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Research Article

MICROBIOLOGICAL PROFILE AND ANTIBIOTIC SUSCEPTIBILITY PATTERN OF UROPATHOGENS IN ANAND DISTRICT OF GUJARAT, INDIA.

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ABSTRACT

Background: Antimirobial drug resistance in urinary tract pathogens is a challenging problem to the medical practitioners & important reason for increased morbidity and healthcare expenditure.

Aim/Objective: To document prevalence of pathogens in Urinary Tract infections (UTIs) and their current antimicrobial susceptibility pattern in Anand region of Gujarat, India.

Materials and Methods: Urine samples from symptomatic UTI cases were processed. Bacterial isolates were identified using standard methods and AST was performed by disc diffusion methods as per CLSI guidelines (2012).

Results: A total of 954 consecutive urine specimens from symptomatic UTI cases were processed.378 samples showed significant bacteriuria. Antimicrobial susceptibility pattern of isolates were studied for 26 different antimicrobials of different classes. Among uropathogens isolated, *E.coli* was found predominant (51.9%) followed by *Klebsiella spp* (18.3%), *Pseudomonas spp* (17.2%), *Proteus spp* (3.2%), *S. saprophyticus* (2.6%) *Enterobacter spp* (1.3%), *Providencia spp* (05%), Yeast (3.2%), *Staphylococcus aureus* (1.6%) and *Alcaligenes spp* (0.3%). Out of antimicrobials tested Ampiillin (92.3%), Cefpodoxime (89.3%), Amoxyclave (84.7%), Piperacillin (84.4%) and Cefotaxime (83.6%), Ceftazidime (73.8%) have shown highest resistance by different uropathogens. Aminoglyciosides, Carbapenem and 3rd/4th generation fluroquinolones showeded low resistance.

Conclusion: *E.coli* was found to be the most dominant uropathogen in this region, prevalence of *Pseudomonas spp* was also found comparatively higher. There has been a fairly high level of drug resistance among the uropatogens isolated.

Key-words: Uropathogen, Antibiotic Sensitivity Pattern, Prevalence, Anand, Drug resistance

INTRODUCTION

Despite of wide spread availability of antibiotics, Urinary tract infection remains a worldwide therapeutic problem [1] ; not only as a nosocomial disease but also as a community acquired infection[2].

UTI represents the second most common microbial infection, after respiratory tract infections, encountered in medical practice today [3], occurring from the neonates to the geriatric age group[4,5].

Nearly 10% of people will experience a UTI during their their life time[6], approximately 150 million people worldwide annually affected by UTIs which results in more than 6 billion US dollar loss to the global economy[7,8].

UTI is documented as an infection of female due to shorter urethra, but other risk factors include age, pregnancy, catheterization, kidney stone, tumours, urethral structures, neurological diseases, congenital/acquired anomalies of bladder, vesicoureteric reflux, suppressed immune system, diabetes mellitus, ureteric stresses & so on[9].

Resistance to commonly prescribed antibiotics for UTI is an expanding global problem in both developed as well as developing countries[10]. In most UTIs, treatment is often started empirically before culture reports are available[11]. Resistance developed in pathogens due to frequent misuse [12]. Urinary tract pathogens have ability to produce ESBLs as well as AmpC in large quantities[13,14]. Infections due to these

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enzymes range from uncomplicated UTI to life threatening sepsis[15]. These enzymes confer multidrug resistance, making UTIs difficult to treat due to limitations of therapeutic options.

It is proven that antibiotic resistance pattern vary according to geographical & regional location[16,17,18]. Recently, Infectious Disease Society of America (IDSA) recommended that each hospital should determine the locally established mechanisms to assess resistance rates among uropathogens[11]. Knowledge of antibiotic patterns of uropathogens in specific geographical location is an important factor for choosing an appropriate empirical therapy for clinician rather than on universal guidelines[11]. The objective of present study was therefore to determine Current scenario of Prevalence & Antibiotic susceptibility pattern of uropathogens in Anand district of Gujarat, India.

Materials and Methods:

Place of study: The prospective study was conducted over a period of two and a half years from June 2012 to January 2015, at Shree P.M.Patel Institute of Paramedical Science and Technology, Anand & at Dr. Krunal Pathology laboratory, Anand, Gujarat, India.

Sample collection: Clean-catch, mid-stream urine (MSU)/catheterized/SPA urine samples were collected in sterile, wide mouthed, universal containers from 945 cases of suspected UTI.

Patients were instructed to wash and dry perineum area before collection of sample. These were processed within one hour of collection.

Patient Profile: Demographic details, clinical features, and underlying illnesses of the patients were recorded. Complicated UTI was defines as UTI developing in anatomically, physiologically or functionally compromised urinary tract[19].

Culture: Semi-quantitative culture on cysteine lactose electrolyte deficient (CLED, Hi-Media, Mumbai) media was used as the gold standard for diagnosing UTI. Other media inoculated were nutrient agar and blood agar. Semi-quantitative culture was done by plating 1µl urine using a calibrated bacteriological loop (1.34mm internal diameter) on CLED agar, and colonies were counted after overnight incubation at 37°C. Number of colonies obtained was multiplied by 1000 to obtain the colony forming units (cfu) / ml. Cut off for significant bacteriuria was taken as 10^5cfu/ml for MSU[20]. Samples showing growth of 2 or more bacterial species (>=10^3 cfu/ml) of doubtful significance were noted and repeat cultures were done. MSU samples showing scanty bacterial growth (<10^3 cfu/ml) prior antibiotic therapy and without significant pyuria were reported as bacterial growth of no significance. Isolates with low count were processed further, if patients showed relevant history, fever, lower abdominal pain or pyuria. All cultured plates were incubated atleast for 48 hours before giving negative report.

Identification of Gram negative bacteria :

The bacterial isolates were subjected to identification tests using microscopic observations and examined their growth patterns by culturing on different media such as Mac Conkey agar, Eosin methylene blue agar, sugar (carbohydrate) fermentation (Lactose, glucose, sucrose and mannitol), TSI, IMViC (Indole, Methyl red (MR), Voges - Proskauer (VP) and Citrate utilization tests[21].

Identification of Gram positive bacteria:

Gram positive bacteria were identified by using microscopic observations and their growth patterns by culturing on different media such as Mannitol salt agar and blood agar, sugar fermentation, oxidase, catalase, coagulase, bacitracin and opptochin tests[21].

Maintenance of clinical isolates:

Stock cultures were maintained in vials by growing the UTI isolates in 3 ml Lurya broth and were overlaid with 3 ml 40% glycerol. Then the vials were freezed at -80°C for further study.

All urinary isolates with significant bacteriuria were tested for antimicrobial susceptibility by Kirby-Bauer(22),disc diffusion technique using Muller Hinton agar as per CLSI guide lines,2012 . The antibiotic discs used were Amikacin (30µg), Gentamicin (10µg), Tobramycin (10µg), Ampicillin (10µg), Piperacillin (100µg), Amoxyclav (20/10µg), Pip-Taz (100/10µg), Ciprofloxacin (5µg), Norfloxacin (10µg), Ofloxacin (5µg), Co-Trimoxazole (23.75/1.25µg), Tetracyclin (30µg), Nitrofurantoin (300µg), Cefotaxime (30µg), Cefpodoxime (10µg), Ceftazidime (30µg), Cefepime (30µgs) Imipenem (10µg), Meropenem (10µg), Ertapenem (10µg), cefoxitin (30µg), Cefoperazone/Sulbactum (75/10µg), Ampicillin /sulbactam (10/10 µg), Gatifloxacin (5 µg), Levofloxacin (5 µg), Tacoclav (75/10 µg) and Aztreonem (30µg). Dehydrated media and antibiotic discs were procured from Himedia, Mumbai,India.

QUALITY CONTROL

Escherichia coli ATCC 25922, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, were used as a quality control for the modified Kirby-Bauer disk diffusion method[22].

Ethical Approval:

Consent was taken from each patient and Ethical approval for this study was taken from Human Research Ethical Committee, Pramukh Swami Medical College, Karamsad-Gujarat, India.

Data analysis was performed using Microsoft Excel.

Results:

During the study period, 954 consecutive urine samples from patients with symptoms of UTI were processed, 378 (39.6%) of these urine samples yielded significant growth of pathogen. Remaining samples had either non-significant bacteriuria or were found sterile urine. Uropathogens isolated were tested for resistance to different antimicrobial drugs as recommended in CLSI guideline, 2012.

Table 1: Number of cases and Percentage of Uropathogenes isolated in this study:

Organism Isolated	Number of cases	Percentage (%)
E.coli	196	51.9
Klebsiella spp	69	18.3
Pseudomonas spp	65	17.2
Proteus mirabillis	12	3.2
Staphylococcus saprophyticus	10	2.6
S. aureus	6	1.6
Enterobacter spp	5	1.3
Providencia spp	2	0.5
Alcaligenes spp	1	0.3
Yeast	12	3.2

Table1 depicts number of case from which particular uropathogen isolated with percentage of prevalence in this study.

E.coli (51.9%) was found the most dominant among the identified urinary tract pathogens followed by *Klebsiella spp* (18.3%), *Pseudomonas spp* (17.2%) and *Proteus mirabilis* (3.2%). Uncommon in UTI, *Alcaligenes spp* was isolated from urine sample of hemodialysis patient.

Table 2: Overall AST pattern of isolated Uropathogen

Antimicrobial Agents	Resistant	Intermediate	Sensitive
Penicillins			
Ampicillin	92.3%	2.5%	5.2%
Piperacilllin	84.4%	8.1%	7.5%
Penicillin with β lactamase inhibitor			
Amoxy clav	84.7%	9.0%	6.3%
Amoxy/sulbactam	52.5%	16.4%	31.1%
Ticarcillin Clavulanata	55.2%	16.5%	28.3%
Pip-Tazobactam	35.3%	15.3%	49.3%
Cephalosporines			
Cephamycin grouped with 2nd generation			
Cefoxitin	51.1%	7.4%	41.4%
3rd Generation:			
Cefotaxime	83.6%	4.4%	12.0%
Cefpodoxime	89.3%	4.4%	6.3%
Ceftazidime	73.0%	6.3%	19.9%
Cefuroxime	82.6%	6.2%	11.2%
Cephoperazone-sulbactam	27.9%	16.1%	56.0%
4th Generation :			
Cefepime	37.2%	12.8%	50.0%
Fluoroquinolones			
Ciprofloxacin	68.8%	6.6%	24.7%
Norfloxacin	61.1%	6.3%	32.6%
Ofloxacin	32.9%	9.6%	57.5%
Levofloxacin	11.7%	15.3%	73.0%
Gatifloxacin	12.0%	18.6%	69.4%
Sulfonamides			
Co-Trimoxazole	69.4%	3.6%	27.0%
Polyketide antibiotic			
Tetracycline	34.0%	28.3%	37.7%
Nitrofurantoin	42.5%	15.6%	41.9%
Aminoglycosides			
Amikacin(AK)	19.4%	9.3%	71.3%
Gentamicin	22.7%	1.6%	75.7%
Tobramycin	23.5%	7.9%	68.6%
Monobactam			
Aztreonem	67.5%	9.0%	23.5%
Carbapenems			
Imipenem	21.0%	7.7%	71.3%
Ertapenem	41.5%	3.8%	54.6%
Meropenem	54%	3.3%	42.1%

Table 2 shows the antibiotic resistance pattern of tested antimicrobials of different groups against the encountered uropathogens. Highest resistance was observed against Ampicillin (92.3%) followed by Cefpodoxime (89.3%), Amoxyclave (84.7%), Piperacillin (84.4%), Cefotaxime (83.6%) by all isolates. Aminoglycosides, Carbapenems, Levofloxacin andGatifloxacin showed lower resistance than other antimicrobials. Levofloxacin (11.7%), Gatifloxacin (12%) showed less resistance followed by Amikacin (19.4%), Gentamicin (22.7%), Tobramycin (23.5%), and Imipenem (21%). Very high resistance (90-74%) to 3rd generation cephalosporins observed which alarming signal is.

Table 3: Percentage Resistant to various Antibiotics by major Uropathogens

Antibiotics	*E.coli* n=196 (%)	*Klebsiella spp* n=69 (%)	*Pseudomonas spp* n=65 (%)
Penicillins			
Ampicillin	93.3	100	89.2
Piperacilllin	86.2	89.9	81.5
Penicillin with β lactamase inhibitor			
Amoxy clav	82.6	94.2	87.7
Amoxy/sulbactam	51.0	66.7	60.0
TicarcillinClavulanata	49.7	71.0	63.1
Pip-Tazobactam	33.3	37.7	44.6
Cephalosporines			
Cephamycin grouped with 2nd generation			
Cefoxitin	41.8	51.7	85.2
3rd Generation:			
Cefotaxime	81.6	84.1	87.7
Cefpodoxime	89.8	88.4	90.2
Ceftazidime	73	85.5	64.6
Cephoperazone-sulbactam	27	33.3	33.8
Fluoroquinolones			
Ciprofloxacin	68.4	71.0	70.3
Norfloxacin	58.2	66.7	65.6
Ofloxacin	24.0	46.4	42.2
Levofloxacin	04.1	15.9	32.3
Gatifloxacin	06.6	14.5	29.2
Sulfonamides			
Co-Trimoxazole	67.4	66.2	72.3
Polyketide antibiotic			
Tetracycline	34.3	23.6	35.8
Nitrofurantoin	23.5	55.0	84.2
Aminoglycosides			
Amikacin(AK)	10.7	29.0	40.0
Gentamicin	15.3	23.2	50.8
Tobramycin	16.8	20.3	53.8
Monobactam			
Aztreonem	64.3	84.1	66.2
Carbapenems			
Imipenem	17.9	11.6	46.2
Ertapenem	38.8	40.6	60.0
Meropenem	47.4	62.3	69.2

Table 3 depicts % Resistance to antimicrobials tested for common uropathogens isolated in this study. In our study, *E.coli* isolates were highly resistant to Ampicillin, Cefpodoxime and Piperacillin with 93.3% , 89.8% and

86.2% resistance respectively. Ciprofloxacin with 68.4% and Norfloxacin with 58.2% resistance, found to be least effective amongst other Fluoquinolones tested in this study. Levofloxacin, Gatifloxacin, Aminoglycoside group and Carbapenem group of drugs retained their usefulness for *E.coli* isolates.

All *Klebsiella spp* isolated were completely resistant to Ampicillin. Other antimicrobials showed high rate of resistance were Amoxyclave (94.2%), Piperacillin (89.9%), Cefpodoxime (88.4%). Imipenem and Gatifloxacin were found to be most effective on Klebsiella isolates. All fluroquinolones were also comparatively less effective on *Klebsiella spp* than *E.coli*.

All isolates of *Pseudomonas spp* were highly resistant to Ampicillin (89.2%), Cefpodoxime (90.2%), Amoxyclav (87.7%), Cefotaxime (87.7%) and Cefoxitin (85.2%). Carbapenems were also less effective on *Pseudomonas spp* compared to *E.coli* and *Klebsiella spp*.

Discussion:

Constant surveillance of antimicrobial resistance plays a key role in the empiric treatment of UTI. In health care setting, a very little extra venture on antimicrobial resistance survey on local level can facilitate extremely important accurate practical information of local resistance pattern.

In this study susceptibility pattern of bacterial isolates of UTI against different antibacterials of different antimicrobial groups were studied in Anand district of Gujarat, India..The data provided by this study allows comparison of current situation of Antimicrobial resistance in Uropathogens in Anand, Gujarat with other part of India and globally as well.

The prevalence of UTI in the studied population was 39.6%, which is higher than some studies which reported 10-31% prevalence[23,24.25] but lower than some other studies(45-66%) carried out elsewhere in India[26,27.28].

E.coli was found to be the most predominatant (51.9%) uropathogen followed by *Klebsiella spp* (18.3%), *Pseudomonas spp* (17.2%), *Proteus spp* (3.2%) in our study which also in concordance with the study of Barate and Ukesh[29] which reported *E.coli* 49.52% and *Klebsiella spp* 20.95%, *Pseudomonas spp* 15.23%, *Proteus spp* 6.66%. A high rate of prevalence of *Pseudomonas spp* as uropathogen was found in this study than other study in Gujarat, by Shirishkumar et al[26] showed only 10.74% prevalence rate of *Pseudomonas spp* in UTI. Also prevalence rate was higher than Study done by Savitha et al[23] which showed only 0.98% prevalence of *Pseudomonas spp*. So, prevalence of *Pseudomonas spp* was thus found comparatively high in this region.

Results of this study showed variation in resistance rate of different antimicrobials when compared to other studies done in India[12,24,26,27,29]. These results confirm that, with changing practices of antimicrobial usage, the resistance patterns of pathogens also show a great deal of variation with place and time.

Generally, uncomplicated UTIs are treated in the community with short courses of empirical antibiotics. In many cases, urine samples are only sent for microbiological evaluation following treatment failure, recurrent or relapsing infection[24]. The high levels of resistance of gram negative uropathogens to Ampicillin, Amoxiclav, Piperacillin, Co‑trimoxazole, Norfloxacin, Ciprofloxacin, 3GC and Monobactams raise concerns over the use of these agents. Our findings are in consistence with the recent data reported from other developing countries[24,30,31]. Our findings thus suggest that empirical treatment with these drugs should no longer be appropriate, and if it is used before AST report, it may lead to a treatment failure and further emergence of drug resistance.

In the present study, *E.coli, Klebsiella spp, Pseudomonas spp* isolates were found highly resistant to Ampicillin with resistance rate of 93.3%, 100% and 89.2% respectively. These findings show similarities with study by Manjunath et al [12]. All *Klebsiella spp* isolates were resistant to Ampicillin. Such high resistance to Ampicillin may be because of extensive use of this inexpensive antibiotic for the treatment of various bacterial infections including Respiratory tract infections. In addition, antibiotics self‑medication is encouraged by free access and over the counter purchase and by an ineffective drug control policy. This could be the responsible factor for very high level of resistance.

E. coli isolates were found resistant to orally administered drugs. Rate of resistance found in this study for antimicrobials Ampicillin (93.3%), Amoxiclave (82.6%), Co-trimoxazole (67.4%), Norfloxacin (58.2%) and Ciprofloxacin (68.4%) were in concordance with study by Sood and Gupta[24].

In this study, among Fluoroquinolones, *E.coli* showed less resistant to Gatifloxacin, Levofloxacin and Ofloxacin than Norfloxacin and Ciprofloxacin. Our findings show much higher rate of resistance than study of Shafali et al[27], with resistance rate of 39%, 23%,7% for Ciprofloxacin, Norfloxacin and Ofloxacin respectively. Ofloxacin, Levofloxacin and Gatifloxacin should therefore be used judiciously to keep them as reserved option of treatment regimen.

In this study, *E.coli, Klebsiella spp* and *Pseudomonas spp* showed 67.4%, 66.2% and 72.3% resistance to Co- trimoxazole respectively. While in similar study in India, Akram et al[25] found resistance of 76% for *E.coli*, 63% for *Klebsiella spp* with all *Pseudomonas spp* resistant to this drug. It has been suggested that such high resistance is due to uncontrolled use and poor quality of antimicrobials in developing county like India, as well as its wide usage for a variety of other indications[24].

In this study, *E.coli* isolates showed 23.5% resistant to Nitrofurantoin, but other isolates of *Klebsiella spp*, *Pseudomonas spp* and *Proteus spp* showed 55%, 84.2% and 75% resistant rate respectively. *E.coli* isolates were less resistant to Nitrofurantoin in this region than other similar studies showed very high resistance of 76%[23] and 79%[29]. As *E.coli* is the most predominant pathogen and in this region these isolates showed good susceptibility to this agent, so in this region, Nitrofurantoin may therefore be used as empirical treatment of UTIs as and when needed.

In this study, all the isolates showed high resistance for Penicillin group, 3rd generation Cephalosporins ,Aztreonem, Cefoperazone sulbactam and Cefoxitin. This may be due to high prevalence of ESBL producers, AmpC producers among Urinary tract pathogens in INDIA[15,24,32,33], *E.coli* isolates were showen 27% resistance to Cefoperazone/sulbactam in this study.

E.coli and *Klebsiella* isolates showed less resistance to Aminoglycosides in this study. *E.coli* isolate showed least 10.7% resistance for Amikacin than other agents of this group. Although *Pseudomonas* isolates showed 40% rate of resistance, which was less for *Pseudomonas spp* than Carbapenems and Cephalosporins. After Gatifloxacin, Levofloxacin and Imepenem, *Klebsiella spp* isolates found to be less resistant to Tobramycin and Gentamicin. Aminoglycosides being injectables are used restrictively in community- care setting and hence have better sensitivity rates that other antimicrobials but increased resistance of *Pseudomonas spp* isolates to these group of antimicrobials is Alarming signal for hospital settings .

In present study, *E.coli, Klebsiella* and *Pseudomonas* isolates showed less resistance to Imipenem, with 17.9%, 11.6%, 46.2% resistance than other two Carbapenem antibiotics. Meropenem found to be less effective with 47.4%, 62.3%, 69.2% rate of resistance for *E.coli*, *Kliebsiella spp* and *Pseudomonas spp* respectively. In similar study Akram et al [25] got 0%, 12% and 0% resistance rate to *E.coli, Klebsiella* and *Pseudomonas* isolates from UTI case while Kothari et al[34] got 100% susceptibility to Meropenem by all isolates from UTI.

Conclusion:

UTI and other infectious diseases are to be considered dangerous due to global escalation of drug resistance pattern, though the Indian scenario is somewhat different than that in the developed country.

In developing country like India, easy access to drugs without prescription increases use of antimicrobial drugs in general population. In India, practice of starting empirical treatment without knowing the current trend of drug resistance in that particular region due to lack of availability of data is quite common. Doctors would go for culture and AST report only when their empiric treatment does not work, this is the main factors which lead to such a bad current situation where most of the pathogens isolated show resistance to first line of drugs. This study provides much needed information on the common uropathogens and currently how the trend changed in Drug susceptibility pattern. Our study data will helpful in choosing empirical treatment in our region and also reveal some unseen threats.

We found potentially drug resistant *Pseudomonas* is emerging as major uropathogens, which is alarming signal for the hospital settings. Precautions must be taken to minimize spread of such infections. Majority of *Pseudomonas* isolates showed resistant to even Aminoglycosides and Carbapenem group of drugs, spread of such pathogens will increase mortality rate. Strict policies in usage of these groups of antibiotics must be followed otherwise the time will come when along with *Pseudomonas*, other isolates will be resistant to these reserved treatment options.

As per our study results we recommend Nitrofurantoin and Ofloxacin to be use as an empirical therapy for treatment of UTIs in Anand region, as due to very low susceptibility rate, prescribing Ampicillin, Amoxyclave, 3rd generation cephalosporin, Ciprofloxacin and Norfloxacin would definitely lead to treatment failure. Aminoglycosides and Carbapenem must be use only as reserve option of treatment after AST report, as misuse of these groups will add to spread of their resistance strains.

Results of this study strongly recommend a regional surveillance of antibiotic resistance every year to assess the effectiveness of current treatment regimens. The data of surveillance must be utilizing to formulate local antibiotic policies and should provided to clinician to prevent misuse or overuse of antibiotic. The era of judicious use of antimicrobial agent already begun, being impulsive will drag us to situation of pre antibiotic era.

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Conflicts of Interest:

Declared none.

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