Evaluation of Antibiotic Resistance Patterns of Uropathogens in Urine Culture Samples Obtained From Patients Admitted To the Tertiary Care Hospital in Pakistan

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Abstract

Introduction

Urinary tract infection (UTI) is a serious health issue that is foremost among bacterial infections. It is globally affecting millions of people of any gender, genetic factors, age, sexual activity, and race. This study is designed to check the prevalence, nature, and frequency of antibiotic resistance of uropathogens encountered in urine samples of patients diagnosed with UTI.

Methods

A retrospective 6 months study was conducted in a tertiary care hospital in Islamabad, Pakistan. The study was performed on 1050 urine samples. These were then tested for the presence of uropathogens and diagnosis of UTI was confirmed when there were at least 10^5 colony-forming units (CFU)/ml of urine. After confirmation antibiotic susceptibility testing was performed with antibiotic discs.

Results

Out of 1050 tested urine samples, 1037 (69.1%) were tested positive for the bacterial pathogens while 13 (1.2%) were negative. UTI is more prevalent in Females 590 (56.0%) and males 447 (43.1%). For the said period the highest percentage of infection was found in young adults aged 16-40 years (640 (61.1%)). most abundantly found was *E. coli* (402 cases), followed by *S. aureus* (202), *S.saprophyticus* (102). E-Coli has shown resistance against almost all the tested antibiotics. The highest resistance was observed with Cefixime, Nalidixic acid, Ampicillin, and Cefipime However ciprofloxacin and ceftriaxone maintained good activity against uropathogens.

Conclusion:

Unnecessary use of antibiotics has also led to the development of resistance against several antibiotics. There is a dire need for continuous surveillance against antibiotic resistance so that the spread of resistant strains can be prevented and healthcare professionals can be provided with better knowledge for the treatment of UTI.

Keywords: UTI, Antibiotic resistance, E.Coli

1 Introduction

Urinary tract infections are the term functional to the variability of clinical conditions extending from an asymptomatic manifestation of bacteria in the urine to severe kidney infections that will result in sepsis [1]. Urinary tract infections occur at all ages, however, certain paradigms play an important role in its prevalence more or less in any specific individuals. These include gender, genetic factors, age, sexual activity, race, circumcision in boys, and nocturnal enuresis [2]. Studies have shown that in developing countries urinary tract infections are foremost among bacterial infections and globally 150 million people are diagnosed with UTI [3].In addition to this Pregnant women and males with prostate enlargement can contribute as predisposing factors to UTI. However, sexually active females are more prone to develop UTI infections as compared to males. One of the backing factors towards UTI development is the extended use of antibiotics because studies have shown that antibiotics' prolonged use can result in the mutilation of periurethral flora, which will result in colonization of uropathogens as well as increased UTI infections [4]. Urinary tract infections are primarily caused by gram-negative bacteria (80–85%), Gram-positive bacteria, and fungi [5]. Among the Gram-negative bacteria, Escherichia coli (E. coli) (75.5–87%) has a major contribution followed by Klebsiella species, Acinetobacter, Proteus, Citrobacter, Enterobacter, Providencia, Serratia, Pseudomonas however, Enterococcus and Staphylococcus attribute towards Gram-positive infections [4, 6]. Key symptoms of UTI take account of painful urination, dysuria, backache, urinary urgency, pyuria, and abdominal pain, however, this infection can be asymptomatic [7].

For the treatment of UTIs, antibiotics are prescribed worldwide, however, antibiotic prescription and use without any proper antibiotic susceptibility testing have predictably headed towards the

raised prevalence of UTIs caused by drug-resistant bacteria [8]. Thus bacterial resistance to an antibiotic is increasing drastically because of inappropriate antibiotic use, self-medication, and inadequate dosing. So this study is projected to check the prevalence of UTIs and the nature and frequency of uropathogens encountered in urine samples of a group of ambulatory Pakistani patients diagnosed with UTIs and to check antibiotic resistance.

2 Materials and Methods

2.1 Study design

This retrospective study involves all urine samples from patients diagnosed with UTI, for the period of 6 months from January to June in the tertiary care hospital of Islamabad, Pakistan.

2.2 Ethical Approval

The study was approved by the Institutional ethical review board/committee of the Gomal University Hospital, D.I Khan KPK Pakistan (976/acad/EC/GU/2007).

2.3 Inclusion and Exclusion Criteria

For inclusion in the study patients of any age who are diagnosed with symptomatic UTIs have been enrolled in this study. However, those with undiagnosed or asymptomatic UTIs were not included in the study.

2.4 Sample collection and handling

A total of 1050 urine samples were taken from the consented patients. It was made sure to properly follow instructions for the urine collection to minimize the potential for any suspected infection. The informed and consented patient volunteers were provided with wide-mouthed and tightly closed sterilized bottles. The patients were advised to collect clean catch and midstream specimens of urine. The collected samples were then sent to the microbiological lab for diagnosis of UTI which was confirmed when there were at least 10^5 colony-forming units (CFU)/ml of urine [9]. For contaminated specimens, a repeat culture was performed. All those samples were discarded which do not meet the selection criteria.

2.5 Chemicals

p-Dimethyl Amino Benzaldehyde, Phenol Red, Methyl Red, Crystal Violet, Bromothymol Blue, Magnesium Sulphate, Hydrochloride Acid, and Agar (Peking, China)

2.6 Instruments

The main apparatus used in the study included: Bectec 9240 (Dikinson); Incubator (Memert, Germany); Burner lamp (Benson Pharma, Pakistan); Petri Dishes and Microscopic Slides (China Import Export Corporations); Microscope (Olympus, China); Auto Clave (LDZV 50-FB); Disc Dispenser (Oxide Pharma, Pakistan); Centrifuge (Centurion Scientific LTD).

2.7 Inoculation of primary culture media

About 5 µl of each urine specimen was inoculated on separate plates containing a blood agar medium, MacConkey´s agar, and cysteine lactose electrolyte deficient (CLED) agar (OXOID-England), using one millimeter sterilized nichrome inoculating wire loop following standardized procedures. These plates were then incubated at 35-37 C° for 18-24 hours. A routine urine examination was performed for each case, according to a previously described method [10, 11]. After the incubation period colonies were counted to square the number of bacteria present per ml of urine. To identify microbes gram staining was performed as described by Beyonova [12] and examined under optical microscopy (zoom magnification x100) to better notice the morphological characteristics. The Gram-positive bacteria appeared purple while Gram-negative cells were red, allowing complementary classification.

2.8 Antibiogram/Antibacterial bioassay

For suspected Staphylococci or Gram-negative bacteria, direct antibiotic susceptibility testing was performed. The isolates were tested for susceptibility to the following discs of antibiotics (n=10) pre-concentrated by the manufacturer: Ciprofloxacin (CFX – 5 µg/mL), Co-Trimoxazole (TMZ *aka* trimethoprim/sulfamethoxazole - 23.75 µg/mL /1.25 µg/mL), Co-Amoxiclav (AXL *aka* Amoxicillin/clavulanic acid - 20 µg/mL/10 µg/mL) and Ceftriaxone (CTX - 30 µg/mL) (Abbott Lab. Ltd, Pakistan); Amikacin (AMK – 30 µg/mL) and Cefixime (CFM -5 µg/mL) (BBL Pharma, Pakistan); Cefipime (CFP - 30 µg/mL), Nalidixic Acid (NA - 30 µg/mL), Imipenem (IPM -10

µg/mL) and Ampicillin (AMP-10 µg/mL) (Oxide Pharma, Pakistan). After incubation at 35-37 °C for 18-24 hours, the zone of inhibition (diameter in mm) formed in the agar plate was measured to determine the antibacterial effectiveness.

2.9 Statistical Analysis

Microsoft Office Excel 2013 was used for the Statistical presentation of data

3 Results:

3.1 Prevalence of UTI among the patients tested

Table 3.1 shows the prevalence of UTI to gender most affected and age.

Out of 1050 tested urine samples, 1037 (69.1%) tested positive for the bacterial pathogens while 13 (1.2%) were negative. From the positive samples, each sample represented one bacterial isolate. Gender-wise prevalence showed 590 (56.0%) female and 447 (43.1%) male patients were found infected at the time of the study **(Table 3.1)**.Concerning the age in which UTI is most prevalent for the said period the highest percentage of infection was found in young adults aged 16-40 years (640 (61.1%)) followed by patients in their early 40s aged 41 and above (330 (22.0%), lowest prevalence was found in younger patients aged 1-15years (67 (6.4%)).

Character	Number	Percentage
Examined patients	1050	100%
Infected	1037	69.1%
Negative	13	1.2%
Gender		
Female	590	56.0%
Male	447	43.1%
Age Group		
1-------15	67	6.4%
16---------40	640	61.1%
41 and above	330	22.0%

3.2 Frequency-wise distribution of bacterial isolates from samples that tested positive

Table 3.2 shows the Frequency distribution of bacterial isolates from samples that tested positive

As shown in Table 3.2 the prevalence order of uropathogens from the samples that tested positive follows the trend as the most abundantly found was *E. coli* (402 cases), followed by *Staphylococcus aureus* (202), *Staphylococcus saprophyticus* (102), *Serratia spp* (83), *Pseudomonas aeruginosa* (54), *Micrococcus* (53), *Streptococci* (50), *Enterobacter spp* (42), *Klebsiella* (30), with the least identified bacterial isolates was *Proteus mirabilis* [13], However, Fungal infections were encountered for *Candida spp* (10) **(Table 3.2)**.

S: No	Isolated Uropathogens	No: cases	%age
1	***E. coli***	**402**	**38.7%**
2	***Staphylococcus aureus***	**202**	**19.47%**
3	***Staphylococcus saprophyticus***	**102**	**9.8%**
4	***Serratia spp***	**83**	**8%**
5	***Pseudomonas aeruginosa***	**54**	**5.1%**
6	***Micrococcus***	**53**	**5.1%**
7	***Streptococci***	**50**	**4.8%**
8	***Enterobacter spp***	**42**	**4.0%**
9	***Klebsiella***	**30**	**2.8%**
10	***Proteus mirabilis***	**9**	**0.86%**
11	***Candida spp***	**10**	**0.96%**
	Total	**1037**	

3.3 Frequency of Resistance of isolated bacterial species (Gram Negative) against the antimicrobial tested

Out of all the uropathogens, isolated antimicrobial sensitivity testing was performed for all gram-negative and gram-positive bacteria as shown in Table 3.3 and Table 3.4 respectively.

Table 3.3 Frequency of Resistance of Isolated bacterial species (Gram Negative) against the antimicrobial tested

Results showed that among the isolated gram-negative bacteria E-Coli showed supreme resistance against all tested antimicrobials with a percentage effective of (97%) ciprofloxacin, (83%)

ceftriaxone, and (69%) Imipenem, (66%) Amikacin, (57%) co-Trimoxazole, and (55%) co-amoxiclav with lowest against Cefixime (46%), Nalidixic acid (44%), Ampicillin (43%) and Cefipime (42%). However with other isolated gram-negative bacteria, *Serratia spp* showed maximum resistance against Nalidixic acid and Cefipime with only (55%) effectiveness, *Enterobacter spp* showed maximum resistance against Cefipime (33%), *Klebsiella spp* Showed resistance against co-Trimoxazole and Cefipime (50%), *Pseudomonas aeruginosa* showed resistance against Cefipime with only (42%) effectiveness however *Proteus mirabilis* showed complete resistance against Amikacin, Cefipime, Nalidixic acid and ampicillin **(Table 3.3)**.

Anti-microbial	*Escherichia coli (402 cases)*			*Serratia spp (83 cases)*			*Enterobacter spp (42 cases)*			*Klebsiella spp (30 cases)*			*Pseudomonas aeruginosa (54 cases)*			*Proteus mirabilis (9 cases)*		
	R	S	%	R	S	%	R	S	%	R	S	%	R	S	%	R	S	%
Ciprofloxacin	2	40	97	1	8	90	0	4	100	0	2	100	0	2	100	0	1	100
Ceftriaxone	7	36	83	0	9	100	1	4	88	0	2	100	0	1	100	0	1	100
Amikacin	12	24	66	0	5	100	2	4	60	0	1	100	0	1	100	1	0	0
Cefixime	23	20	46	4	5	55	1	3	75	1	1	50	0	1	100	1	0	0
Cefipime	23	7	42	2	5	71	2	1	33	1	4	90	23	7	42	--	--	---
Nalidixic acid	24	19	44	4	5	55	1	3	75	2	2	50.	1	-	00	1	0	0
CoAmoxiclav	19	24	55	3	6	66	2	2	50	2	2	50	1	0	00	0	1	100
Imipenem	13	30	69	3	7	70	1	3	80	1	2	69	1	2	80	0	1	100
Ampicillin	17	13	43	1	7	87	1	3	80	2	3	60	3	0	0	1	0	0
Cotrimoxazole	16	22	57	0	8	100	1	3	75	1	1	50	-	-	-	0	1	100
	S stands for "Sensitive" or "Susceptibility". R-Stands for "Resistance"																	

3.4 Frequency of Resistance of isolated bacterial species (Gram-Positive) against the antimicrobial tested

Table 3.4 Frequency of Resistance of isolated bacterial species (Gram-Positive) against the antimicrobial tested

Among the isolated gram-positive bacteria, *Staphylococcus aureus* showed resistance against all tested antimicrobials except ciprofloxacin with percentage effeteness of Imipenem (88.7%), ceftriaxone (84.7%), Amikacin (76.6%), Cefipime, co-amoxiclav, and ampicillin (57.8%), co-Trimoxazole (55.8%), Nalidixic acid (47%) and Cefixime (42.5%) effectiveness. However with other isolated gram-negative bacteria *Staphylococcus saprophyticus* Showed maximum resistance against Amikacin with only (28.5%) effectiveness, *Micrococcus* Showed maximum resistance against Nalidixic acid (25. %), *Micrococcus* Showed resistance against ceftriaxone and Cefipime (50.7%) effectiveness **(Table 3.4)**.

Anti-microbial	*Staphylococcus aureus (202 cases)*			*Staphylococcus saprophyticus (102 cases)*			*Micrococcus (53 cases)*			*Streptococci (50 cases)*		
	R	S	%	R	S	%	R	S	%	R	S	%
Ciprofloxacin	00	18	100	1	10	90.9	00	3	100	00	5	100.
Ceftriaxone	3	16	84.7	2	9	82.7	00	4	100	3	2	50.7
Amikacin	4	13	76.6	5	2	28.5	1	5	90.6	00	4	99.6
Cefixime	11	8	42.5	4	7	63.6	1	3	80.5	2	3	70.5
Cefipime	6	8	57.5	3	8	72.5	1	2	66.5	3	2	41.5
Nalidixic acid	10	9	47.1	6	5	44.1	3	1	25.2	1	4	80.1
CoAmoxiclav	8	11	57.8	6	5	45.8	00	4	100	2	3	60.8
Imipenem	5	38	88.7	6	2	70.7	5	3	69.7	2	4	69.7
Ampicillin	8	11	57.3	4	6	60.3	5	8	60.2	2	3	60.3
Co-Trimoxazole	8	10	55.8	4	7	63.8	1	3	75.8	2	3	60.8

4 Discussion

Urinary tract infections are one of the prevalent bacterial infections that affect people from all age groups and ethnicities [14].In this study, the prevalence and antibiotic resistance against different uropathogens isolated from the urine samples were studied. For the said period results have shown

that UTI was more prevalent in females (590 (56.0%)) as compared to males (447 (43.1%)) **(Table 3.1)**. This result is in coherence with the studies that have reported that the female-to-male ratio to developing UTI is 3:2 [15, 16]. However the age group most affected with the premier percentage was in patients of 16-40 years (640 (61.1%)) followed by aged 41 and above (330 (22.0%), however lowest prevalence was observed in younger patients aged 1-15years (67 (6.4%)) **(Table 3.1)**. The study conducted in the US showed that 5% of elders and 3% of adults were diagnosed with UTI [17]. Another study showed that UTI is the most common infection among prepubertal girls (3%) and prepubertal boys (1%). The risk to suffer from UTI increases with age in females as compared to males. However male incidence to develop UTI in adult age is dependent on changes in prostatic function and elder females, it's the Childbearing and reproductive surgeries, Mucosal/smooth muscle changes from menopause, Changes in vaginal flora, Urinary incontinence that plays as one of the important factors towards the development of UTI at any age [18]. From this study, it was manifested that E-Coli was the most isolated bacteria (38.7%) in the tested urine samples as shown in table 3.2. This study data is in coherence with the literature that states E. coli is a major causative agent of all complicated and uncomplicated urinary tract infections [14]. Results have also shown that bacteria of the Enterobacteriaceae family were the most isolated uropathogens and major UTI infections were caused by E-coli and were isolated and identified in 38.7% urine samples, *Serratia spp* (8%), *Enterobacter spp* (4.0%), *Klebsiella spp* (2.8%), *Pseudomonas aeruginosa* (5.1%), *Proteus mirabilis* (0.86%) **(Table 3.2)**. Among the gram-positive bacteria *Staphylococcus aureus* was identified in *(*19.47%) of urine samples, *Staphylococcus saprophyticus (*9.8%), *Micrococcus (*5.1%), *and Streptococci* was isolated from 4.8% urine samples **(Table 3.1).**UTI is the infection for which most antibiotics are prescribed worldwide [19]. World Health Organization has listed that 80% of antibiotics are used daily in the community for the treatment of different ailments and out of which 20-50% are used with no proper guidelines[20].In this study, E-Coli has been found not only to be the most prevalent causative agent of UTI but also to be resistant to almost all the antibiotics used for the treatment. The highest resistance was observed with Cefixime, Nalidixic acid, Ampicillin, and Cefipime **(Table 3.3)** which are somewhat comparable to the previous readings [21]. Resistance to co-trimoxazole and ampicillin has been increased in recent years against UTI-causing uropathogens [22]. Urinary tract

infection etiology and resistance to antibiotics patterns change from country to country because prescribing practices are different. In the present study, most gram-negative showed elated resistance against Cefipime followed by Nalidixic acid, Cefixime, Co-Trimoxazole, and ampicillin. It is evident in the literature that resistance of E. coli to Co-Trimoxazole and ampicillin is significantly higher in complicated UTIs [23, 24]. The study also showed Gram-positive bacteria that showed resistance to antimicrobials and a significantly higher number of resistant cases were seen with Nalidixic acid, ampicillin, Cefixime, and Imipenem **(Table 3.4)**.During the past year's resistance of antibiotics towards *Staphylococcus aureus* has increased significantly [25]. This study has also shown resistance of *Staphylococcus aureus* and *Staphylococcus saprophyticus* with all the tested antibiotics.

4.1 Conclusion

Gram-negative bacteria that are isolated from urine sample has been found to have more resistance towards antimicrobial agents. Uncontrolled and non-prescribed use of antibiotics has also led to the development of resistance against several antibiotics. There is a dire need for continuous surveillance against antibiotic resistance so that the spread of resistant strains can be prevented and healthcare professionals can be provided with better knowledge for the treatment of UTIs. From the study is concluded that the drug that showed the least resistance against both gram-positive and negative bacteria is ciprofloxacin and ceftriaxone however Cefipime, Nalidixic acid and Cefixime are not effective drugs against UTI infections

4.2 Limitations

This was a short retrospective study that was conducted in only one health care system so it does not represent or cover the health care system of Pakistan, so these findings cannot be generalized Secondly the duration of the study was short around 6 months, this did not include all the cases. A large-scale retrospective study is recommended to have sound knowledge about the prevalence of UTI among different age groups with a more significant approach and resistance towards a wide range of antibiotics so that health provision facilities can be improved.

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The authors declare no competing interest

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Authors Contribution Statement

The authors confirm their contribution to the paper as follows:

➢ The complete study was performed and manuscript was written by Dr.Naeem Ur Rehman

➢ Results: Dr.Mehreen Arif

➢ Draft Checking: Dr.Hammad Ahmad

➢ Final approval: Dr.Naeem Ur Rehman

Authors have reviewed the results and approved the final version of the manuscript

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