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Prevalence of Antimicrobial Resistance in Bacterial Isolates Causing Urinary Tract Infection in Patients attending at IIMS&R Hospital, Lucknow

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ABSTRACT- This study was an attempted to estimate the prevalence of antimicrobial resistance in patients attending the OPD and IPD of IIMS&R, hospital, Lucknow. Total 453 urine samples were included in this study. Urinary isolates from symptomatic UTI cases were identified by conventional methods. A total of 453 processed samples, 166 samples shown significant colony count of pathogens among, which the most prevalent were *E. coli* (49.39%) followed by *Klebsiella* species (7.83%). The majority of the isolates were from female (68.67%), while the remaining was from male (31.32%). Dysuria was the most common clinical presentation followed by fever and abdominal pain. Diabetes and urogenital instrumentation were the major risk factors for UTI. Among the 166 urine samples, which showed significant colony count, 152 (91.56%) of specimen showed pus cells in the wet film examination. Among the gram-negative enteric bacilli, high prevalence of resistance was observed against Ampicillin, Cefotaxime, Ciprofloxacin, Nalidixic acid and co-trimoxazole. The 44% of isolates were detected to produce the ESBL among the gram negative bacteria. Carbapenemase production was seen in 13 (11.71%) isolates. Among the 32 *Enterococcus* isolates 14 (43.75%) were resistant to high level Gentamicin, 2 (6.25%) were resistant to High level Streptomycin while 12 (37.50%) of isolates were resistant to both of the antimicrobial drugs. Among the 16 *Staphylococcus* species, 8 (50%) were MRSA.

Key-Words: MRSA, Antimicrobial resistance, UTI, ESBL, Gram-negative bacteria

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INTRODUCTION

Urinary tract infections (UTIs) are one of the most common types of bacterial infections in humans occurring both in the community and health care settings. UTI ranks the highest among the most common reasons that compel an individual to seek medical attention [1]. Today it represents one of the most common diseases encountered in medical practices, affecting people of all ages, from the neonate to the geriatric age group [2].

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The term urinary tract infection (UTI) denotes several distinct entities with the common feature of significant Pyuria and Bacteriuria [3]. The causative pathogen profile varies from region to region, but *Escherichia coli* remain the most common causative pathogen. The sensitivity of uropathogens to different drugs varies in different areas, and changes with time. This necessitates periodic studies of the causes uropathogens and their antibiotic sensitivity pattern [4].

UTIs are often treated with different broad-spectrum antibiotics when one with a narrow spectrum of activity may be appropriate because of concerns about infection with resistant organisms. Fluoroquinolone are preferred as initial agents for empiric therapy of UTI in area where resistance is likely to be of concern. [5,6] This was because they have high bacteriological and clinical cure rates, as well as low rates of resistance, among most

common uropathogens. [7-9] The extensive uses of antimicrobial agents have invariably resulted in the development of antibiotic resistance, which, in recent years, has become a major problem worldwide. [10] Current knowledge of antimicrobial susceptibility pattern is essential for appropriate therapy. Emerging multidrug resistant strains are of major concern to treat UTI. This study has been designed to evaluate the profile of isolates causing UTI and their resistance to various antimicrobial agents.

MATERIAL AND METHODS

It was a cross- sectional study of clinically suspected cases of Urinary tract infection attending the OPD and IPD of Integral Institute of Medical Sciences and Research, Hospital. Urine samples were sent to the Microbiology laboratory for bacteriological examination. The study period was 6 months from January 2015 to June 2015. The data were analyzed using SPSS Statistical version 16.0. Proportions for categorical variables were compared using chi-square test and t- test. In all cases p- value less than 0.05 was taken as statistically significant.

Patients not willing to give their consent were excluded from the study. Adults and children with the suspected symptoms of UTI were included in the study. One specimen per patient was taken. Only patients with significant bacteriuria ($\geq 10^5$ cfu/ml) were included in the microbiological analysis.

From the clinically suspected patients of UTI, midstream clean catch specimen of urine from both the male and female was collected in a sterile, screw-capped, wide mouthed universal container. Wet mount preparation was made from all urine samples to look for the presence of pus cells and epithelial cells. The film was usually observed with the high power (40X) dry objective of the microscope. The bacterial count in the urine sample was determined by Semi-quantitative culture method using 3.26 mm internal diameter standard loop (Hi- Media laboratories limited). [11]

The urine samples were inoculated on a plate of cysteine lactose electrolyte deficient (CLED) agar, MacConkey agar or Blood agar by using the calibrated loop and were incubated aerobically for 18-24 hours at 37˚C. Urinary isolates from symptomatic UTI cases were identified on the basis of colony morphology, Gram's staining, catalase test, oxidase test, coagulase test and standard biochemical tests.

Mueller Hinton agar was used for Antimicrobial sensitivity testing of isolates. Isolated colonies were inoculated in a suitable broth medium and incubated at 35-37˚C for 4-6 hours. The density of the organism in broth was adjusted to approximately 10^7cfu/ml by comparing its turbidity with 0.5 McFarland opacity standard tubes. Antimicrobial susceptibility testing was performed by Kirby Baur's disc diffusion method using the appropriate antibiotic disk. A commercially available antibiotic disc of 6 mm (Hi- Media laboratories limited) were used. Antibiotic disc were selected according to bacterial isolates. In the present study the antibiotic disc tested were [12].

For *Enterobacteriaceae* species

Ampicillin (10 µg), amoxicillin-clavulanic acid (20/10 µg), Ampicillin/sulbactum (10/10 µg), Cefotaxime (30 µg), Cefotaxime/clavulanic acid (30/10 µg), Ceftriaxone (30 µg), Ceftriaxone/sulbactam (30/15 µg), Co-trimoxazole (25 µg), Tetracycline (30 µg), Amikacin (30 µg), Gentamicin (10 µg), Nalidixic acid (30 µg), Ciprofloxacin (5 µg), Levofloxacin (5 µg), Ceftazidime (30 µg), Ceftazidime/clavulanic acid (30/10 µg), Cefixime (5 µg), Cefepime (30µg), Ticarcillin/clavulanic acid (75/10µg), piperacillin/tazobactam (100/10µg), tobramycin (10µg), netillin (30µg), Aztreonam(30µg), Imipenem/cilastin (10/10µg), Meropenem (10µg), Ertapenem (10µg), Norfloxacin (10µg), Nitrofurantoin (300 µg).

For *Pseudomonas* species

Aztreonam (30 µg), Ticarcillin (75 µg), Ticarcillin/clavulanic acid (75/10 µg), piperacillin (100 µg), piperacillin/tazobactam (100/10 µg), Imipenem/cilastin (10/10 µg), Ceftazidime (30 µg), Ceftazidime/clavulanic acid (30/10 µg), Meropenem (10 µg), tobramycin (10 µg), Amikacin (30 µg), Gentamicin (10 µg), Ciprofloxacin (5 µg), Polymixin B (300 units).

For *Staphylococcus* and *Streptococcus* species

Penicillin (10 units), amoxicillin-clavulanic acid (20/10 µg), Ampicillin/sulbactum (10/10 µg), Co-trimoxazole (25 µg), Tetracycline (30 µg), Cefprozil (30 µg), Cefaclor (30 µg), Cefoxitin (30 µg), Gentamicin (10 µg), Amikacin (30 µg), Ciprofloxacin (5 µg), Levofloxacin (5 µg), Gemifloxacin (5 µg), Vancomycin (30 µg), Linezolid (15 µg), Teicoplanin (30 µg), Norfloxacin (10 µg), Nitrofurantoin (300 µg).

For *Enterococcus* species

Penicillin (10 units), Ampicillin (10 µg), Linezolid (15 µg), vancomycin (30 µg), high level Gentamicin (120µg), high level streptomycin (300 µg), Ciprofloxacin (5 µg), Levofloxacin (5 µg), Tetracycline (30 µg), Doxycycline (30 µg), Teicoplanin (30 µg), Norfloxacin (10 µg), and Nitrofurantoin (300 µg)

Phenotypic detection of antibiotic resistance

MRSA was detected by using Cefoxitin disk (30 µg) [12]**.** Isolates resistant to third generation cephalosporin were tested for ESBL production by double disk synergy test method by using Cefotaxime (30µg) and Cefotaxime- clavulanic acid (30 µg/10 µg) and Ceftazidime (30 µg) and Ceftazidime- clavulanic acid (30 µg/10 µg) [12]. Isolates resistant to Meropenem was tested for MBL production by the EDTA disk synergy method [13]. Detection of High level Aminoglycoside resistance was done by using High level Gentamicin disk (120 µg) and High level Streptomycin disk (300µg) [12] .

RESULTS AND DISCUSSION

Total 453 samples were included in the present study to estimate the prevalence of Antimicrobial resistance in patients suffering from Urinary tract infection attending the OPD and IPD of IIMS&R, hospital. Of the 453 processed samples 166 samples showed significant colony count of pathogens. Among the total processed urine samples, 166 (36.64%) of them yielded significant growth of a bacterial isolates. Remaining 287 samples had either contaminated or had a very low bacterial count or were sterile urine.

Table 1: Details of samples with significant colony count

Significant Growth	OP= 63	IP= 103	Culture Positive
Percentage	37.95%	62.04%	36.64%
Number	63	103	166

Highest samples were received from the Department of Medicine (49.39%) followed by O&G (22.89%), Pediatrics (13.25%), Surgery (6.02%), Skin & VD (3.61%), MICU (1.8%), ICU (2.4%) and TB & chest (0.6%).

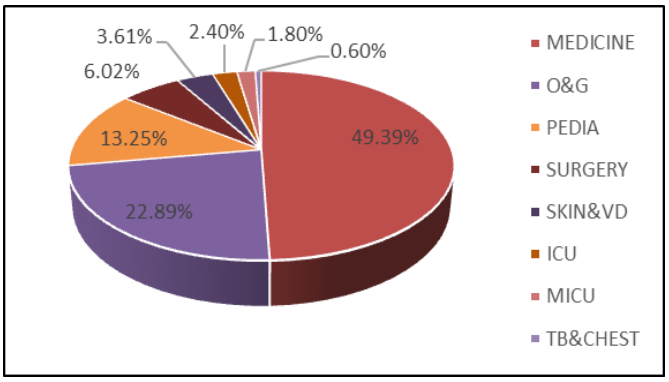

Fig. 1: Pie-chart showing details of samples from different Departments

Dysuria (95.18%) was the most common clinical presentation followed by fever (89.15%) and abdominal pain (68.67%). Diabetes (28.91%) and urogenital instrumentation (16.26%) were the major risk factors for UTI. Among the 166 urine samples which showed significant colony count, 152 (91.56%) of specimen showed pus cells in the wet film examination.

The patients were between the ages 0 and 85 years. UTIs were reported in total 52 (31.32%) males and 114 (68.67%) females. Females of the reproductive age group (between 21 and 50 years) constituted 41.56% of the total patients with UTI. However, males (50 years or more) had a higher incidence of UTI (44.23%) compared to the females of the same age group (14.91%).

Table 2: Age and sex distribution of Urinary tract infection cases

AGE GROUPS (YEARS)	MALE n (%)	FEMALE n (%)
0-10	8 (15.38)	12 (10.52)
11-20	0(0)	16 (14.03)
21-30	5 (9.6)	28 (24.77)
31-40	9 (17.30)	25 (21.92)
41-50	7 (13.46)	16 (14.03)
51-60	11 (21.1)	12 (10.52)
61-70	8 (15.38)	5 (4.38)
71-80	2 (3.84)	0(0)
81-90	2 (3.84)	0(0)
TOTAL	52 (31.32%)	114 (68.67%)
t (8 d.f.) 1%	4.642**	3.824**

** = p<0.01; highly significant

Of the 166 isolates, 111 were Gram negative while 55 were Gram positive bacteria. *Escherichia coli (E. coli)* was the most common organism isolated accounting for 82 (49.39%) and the second highest organism was *Enterococcus* (n=32; 19.27%) followed

by *Staphylococcus* species (n=16; 9.63%) and *Klebsiella* species (n=13; 7.83%). The other bacterial isolates obtained in the study were Citrobacter, Acinetobacter, Proteus, Pseudomonas, Enterobacter, Streptococcus and CoNS.

Table 3: Frequency and distribution of bacterial isolates from UTI cases

ISOLATES	n (%)	IP	OP
E. coli	82 (49.39)	49	33
Enterococcus species	32 (19.27)	24	8
S. aureus	16 (9.63)	12	9
Klebsiella species	13 (7.83)	7	6
Pseudomonas species	6 (3.61)	5	1
CoNS	5 (3.01)	1	4
Citrobacter species	4 (2.4)	2	2
Acinetobacter species	3 (1.8)	1	2
Proteus species	2 (1.2)	1	1
Streptococcus species	2 (1.2)	1	1
Enterobacter species	1 (0.6)	1	0
TOTAL	166	103	63

Table 4: Antibiotic susceptibility pattern of Gram positive isolates (% Resistance)

Organism	ANTIBIOTICS TESTED						
	Penicillin	Tetracycine	Norfloxacin	Nitrofurantoin	Cefoxitin	Ciprofloxacin	Vancomycin
Staphylococcus species (n=21)	18 (85.7%)	6 (28.57%)	5 (23.8%)	1 (4.76%)	9 (42.8%)	6 (28.5%)	0
Streptococcus species (n=2)	0	1 (50%)	0	0	0	0	0
Enterococcus species (n=32)	15 (46.8%)	15 (46.8%)	16 (50%)	24 (75%)	1 (3.1%)	_	0

Table 5: Antibiotic susceptibility pattern of Gram negative isolates (% Resistance)

ANTIBIOTICS	*E. coli* (n=82)	*klebsiella* species (n=13)	*Pseudomonas* species (n=6)	*Citrobacter* species (n=4)	*Proteus* Species (n=2)	*Enterobacter* species (n=1)	*Acinetobacter* Species (n=3)
Ampicillin	71 (86.5%)	11 (84.61%)	_	1 (25%)	_	1 (100%)	1 (33.3%)
Piperacillin tazobactum	11 (13.4%)	2 (15.38%)	3 (50%)	0	_	1 (100%)	0
Ceftazidime	43 (52.43%)	9 (69.23%)	2 (33.3%)	1 (25%)	_	1 (100%)	1 (33.3%)
Cefotaxime	57 (69.51%)	11 (84.61%)	_	1 (25%)	_	1 (100%)	0
Gentamicin	14 (17.07%)	3 (23.07%)	3 (50%)	1 (25%)	_	1 (100%)	0
Amikacin	9 (10.97%)	2 (15.38%)	2 (33.3%)	0	_	1 (100%)	0
Norfloxacin	30 (36.58%)	2 (15.38%)	3 (50%)	0	_	1 (100%)	1 (33.3%)
Ciprofloxacin	59 (71.95%)	5 (38.46%)	3 (50%)	1 (25%)	_	1 (100%)	0
Nalidixic acid	74 (90.24%)	8 (61.53%)	_	1 (25%)	_	1 (100%)	2 (66.6%)
Co- trimoxazole	57 (69.51%)	6 (46.15%)	_	1 (25%)	_	1 (100%)	1 (33.3%)
Nitrofurantoin	9 (10.97%)	4 (30.76%)	5 (83.33%)	1 (25%)	2 (100%)	1 (100%)	2 (66.6%)
Meropenem	44 (53.65%)	5 (38.46%)	3 (50%)	1 (25%)	_	1 (100%)	0
Imipenem	2 (2.43%)	0%	1 (16.6%)	0	0	0	0

From the total gram negative bacterial isolates (n=111), 29.72% of them were simple β- lactamase producer, 39.63% were ESBL producer, 11.71% were Carbapenemase (MBL TYPE) producers.

Table 6: Resistance pattern of Gram negative isolates

Resistance Type	n (%)	IP	OP
β-lactamase producer	33 (29.72)	15	18
ESBL producer	44 (39.63)	30	14
Carbapenemase producer	13 (11.71)	12	1

Out of the total *Enterococcus* species (32) isolated, 14 (43.75%) were resistant to High level Gentamicin (HLG), 2 (6.25%) were resistant to High level of Streptomycin (HLS), while 12 (37.50%) of isolates were resistant to both of the Aminoglycosides.

Table 7: Aminoglycoside resistance pattern of *Enterococcus* isolates

Saminoglycoside resistance pattern	n (%)	IP	OP
HLS-R	2 (6.25)	1	1
HLG-R	14 (43.75)	9	5

Out of the total *Staphylococcus aureus* (16) isolated, 8 were Methicillin resistant (MRSA).

Table 8: Methicillin resistance pattern in *S. aureus* isolates

Sensitivity Pattern	n (%)	IP	OP
Methicillin resistant	8 (50)	6	2
Methicillin sensitive	8 (50)	5	3

DISCUSSION

Urinary tract infections are one of the most common types of bacterial infections occurring in humans [14]. This study was undertaken to identify pathogenic bacteria responsible for Urinary tract infection and to determine their Antimicrobial resistance pattern.

Out of the total urine samples, 166 (36.64%) samples yielded significant colony count, 237 (52.31%) samples were sterile, 30 (6.62%) samples showed multiple isolates (samples grossly contaminated during collection) and 20 (4.41%) samples showed an insignificant colony count.In a study done by Mandal *et al.* [15], in their study, 62% samples were sterile, 26.01% showed significant growth, 2.3% showed insignificant growth and 9.6% were found contaminated. While in the study of Niranjan and Malini [16], 547 samples (18.5%) yielded significant bacteriuria; 2323 samples (79.1%) showed no growth and 74 samples (2.4%) showed mixed growth. It showed that culture positivity rate varies from area to area.

In this study, the prevalence of UTI was recorded higher in females than in males. Females were at higher risk for with UTI showing 114 (68.67%) of urine culture positivity whereas the male subjects showed only 52 (31.32%) of culture positivity. Similar observations were recorded by Astal *et al.* [17] and Khalifa and Khedher [18].

Females of the reproductive age group (between 21 and 50 years) constituted 41.56% of the total patients with UTI. However, males (50 years or more) had a higher incidence of UTI (44.23%) compared to the females of the same age group (14.91%). The distribution of isolates according to different age group is significantly associated with Gender (p=0.001). Approximately same findings were reported by Akram *et al.* [19], women of the reproductive age group formed the main group of adult patients with UTI (42.34% of all UTI detected in women of age 21-50 years), UTIs were reported in 62.42% of females and in 37.67% of males. It has been extensively reported that adult women have a higher prevalence of UTI than men, principally owing to anatomic and physical factors.

We found dysuria in 158 (95.18%) patients as the most common clinical presentation of UTI followed by fever 148 (89.16%) and abdomen pain in 114 (68.67%) cases. Diabetes 48 (28.91%) was the most common associated risk factor with the UTI and Catheterization (16.26%) was the second most common associated risk factor in the present study. Similar findings were reported by Eshwarappa *et al.* [20].

It was seen in the present study that among the 166 samples with significant colony count, 152 (91.56%) of them were having abundant pus cells, While the 26 (9.05%) of culture negative samples showed the presence of pus cells but no growth. Patients with signs and symptoms of UTI sometimes produce samples of urine that show pus cells but do not yield a significant growth of bacteria on routine culture. The explanation may be that the patient has been taking antibiotics prescribed on a previous occasion. Alternatively, there may be an infection with an

organism that does not grow on the media normally used for routine investigations. In such cases it is important to consider genitourinary tuberculosis or gonococcal infection and infection with nutritionally exacting or anaerobic bacteria [21]. But many patients with frequency and dysuria do not have a bacterial infection of the bladder, nor significant numbers of bacteria in their urine (abacterialpyuria). Their condition is known as non-bacterial urethiritis or cystitis, or the urethral syndrome, the cause of which may be urethral or bladder infection with a chlamydia, Ureaplasma, Trichomonas or virus which often remain unrecognized [22]. This study showed that *E. coli* 82 (49.39%) was the commonest pathogen causing UTI and it was similar to the findings of [15,16,23].

The antimicrobial sensitivity pattern of the *E. coli* isolates in our study was similar to previous studies done in India. The comparison of resistance patterns of uropathogenic *E. coli* in various studies is shown in Table 9.

Table 9: Comparison of resistance patterns of uropathogenic *E. coli* in various studies from India and other parts of the world

Authors	Country	Year	AMP	CIP	COT	NIT
Colodner *et al* [24]	Israel	2001	66	6	26	1
Gupta *et al* [25]	India	2002	74	38	70	12
Farrell *et al* [26]	UK	2003	S48.7	2.3	---	3.7
Andrade *et al* [27]	Latin America	2006	53.6	21.6	40.4	6.6
Biswas *et al* [28]	India	2006	63.6	35.1	40.3	9.3
Garcia *et al* [29]	Spain	2007	58.7	22.7	33.8	5.7
Akram *et al* [19]	India	2007	_	69	76	80
Kothari & Sagar [30]	India	2008	85.3	72	74	24.4
Niranjan & Malini [16]	India	2014	88.4	75	64.2	17.9
Present study	(Lucknow) India	2015	86.58	71.95	69.51	10.97

E. coli and *Klebsiella* species isolates are equally resistant to Ampicillin (86.5% and 84.6% respectively) while for Co- trimoxazole. *E.coli* is more resistant (69.5%) than *Klebsiella* (46.1%) in this region. Indian isolates showed higher resistance against Ampicillin and Co- trimoxazole than the isolates from the USA (39.1% and 18.6%) [31,32].

Nitrofurantoin has been used for more than five decades for the treatment of uncomplicated cystitis and it was found to remain active against most of the uropathogens. Recent data suggest that Nitrofurantoin has retained a good amount of sensitivity (90.98%), both against ESBL producers and non-ESBL producers.[33]

In this study, 44 (39.63%) out of all gram negative isolates were found to produce ESBL. 35.13% of *E.coli* isolates were ESBL producers, followed by 2.7% of *Klebsiella* species. It might be possible that the high level of multi-drug resistance was most probably due to production of extended spectrum beta lactamases in these isolates [34].

Overall Imipenem resistance was 16.6% of Pseudomonas species and 2.4% of *E. coli,* whereas, other isolates of uro-pathogen were found to be sensitive to Imipenem. Among a total of 55 (49.5%) Meropenem resistant gram negative bacilli, we found 7 (12.7%) of *E.coli*, 4 (7.27%) of *Klebsiella* species and 2 (3.6%) of Pseudomonas species as carbapenemase producing isolates. They were confirmed as MBL by EDTA double disk synergy test.

Carbapenems have a broad spectrum of antibacterial activity, and these are resistant to hydrolysis by most β-lactamases including extended spectrum β-lactamases (ESBL) and AmpC β-lactamases [35].

In this study frequency of *Enterococcus* species in urinary tract infection was 32 (19.27%), the second most common isolate of this study. The overall prevalence of high level resistance to any Aminoglycoside among the study isolates was 37.5%. HLAR *Enterococci* were first reported in France in 1979 and since then have been isolated from all the continents [36,37] reported prevalence rate of high level Gentamicin resistance in *Enterococci* varying from 1% to 49% in the 27 European countries studied.

Resistant to Methicillin is documented in 8 (50%) of 16 *Staphylococcus* isolates. In this study, though all gram positive isolates were sensitive to vancomycin, a watchful vigilance is required for the emergence of Vancomycin resistance in view of recent reports of reduced susceptibility to *S. aureus* to Vancomycin [38].

The susceptibility patterns seen in our study seem to suggest that it is absolutely necessary to obtain sensitivity reports before

initiation of antibiotic therapy in cases of suspected UTI.

CONCLUSIONS

E. coli was the predominant bacterial pathogen of Urinary tract infection in IIMS & R, Lucknow. The study showed high resistance among uropathogenic *E. coli* to Ampicillin, Cephalosporins and Fluoroquinolones. High level of resistance among gram negative isolates were seen to commonly used antimicrobial agents such as Ampicillin, Cefotaxime, Nalidixic acid, Cotrimoxazole and Ciprofloxacin. ESBL production was seen in 44 (39.63%) isolates, out of the 111 Gram negative isolates. Carbapenemase production was seen in 13 (11.71%) isolates by EDTA-DST, out of 111 Gram- negative isolates. Among the 32 *Enterococcus* isolates 14 (43.75%) were resistant to High level Gentamicin, 2 (6.25%) were resistant to High level Streptomycin while 12 (37.50%) of isolates were resistant to both of the Aminoglycosisdes. Among the 16 *Staphylococcus* species, 8 (50%) were MRSA.

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