatment[22]. In the light of these observations, this study was conducted to evaluate etiology of UTIs in a population of Southern Punjab, Pakistan and antibiotic susceptibility profiling of MDR *P. aeruginosa* was evaluated. It was observed that UTI was more prevalent in females as compared to males, is due to the differences in the anatomy of their urogenital organs; as short urethra in females allows microbes to gain relatively easy access to bladder so as to cause infection[23]. In addition, females are inclined towards several circumstances like vaginitis as well as decay and prolapse of vagina or womb which leads towards the development of UTI[24]. The symptoms of UTI were also more prevalent among females which reinforces the previous observations in this regard[25].

It has been reported that UTI is the most significant cause of hospital-acquired infections. Among patients who are hospitalized, urinary catheter has been revealed as the major predisposing factor for UTIs[26]. Accordingly, the most substantial risk factor for UTI detected in the present study was presence of indwelling catheter. Previously, this has been reported that the duration of catheterization is directly proportional to the risk of developing UTI[27]. Another important risk factor observed here was pregnancy which has been commonly reported as a factor responsible for making females vulnerable to the development of UTIs[28]. We found that majority of the patients were 20 to 30 years old which has been scarcely reported previously and mostly, old age has been documented as a risk factor for UTIs[29]. This could possibly be explained based on the sexual behavior and use of contraceptive agents[30]. Conceivably due to the rise in rate of sexual action, as well as associated rise in the number of pregnancies and utilization of various kinds of contraceptive agents, younger individuals were the most affected ones[31]. However, study on a larger sample population is required to confirm this speculation.

E. coli was the most commonly isolated uropathogen in individuals belonging to both genders, and *P. aeruginosa* was responsible for 7% of the overall cases, approximately. Similar observations have been reported previously in another population of Pakistan[32]. A vast majority of the *P. aeruginosa* isolates were revealed as being MDR here which is in line with the emerging data regarding prevalence of MDR uropathogens[33]. Cefixime was reported here as being the most effective of all the drugs tested against *P. aeruginosa* whereas amikacin was the least effective owing to high degree of resistance against it. Previously, in various populations the drug resistance patterns have been similar as well as dissimilar implying that antibiotic resistance profile of uropathogens varies across the globe[34,35]. Over-enthusiastic use of antibiotics has led to the global emergence of resistance among various bacteria represented by recommendation of antibiotics without susceptibility reports or prolonged usage of drugs[36]. Antibiotics resistance has been declared as global human health issue by WHO and over-ambitious usage of broad-spectrum antibiotics has elevated the rate of drug resistance across the world[37].

CONCLUSION

UTIs account for a considerable burden of antibiotic prescriptions and gradual rise in resistance against commonly used antibiotics needs to be deliberated immediately. Such growing resistance in UTI patients by *P. aeruginosa* can be addressed by adopting essential management options by physicians as well as medical professionals based on the knowledge of etiology and antibiotic susceptibility of pathogens. Quest for alternative treatment options which may be combined with antimicrobial drugs is the need of the hour.

ETHICAL APROVAL

Ethical approval for the study was obtained from Ethical Review Board of Nishtar Hospital, Multan, Pakistan.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING SOURCE

The study received no external funding.

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LIST OF ABBREVIATIONS

AK	Amikacin
AMX	Amoxicillin
CFM	Cefixime
CIP	Ciprofloxacin
CLED	Cysteine Lactose Electrolyte Deficient
CLSI	Clinical and Laboratory Standard Institute
CN	Gentamicin
IPM	Imipenem
MDR	Multiple Drug Resistant
MH	Mueller Hinton
NF	Nitrofurantoin
TZP	Piperacillin/Tazobactam
UTIs	Urinary Tract Infections

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