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Original Article

Frequency and antibiotic susceptibility pattern of uropathogens isolated from patients with urinary tract infection

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Abstract

Background: Urinary tract infection is one of the commonest disease of the community and hospitals resulting in high rates of morbidity and economic burden associated with its treatment. Urinary tract infection (UTI) is caused by both gram positive and negative bacteria but most common agents are the gram negative bacilli. Distribution of urinary pathogens and their resistance pattern to antimicrobial drugs vary regionally and even in the same region. **Objective:** The aim of the study is to isolate and identify the uropathogens causing UTI & to see the antibiotic susceptibility pattern of the uropathogens in the region. **Materials and Methods:** This study has been carried out in the Department of Microbiology of Rajshahi Medical College in the period from July 2014 to June 2015. Midstream urine were processed for microscopy and culture and the pathogens were identified by standard methods. Antimicrobial sensitivity was carried out by Kirby-Bauer disc diffusion method according to clinical and laboratory standards institute guidelines. **Results:** Out of 254 urine samples, 96(37.79%) shows significant growth and among them *E.coli* 66(68.75%) was the most prevalent gram negative bacilli followed by *Klebsiella* spp. 6(6.25%), *Enterobacter* spp. 4(4.16%) and *Citrobacter* spp. 4(4.16%). *Pseudomonas* spp. 6(6.25%), *Proteus* spp. 5 (5.20%) and in gram positive cocci group *staph.Saprophyticus* 3(3.12%) and *Staph.aureus* 2 (2.08%). Out of 96 positive bacterial strains 59(61.45%) were resistant to multiple groups of antibiotics. A good number of gram negative isolates were resistant to commonly used drugs such as ampicillin, ceftazidime, cephadrine, ciprofloxacin, co-trimoxazole, azithromycin and fewer number are moderately resistance to imipenem, amikacin and nitrofurantoin. **Conclusion:** *Escherichia coli* is still the most common uropathogen and the antibiotic selection is very difficult without antibiogram due to wide range of resistance of commonly used drugs which have been used previously. Since most UTIs are treated empirically. Therefore there is a need for periodic monitoring of aetiological agents of UTI and their resistance pattern in this community.

Key words: Antimicrobial susceptibility test, Uropathogen, *Escherichia coli*.

Introduction

Urinary tract infection is one of the commonest disease of the community and hospitals resulting in high rates of morbidity and economic burden associated with its treatment. Although UTI's are encountered in both sexes and all ages, but it is commoner in females. Out of every two female one has suffered from a urinary infection at least once in her life; 12% with an initial infection and 48% with a recurrent episodes¹. Frequent (3-6 per year) recurrences

of infection follow the initial Episode, producing additional morbidity and time lost from work. The principal reservoir of infectious agents for urinary tract is the flora of the bowel, external genitalia, perineal and perianal regions. Most UTI is caused by a single pathogen, usually enteric gram-negative bacteria originating from the fecal flora of the host. *Escherichia coli* is responsible for approximately 80% of all nosocomial and >90% of all community acquired

infections. It colonize the perineum and then ascend the urethra to multiply and infect the bladder, kidney and adjacent structures. The most common site of infection is the urinary bladder. UTI is considered significant and requires treatment when more than 10^5 microorganisms per ml of urine are present in a properly collected sample², where lower count usually associated with contaminant from urethra or external genitalia³. Inappropriate and empirical usage of wide spectrum antibiotics, insufficient hygiene, immunosuppression and prolonged hospitalization are some of the major aetiological factors that elevate the chances of infection. Other factors including age, sex, cultures, sexual hygiene, obstruction of the urinary tract, toilet wiping method, use of irritant soap, vagina deodorant and contraceptives are also reported to predispose to UTI but the involvement of pathogens like *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* have a high preponderance for catheter use⁴. Depending on site of isolates and infection, many virulence factors may be associated with many pathogens.

The uropathogens are detected in the laboratory by culture of urine on Blood agar, MacConkey's agar and cystine lactose electrolyte deficient agar media and are identified with different identification tests. Chromogenic media allows the differentiation of genus and species of uropathogens by changing different colors due to present of specific enzymes. Thus, save times and uropathogens expenditure. Multiple drug resistance of gram negative bacteria have been a long and well recognized problem especially in urinary tract infection. This study had been carried out to isolate the pathogens and to investigate the drug resistance pattern. Bacterial isolates considered to be Multi drug resistance (MDR) when shows resistance to at least three or more groups of antibiotics.⁵ Antibiotic selection against UTI is done by susceptibility test. But sometimes bacteria develop resistant to multiple antibiotics and create a major problem. Whereas in Bangladesh *E.coli* and *Klebsiella* 87% resistant to more than 3 drugs and 80% of them harboured plasmids⁶. In present

scenario, antimicrobial drug resistance of major uropathogens has posed a global threat. Of the various uropathogens, the most common organisms are *E.Coli*, *Klebsiella* spp., *Proteus* spp. and most of these organisms have developed resistance to antimicrobial agents like co-trimoxazole, ampicillin, cephalosporins, Fluoroquinolones, beta lactum drugs etc. The development of extended spectrum cephalosporins in the early 1980s was regarded as a major addition to our therapeutic armamentarium in the fight against beta-lactamase mediated bacterial resistance but recently the emergence of *Escherichia coli*, *Klebsiella pneumoniae* and other uropathogens resistant to ceftazidime and other cephalosporins seriously compromised the efficacy of these life saving antibiotics⁷. The inappropriate use of antimicrobial agents does not achieve the desired therapeutic outcomes and is associated with the emergence of resistance. Lack of access, inadequate dosing, poor adherence and sub-standard antimicrobials may play as important a role as overuse. Due to the widespread use of these drugs, new forms of antimicrobial resistance have emerged⁸. So, the present study has designed to isolate uropathogens and its susceptibility to find out the resistant pathogens. This study will not only help the individual patients but also will provide early warning of the emergency of resistant isolates to clinicians for better management and will prevent spread of MDR uropathogens in community and in the hospitals.

General Objective

To isolate and identify the uropathogens causing UTI and to see the antibiotic sensitivity and resistance pattern of the isolated strains in department of Microbiology of Rajshahi Medical College Hospital.

Specific Objectives

1. To isolate and identify the uropathogens causing UTI.
2. To see the antibiotic resistance pattern of the uropathogens.
3. To calculate the percentages of multi drug resistance (MDR) strains of uropathogens.

Materials and Methods

This descriptive type cross sectional study was conducted in Microbiology Department of Rajshahi medical college from July 2014 to June 2015. A total of 254 urine samples from OPD and IPD irrespective of age and sex at Rjshahi medical college were examined by standard laboratory methods. Relevant history, laboratory records and findings were recorded in a predesigned data sheet analyzed manually and using SPSS computer programme.

Specimen collection: The early morning mid stream urine was collected in a sterile, wide mouth, leak proof, detergent free container labelled with patients identification number and date.

Microscopic examination of urine (Wet film preparation for centrifuged urine)

After centrifugation at 4000 rpm for 5 minutes the supernatant fluid was discarded and the sediment was put on to a clean labeled glass slide and covered with a clean cover slip and then examined under light microscope using 10x and 40x objectives.

Isolation of organisms: Semiquantitative urine culture using a calibrated loop was having 23G and internal diameter of 3.26 mm which hold 0.004 ml of urine performed. Samples were transferred to the laboratory immediately and inoculated on Blood agar, MacConkey's agar and Highchrome agar media and incubated aerobically at 37°C for 24 hours for bacterial growth.

Cultural and biochemical findings: After 24 hours incubation morphological characteristics (size, shape, colour, surface, texture, elevation, opacity) were carefully observed and recorded. If growth occurs, colony count was done to calculate the number of colony forming unit per ml of urine.

The threshold used for defining significant bacteriuria is 10^5 or more colony forming units (CFU) of bacteria/ml of voided urine. More recently studies suggest that a threshold of 10^2 CFU of bacteria/ml of urine may be sensitive indicator of infection in acutely symptomatic women while being only slightly less specific than a value of 10^5 /ml.⁹

Gram negative bacteria were identified by their colony morphology, pigment production, motility test, and corresponding oxidase test, indole production, citrate utilization, urease production and triple sugar iron for sugar fermentation and H_2S production test. Gram positive microorganisms were identified with the catalase, coagulase test and subculture on manitol salt agar for *S.aureus*

Antimicrobial susceptibility test: Antimicrobial susceptibility test of the identified isolates were performed by Kirby-Bauer disc diffusion technique using Muller-Hinton agar media and commercially available antimicrobial discs. Antibiotic discs used for gram negative bacilli were cephadrine, ceftazidime, amoxycylav, cotrimoxazol, azithromycin, ciprofloxacin, imipenem, amikacin and nitrofurantoin. The inoculating plates were examined and the diameter of zone of inhibition was measured and compared with the the supplied inhibitory zone chart of respective antibiotic. The zone of inhibition was equal to or larger than or less than that of zone chart was treated as sensitive and resistant. Zone of inhibition was measured in millimeter by using a ruler over the surface of the plate with the lid open. Standard strains of *E.coli* (ATCC 25922) was used routinely in this study as control.

Results

A total of 254 urine samples were collected from different age groups and were cultured on appropriate bacteriological culture media. Isolated uropathogens resistant to more than three groups of antibiotic were obtained by antibiotic sensitivity test.

Table-I: Rate of isolation of uropathogens from culture of urine along with gender distribution. N=254

Sex	No growth	Growth of Isolated pathogen
Female	113(71.51%)	58(60.41%)
Male	45(28.48%)	38(39.58%)
Total	158(62.20%)	96(37.79%)

Table I shows gender distribution for the rate of isolation of urinary pathogens in urine culture.

Among 254 urine samples 96 revealed presence of uropathogens in culture of urine.

Among which female and male were 58 and 38 respectively

Table-II: Culture yielded growth of uropathogens from urine culture

Isolated pathogens	Number	Percentage
<i>E.coli</i>	66	68.75
<i>Klebsiella spp.</i>	6	6.25
<i>Enterobacter spp</i>	4	4.16
<i>Citrobacter spp.</i>	4	4.16
<i>Pseudomonas spp.</i>	6	6.25
<i>Proteus spp.</i>	5	5.20
<i>Staph. saprophyticus</i>	3	3.12
<i>Staph.aureus</i>	2	2.08
Total	96	100

Table-II shows, pattern of bacteria isolated from urine culture. Among 254 urine samples 96(37.79%) shows significant growth. Among them gram negative bacilli *E.coli* 66(68.75%) is predominant followed by , *Klebsiella spp.* 6(6.25%), *Enterobacter spp.* 4(4.16%) and *Citrobacter spp.* 4(4.16%) *Pseudomonas spp.* 6(6.25%), *Proteus spp.* 5 (5.20%) and in gram positive cocci group *staph.Saprophyticus* 3(3.12%) and *Staph.aureus* 2 (2.08%) found .

Among all uropathogens maximum isolates were *E.coli* 66(68.75%) and the second most prevalent isolates were *Klebsiella spp.* 6(6.25%) and *Pseudomonas spp.* 6(6.25%),

Table-III: Resistance pattern of identified uropathogens against different antimicrobial agents. N(%)

Groups	Antimicrobial agents	Identified bacteria							
		<i>E.coli</i> N=66	<i>Klebsiella</i> N=06	<i>Enterobacter</i> N=04	<i>Citrobacter</i> N=04	<i>Pseudomonas</i> N=06	<i>Proteus</i> N=05	<i>Staph. aureus</i> N=02	<i>Staph. Saprophyticus</i> N=03
A	Cephadrine	59(89.39)	6(100)	4(100)	4(100)	6(100)	5(100)	2(100)	1(33.33)
	Ceftazidime	49(74.24)	4(66.66)	4(100)	4(100)	4(66.66)	3(60)	2(100)	1(33.33)
B	Ampicillin	49(74.24)	5(83.33)	3(75)	4(100)	6(100)	4(80)	2(100)	1(33.33)
	Oxacillin	ND	ND	ND	ND	ND	ND	00	2(66.66)
	Carbencillin	ND	ND	ND	ND	5(83.3)	ND	ND	ND
	Pipercillin	ND	ND	ND	ND	6(100)	ND	ND	ND
C	Imipenem	5(8.0)	2(33.33)	2(50)	1(25)	2(33.33)	1(20)	00	00
D	Nitrofurantoin	21(32.0)	2(33.33)	1(25)	1(25)	4(66.66)	3(60)	1(50)	2(66.66)
E	Azithromycin	38(57.0)	3(50)	2(50)	2(50)	1(16.66)	3(60)	00	1(33.33)
F	Amikacin	6(9.09)	1(16.6)	1(25)	00	3(50)	1(20)	00	00
G	Ciprofloxacin	36(54.54)	3(50)	2(50)	2(50)	00	1(20)	00	2(66.66)
H	Co-trimoxazole	36(54.54)	4(66.66)	2(50)	4(100)	1(16.66)	3(60)	00	1(33.33)
J	Vancomycin	ND	ND	ND	ND	ND	ND	00	00
	Novobiocin	ND	ND	ND	ND	ND	ND	00	3(100)

A-Cephalosporin group B-Penicillin group C-Carbapenem group D-Furanes group E-Macrolide group

F-Aminoglycoside group G-Quinolone group H-Anti folate antagonist Note: ND=Not Done

J-Glycopeptide group

Table-III shows anti microbial resistance pattern of uropathogens. Fourteen antimicrobial agents distributed into A to J group were used. All the uropathogens except *E.coli* were 100% resistant to cephradine. *Enterobacter* spp, *Citrobacter* spp and *Staph. aureus* were 100% resistant to ceftazidime. Similarly *Citrobacter* spp, *Pseudomonas* spp and *Staph. aureus* were sent percent resistant to ampicillin. Other uropathogens were variable resistance to other groups of antibiotics such as ciprofloxacin, co-trimoxazole, azithromycin and fewer number are moderately resistance to imipenem, amikacin and nitrofurantoin.

Among gram positive cocci *Staph.aureus* are 2 and they are 100% resistant to ampicillin, ceftazidime, cephradine and 1 (50%) to nitrofurantoin. Similarly *Staph.saprophyticus* are 3 and 100% resistant to novobicin and 2 (66.66%) to ciprofloxacin, nitrofurantoin and oxacillin and incidence of resistancy lower to ampicillin, ceftazidime, cephradine, azithromycin, co-trimoxazole respectively.

Table-IV: Rate of multi drug resistance (MDR) uropathogens among different isolates

Identified isolates	Number of detected MDR isolates (%)
<i>E.coli</i> (N=66)	38(57.57)
<i>Klebsiella</i> spp (N=06)	03(50)
<i>Enterobacter</i> spp (N=04)	04(100)
<i>Citrobacter</i> spp (N=04)	04(100)
<i>Pseudomonas</i> spp (N=06)	04(66.66)
<i>Proteus</i> spp (N=05)	04(80)
<i>Staph. Aureus</i> (N=02)	01(50)
<i>Staph saprophyticus</i> (N=03)	01(33.33)
Total=96	59(61.45%)

Table-IV:shows, Out of 96 (37.79%) identified bacterial isolates MDR pathogen are 59(61.45%). Bacteria considered to be MDR when it shows resistance to more than three groups of drugs. Bacteria resistant to multiple drugs 38 (57.57%) on *E.coli*, 03 (50%) on *Klebsiella* spp, 4(100%) on *Enterobacter* spp, 4(100%) on *Citrobacter* spp, 04(66.66%) on *Pseudomonas* spp, 04(80%) on *Proteus* spp and 01 (50%) on *Staphylococcus aureus*. and 01 (33.33%) on *Staph saprophyticus*.

Discussion

Multiple drug resistance of gram negative bacteria have been a long and well recognized problem especially in urinary tract infection. This study had been carried out to investigate the drug resistance pattern. In developing countries antibiotics are available freely without prescription and this widespread inappropriate antibiotic uses exert a selective pressure that acts as a driving force in the development of antibiotic resistance. When bacteria develops resistant to “first-line” antibiotics, therapy with second-line or third-line antibiotics will increased the chance to develop of resistance to the new class of antibiotics.

A total of 254 urine samples, 96(37.8%) had yielded growth of significant pathogens which is nearly similar with the observation of Dash *et al.*(2013)¹⁰ in and Mehta *et al.*(2013)¹¹ both in India and Rahman *et al.*(2008)¹² in Bangladesh and their findings were 34.5%, 36.68% and 30.8% respectively. Comparatively higher isolation were observed in Pakistan¹³, South Trinidad¹⁴ and Mexico¹⁵ and their isolation were 42.4%, 49% and 97.3% respectively. This higher isolation may be due population living in poor socioeconomic status and maintenance of poor hygiene in this region and geographical variation also. Among 96 significant bacteria *E.coli* was 66(66.75%), predominant. This finding is consistent with other studies done in Bangladesh¹², Iran¹⁶ and India¹⁷ and their isolation were 66.92%, 68%, 68.6% respectively. The high prevalence of *E.coli* in UTI cases may be due to its existance as a normal flora in the large intestine and colonization in the perineal area, bad toilet behaviour (wipe from back to front). Lower isolation was also observed in Nigeria¹⁸ and in Mexico¹⁵ their isolation were 18.6% and 24.7%. There studies did not support to our study. The reason behind these lower isolation is the replacement of *E.coli* to other uropathogens.

Klebsiella 6(6.25%) was the second common cause of UTI in our study which is similar to other studies done in Jaipur of India¹⁵ and in Lahore of Pakistan¹³ and

their isolation were 6.6% and 6.52% respectively. Higher isolation was observed in Nigeria¹⁹ which was 14.8%. In this study, the isolated *Citrobacter* and *Enterobacter* spp. were a few in number because major number of samples in our study were taken from out patient department and these pathogens are rarely encountered as community acquired UTI pathogens.

Another gram negative uropathogens *Proteus* spp. were 05(5.20%) which correlates to other studies²⁰ and *Pseudomonas* spp. were 06(6.25%) which correlates to a study of Bangladesh¹² and Nepal²⁰ which were 6.7% and 4% respectively but dissimilarities were also found in a study of Pakistan²¹ (0.2%). This difference may be due to differences in geographical location, temperature, humidity and hospital environment, availability of medical facilities. In Gram positive cocci, 02(2%) were *staphylococcus aureus* and another cocci *staph. saprophyticus* were 3(3.12%) in our study. Which is similar to the findings of Noor *et al.* (2013)²² in Bangladesh. But dissimilar finding was reported by Sharma *et al.* (2013) in Nepal (21.3%)²⁰.

The dissimilarities of the rate of isolation and isolated bacterial species between the present study and various other studies may be due to passage of time, difference among sexes, , presence of many systemic diseases. Method of collection of urine samples are also responsible for these variations.

Antibiotic resistance pattern of uropathogens isolated from confirmed UTI cases were also studied. In our study, the incidence of resistance to *E.coli* were higher in commonly used antibiotics like- ampicillin (74.24%), ceftazidime (74.24%), cephadrine (89.39%). This study is similar with Rahman *et al.* (2008)¹² in Bangladesh. In our study, *E.coli* was 54.54% resistance to both ciprofloxacin and cotrimoxazole which is compatible with Dash *et al.* (2013)¹⁰ and Shaifali *et al.* (2012)²³ in India showed 53.4% and 60.9% resistant to ciprofloxacin respectively but it did not correlate to the study conducted by Khameneh *et al.* (2009)²⁴ in Iran (83.2%).

Over the last few decades the resistance pattern of urinary isolates has been showing great changes all over

the world. Resistance to cotrimoxazole is generally associated with resistance to additional antibiotics often to penicillin, cephalosporins, quinolones and multidrug resistance may be transferred on a single plasmid. Our study, *Klebsiella* spp. was highly resistant to ampicillin, cephadrine, ceftazidime and cotrimoxazole which correlate with the findings of Pakistan²⁵ but dissimilarity is seen with cotrimoxazole(93.48%), amikacin (32.16%) and nitrofurantoin (32.61%). The reason for higher resistance to commonly used drugs may be due to the higher selection pressure exerted by prolonged and irregular use of these antibiotics in this region.

Lower resistance was noted to imipenem (8%), amikacin (9.09%) and nitrofurantoin (32%) against *E.coli* and *Klebsiella* spp. which is similar with other studies in Bangladesh²⁶ as well as other neighbouring countries such as India²⁷ and Pakistan⁵. Restricted and limited use of the drugs in clinical practice is the reason for high sensitivity.

Enterobacter spp, *Citrobacter* spp, *Proteus* spp, *Pseudomonas* spp are the causative agent of hospital acquired UTI and they are 60-100% resistant to commonly used antibiotics which were previously sensitive. *Pseudomonas* spp. in our study were 100% resistant to ampicillin, piperacillin, but no resistance was observed in ciprofloxacin which is supported by Bhowmick *et al.* (2004)²⁸ in Bangladesh.

In our study, *Proteus* spp, *Pseudomonas* spp and were 60-80% resistant to commonly used drugs such as ampicillin, cephadrine, cotrimoxazole, azithromycin, ceftazidime and nitrofurantoin. Other studies showed different rate of sensitivity such as by Raja *et al.* (2007)²⁹ in Malaysia and by Brown *et al.* (2004)³⁰ in Jamaica and they were 11.3%, 19.6% respectively resistant to ciprofloxacin. Dissimilarity with our study was noted in a Nigerian study conducted by Akingbade *et al.* (2012)³¹ which was 35.5%. The higher isolation in their studies might be due to the higher prevalence of pathogens where the studies were conducted or prescribing the antibiotics without doing antibiogram. This higher drug resistance against gram negative uropathogens may be as a result of misuse or overuse of this antibiotic over many decades.

The majority of the isolates were variable resistant to ampicillin, ceftazidime, cephradine, ciprofloxacin, cotrimoxazole, azithromycin except imipenem and amikacin may be explained as uncontrolled consumption of these antibiotics during the past decade in our region.

The prevalence of multidrug resistance isolates in our study was 59(61.45%). Maximum patients attending in this hospital belonged poor socio-economic status and consumed antibiotic without antibiogram. This indicates that unqualified practitioners, untrained pharmacist and nurses spread the beta-lactam drugs indiscriminately. Table IV shows *Enterobacter* spp, *Citrobacter* spp, *Proteus* spp, *Pseudomonas* spp were 66-100% resistant to more than three groups of drugs which is similar to the study conducted by Gulbahar *et al.* (2010)³² in Iraq and Akingbade *et al.* (2012)³³ in Nigeria respectively. *Escherichia coli* and *Klebsiella* spp were 50-57% resistant to multiple drugs which is nearly similar with the studies of Azra *et al.* (2007)³³ in New Delhi, India and Alzohairy *et al.* (2011)³⁴ in Saudi Arabia where 52.9% and 53.6% respectively. But in cocci groups the MDR rate was low. Prolonged misuse of common antibiotics against in this locality may be the reason for high MDR *E. coli*.

Conclusion

In conclusion, physicians should be aware of current antimicrobial susceptibility patterns of UTI pathogens in their local communities through sensitivity testing, because it changes over time and varies geographically. Results of MDR isolates may complicate and limit the therapeutic management of patients. This important issue is to be addressed by the policy makers to formulate a strict antibiotics prescription policy in our country. From this study we may conclude that *Escherichia coli* is predominant uropathogen. A good number of gram negative isolates were resistant to ampicillin, ceftazidime, cephradine, ciprofloxacin, co-trimoxazole, azithromycin and many of them were sensitive to imipenem, amikacin and nitrofurantoin. So, all the UTI cases need culture of urine for identification of pathogen and selection of appropriate antibiotic to prevent drug resistance mediated by chromosomal or plasmid genes.

Ethical issues

Informed written consent was taken from all study populations. The study was not involved in any additional investigative procedures and significant risk as well as economic burden to the patient.

Conflict of Interest Statement

No potential conflicts of interest were disclosed.

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