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Retrospective study of antibiotic resistance among uropathogens from rural teaching hospital, Tamilnadu, India

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ABSTRACT

Objective: To determine the community associated urinary tract infection (UTI) causing uropathogen´s prevalence, antibiotic resistance pattern and the risk factors predisposing infection in Indian rural settings. **Methods:** A pilot study was conducted between January and December 2010 among out patients attending rural teaching medical college hospital at Tamilnadu, India. The demographic details, culture, common antibiotic Kirby-Bauer disc diffusion assay susceptibility profiles of the isolates and the resistance analysis by WHONET 5.6 software were performed. **Results:** During this surveillance study, a total number of 1 359 urinary samples were collected, among which 309 (22.78%) gave positive culture. The common uropathogens encountered were *Escherichia coli* (66.02%), *Staphylococcus* sp. (12.62%), *Klebsiella* sp. (5.83%), *Streptococcus* sp. (5.18%), *Enterococcus* sp. (2.59%) and *Proteus* sp., (2.26%). Antibiotic resistance analysis revealed the multiple drug resistance nature of the isolates to the commonly used antibiotics. It is also found that both genders at the specific age group of 40-50 were more prone to infection and seasonal variations also play an important role in their establishment. **Conclusions:** The obtained results suggest that antibiotic selection for empirical treatment should be based on individual drug-sensitive test results. There is also an urgent need to develop a new combination of chemotherapeutic agents and awareness on antibiotic use for the effective UTI management in rural settings.

1. Introduction

Infections of urinary tract (UTI) is one of the most common diseases next to respiratory tract affecting peoples of all age worldwide[1]. They are the most common type of body infection clinicians encounter in the developing countries causing serious health problems to millions and displays an overall estimated incidence of 18/1000 persons per year[2,3]. It can cause life-threatening sepsis although most are less severe. Nevertheless, UTI causes significant distress to the individuals and is associated with high healthcare and social costs. In USA, they are accountable for 7 million clinic visits annually with a cost exceeding $1.6 billion[4]. UTIs became quite alarming as isolated uropathogens exhibits high percentage resistance to almost all antibiotics[5].

Among the several UTI implicated microorganisms, bacteria are the major causatives accounting more than 95% cases[6]. Early diagnosis and apt treatment are the identified imperative factors for their elimination and thereby associated urosepsis plus renal scarring risk decline[7]. Rural health centers limited diagnostic laboratory facilities coerce frequent use of empirical antibiotic treatment for these infections. Also apposite treatment may vary according to the patient's age and sex, any underlying diseases, lower or upper UTIs and the infecting agent[8]. Hence the escalating prevalence of uropathogen's antimicrobial-resistance is a cause of anxiety among primary care providers who mostly reliant on empirical therapy[9]. Surveillance uropathogen's susceptibility profile are necessary to increase efficacy of empirical therapy[10], which could help in target bacterial real antibiotic resistance data based antibiotic prescription. Monitoring antibiotic susceptibility patterns of uropathogens at a local level is imperative to be guided not only on emerging problems of antibiotic resistance but also to provide assistance in managing empirical therapy[11]. This information would be relevant not only for local area

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but also useful as regional reference data for physicians[12]. Hence each institution must undertake its own local evaluation / drug policy.

The currently recommended bacterial UTI treatment chemotherapeutic classes and anti-infective agent includes the β-lactams, fluoroquinolones, pyrimethamines, aminoglycoside, oxazolidinones glycopeptides[13]. As suggested by Andrade *et al*[14]the spectrum and antimicrobial resistance of UTI bacteria may vary temporally and geographically. A tertiary care center study conducted between January and December 2008 in Bangalore, South India accounted *E.coli* as a causative agent for 65.7% of the total UTIs. It also recorded high degree of ESBL production (66.78%) and fluoroquinolones resistance (76.9%) among the isolates[15]. A multi-center study carried out at Delhi on adult non-pregnant females recognized the high levels of ESBL producers among Gram-negative community-associated uropathogens, along with the alarming rate of ciprofloxacin, TMP-SMX and amoxicillin resistance[16]. In 2009, one Mumbai tertiary care hospital surveillance study revealed the higher (63%, floor; 41% ICU) prevalence of UTI causing *E. coli* and their unusual susceptibility[17].

Population-based comparative studies conducted on reproductive tract infection (RTI) among women attending rural Maharashtra and Bombay hospitals signify the rural and urban centre difference. Brabin *et al* reported low prevalence of genital tract infections among women in Bombay[18]. Whereas Bang *et al* reported a high prevalence of RTI signs and symptoms in older women from rural Maharashtra where they did not have access to good healthcare facilities[19]. Regrettably most of the data available on UTI pathogens are from urban centers. Among all UTI predisposing factors, sex is recognized as significant epidemiological factor and its role in UTI development as well as its outcome has been extensively studied. Unfortunately, nearly all available current data on uropathogens antibiotic resistance pattern are derived mostly from female patients. Uropathogens causing UTIs in different age groups of male patients and their antibiotic susceptibility are scarcely available one[20]. The epidemiology of the causatives, environmental and meteorological, human behavior adaptations, and host physiology seasonal changes are the recognized as factors accountable in the infectious diseases seasonal variation incidences. But still, the association between environmental parameters and UTI occurrences has not been sufficiently studied[21] in India particularly in rural settings.

The present study was formulated to investigate and report the current scenario of growing multiple drug resistance among uropathogens against the currently used antimicrobials. Also it aims to draw a parallel between uropathogen species and the reported risk factors like host characteristics, seasonal variations *etc.*, to obtain guidance for selecting appropriate antibiotic empirical treatment and to device an up-dated treatment policy for the rural area.

2. Materials and methods

2.1. Design, population and demography

Between January and December 2010, a surveillance study on culture and sensitivity profiles of uropathogens was carried out at Perundurai Medical College Hospital, Tamilnadu, India. The study designed was not categorized between an uncomplicated UTI and the first UTI developing to a complicated or recurrent course. Therapeutic information of all outpatients with symptoms indicative of a UTI descriptive for age, gender, regional distribution, degree of urbanization, *etc.*, were also collected. All patients received care as usual, *i.e.*, diagnostic tests and empirical therapy according to the daily practice[20].

2.2. Urine sampling and processing

Uropathogens were isolated from a total 1 359 suspected UTI patient's midstream urine samples collected and identified according to NCCLS standard procedure. Growth of 105 colony forming units (CFU)/mL was considered a positive urine culture[22]. Only one strain of each species from an individual patient was included. The obtained isolates were identified using standard morphological, cultural and biochemical methods as described[23] and preserved at -4 ℃ in refrigerated condition.

2.3. Determination of antimicrobial susceptibility

Kirby-Bauer disc diffusion assay on Muller Hinton agar was carried out to determine the antimicrobial susceptibility profiles[24]. The panel antimicrobials include β-lactam antibiotic (amoxicillin 30 μg), aminoglycosides (amikacin 30 μg, gentamicin 10 μg), cephalosporin antibiotics (gefixime 5 μg, cefotaxime 30 μg, cefpodoxime10 μg), synthetic quinolone fluoroquinolones antibiotics (nalidixic acid 30 μg, ciprofloxacin 5 μg, ofloxacin 5 μg, norfloxacin 10 μg, levofloxacin 5 μg), macrolide (erythromycin 15 μg) semisynthetic penicillin (cloxacillin 5 μg, penicillin V 10 μg), glycopeptide antibiotic (vancomycin 30 μg), aminocoumarin (novobiocin 30 μg), nitrofuranes (nitrofurantoin 300 μg) and tetracycline 30 μg. The standard antibiotic discs (Himedia laboratories, Mumbai, India) available were used for this study.

2.4. Statistical analysis

The obtained sensitivity profile statistics were analyzed using WHONET5.6 (World Health Organization NET) software. Organism prevalence rate calculations, frequency distributions, susceptibility patterns and other descriptive statistics were computed and reviewed. The data was also analyzed statistically using SPSS statistics version 9.0

(Chigago, IL, USA) and values of $P<0.05$ were considered statistically significant[25].

3. Results

Through the one year surveillance period (January 2010 to December 2010) a total number of 1359 non-duplicative urinary samples were collected, wherein 309 were come up with a positive urine culture (22.78%). The positive samples were collected from both 148 (47.90%) male and 161 (52.10%) female patients of various age groups (Figure 1). The *E.coli* is a main successfully isolated uropathogen. The frequencies of other uropathogens include *Klebsiella* sp., *Proteus* sp., *Staphylococcus* sp., *Streptococcus* sp. and *Enterococcus* sp. as shown (Table 1). The degree of association between the gender of the patients and the incidence of uropathogens is also determined. Among the total 148 (47.90%), 108(34.95%) were caused by Gram negative and 37(11.97%) were caused Gram positive organisms in males. In females, the percentage of Gram positive and Gram negative organism infections were found to be in the ratio of 39.16% (121) and 11.65% (36). The obtained results upon statistical analysis (ANOVA and chi square test) revealed the insignificant difference in the gender and age group wise incidence of uropathogens. The gender wise and age group wise distribution of UTI were presented (Figure 2). The distribution by age (male: female) was as follows: <10 years (51 patients, 7.77%:8.74%), persons aged 11- 20 years (39 patients, 3.56%:9.06%), 20-30 (35 patients, 5.50%:5.82%) 30-40 years (34 patients, 5.50%:5.50%), 40-50 (48 patients, 8.41%:8.74%), 51-60(46 patients, 7.12%:6.80%) 61-70(39 patients, 7.12%:5.50%) and no data available (16 patients). Interestingly the female gender up to the age of 50 exhibited an increased tendency enrooted for becoming victim of UTI.

Since most of the obtained isolates are endogenous and commensals, the seasonal variations in the incidence of UTI caused by them has also been determined among the present study population. From the season wise UTI incidences among male and female patients are data presented (Table 2), it is found that the highest rate (27.83%) of UTI has occurred during the months of October to December followed by 26.21% between July and September (Figure 3).

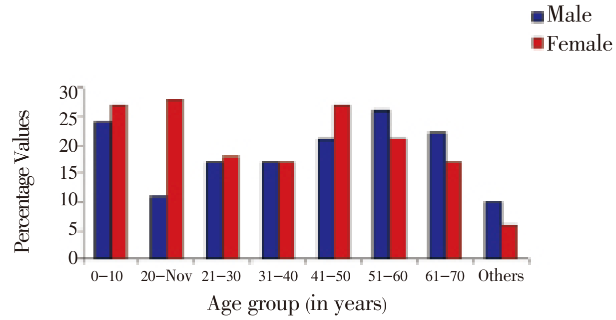

Figure 1. Incidence of UTI among different age group people and its gender wise distribution.

Table 1

The baseline pathogens caused UTI among positive urine culture samples.

Identification of the isolate	Frequency of the isolate [n (%)]	Patients
E. coli	204 (66.02)	
Klebsiella sp.	18 (5.83)	N=229
Proteus sp.	7 (2.26)	
Staphylococcus sp.	39 (12.62)	
Streptococcus sp.	16 (5.18)	N=63
Enterococcus sp.	8 (2.59)	
No identification	17 (5.50)	N=17
Total	309 (100)	N=309

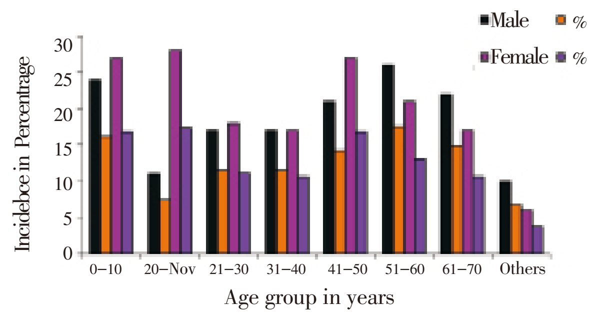

Figure 2. Incidence of UTI in age groupwise and genderwise distribution.

The predominant Gram negative uropathogen isolated *E. coli* (n=44) showed resistance to nitrofurantoin (1.5%), amikacin (10.5%), gentamicin (30.4%), novobiocin (50.0%), levofloxacin (64.5%), cefixime (70.1%), ciprofloxacin (70.4%), tetracycline (72.7%), cefpodoxime (72.6%), cefotaxime (74.8%),

Table 2

Represents seasonal distribution of UTI among gender.

Period	Male									Female									Total	%
	1	2	3	4	5	6	7	Total	%	1	2	3	4	5	6	7	Total	%		
Jan to Mar	20	-	2	4	2	2	3	33	22	22	6	3	4	1	-	-	36	22.64	69	22.33
Apr to Jun	21	1	1	4	2	5	2	36	24	27	3	1	1	-	2	3	37	23.27	73	23.62
Jul to Sep	26	2	-	3	2	2	1	36	24	27	2	-	10	1	1	4	45	28.30	81	26.21
Oct to Dec	31	3	-	5	-	3	3	45	30	30	1	-	8	-	1	1	41	25.79	86	27.83
Total	98	6	3	16	6	12	9	150	100	106	12	4	23	2	4	8	159	100	309	100.00
Percentage (%)	31.72	1.94	0.97	5.18	1.94	3.88	2.91	48.54	-	34.30	3.88	1.29	7.44	0.64	1.29	2.59	51.46	-	100	-

1: *E.coli*; 2: *Klebsiella* sp.; 3: *Proteus* sp.; 4: *Staphylococcus* sp; 5: *Streptococcus* sp; 6: *Enterococcus* sp.; 7: Others.

Table 3
Antibiotic resistant pattern of isolated uropathogens (%).

Antibiotics	Gram negative organisms			Gram positive organisms		
	E. coli	*Klebsiella* sp.	*Proteus* sp.	*Staphylococcus* sp.	*Streptococcus* sp.	*Enterococcus* sp.
Amoxicillin	96.2	87.5	66.7	81.8	41.2	30.8
Amikacin	10.5	7.7	50.0	11.1	54.5	66.7
Cefixime	70.1	46.7	20.0	31.2	54.5	66.7
Cefotaxime	74.8	40.0	50.0	38.1	60.0	0.0
Cefpodoxime	72.6	40.0	33.3	25.0	57.1	100.0
Ciprofloxacin	70.4	16.7	14.3	46.9	62.5	50.0
Gentamicin	30.4	16.7	66.7	18.8	41.7	33.3
Levofloxacin	64.5	25.0	33.3	47.4	50.0	50.0
Nalidixic acid	98.5	57.1	83.3	90.0	100.0	66.7
Norfloxacin	75.4	23.5	14.3	59.1	42.9	66.7
Nitrofurantoin	1.5	25.0	42.9	0.0	40.0	42.9
Ofloxacin	80.4	30.0	0.0	74.1	66.7	50.0
Erythromycin	100.0	0.0	0.0	41.7	66.7	87.5
Cloxacillin	100.0	100.0	100.0	59.1	50.0	0.0
Novobiocin	50.0	100.0	0.0	8.7	0.0	0.0
Tetracycline	72.7	100.0	0.0	33.3	100.0	50.0
Vancomycin	100.0	0.0	0.0	20.0	0.0	83.3
Penicillin V	–	–	–	79.2	40.0	28.6

norfloxacin (75.4%), ofloxacin (80.4%), amoxicillin (96.2%), nalidixic acid (98.5%), erythromycin (100%), cloxacillin (100%) and vancomycin (100%). The *E. coli* shows higher susceptibility (about 90%) only to nitrofurantoin and amikacin was presented.

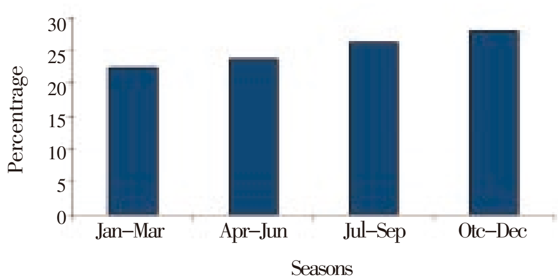

Figure 3. Season wise distribution of UTI.

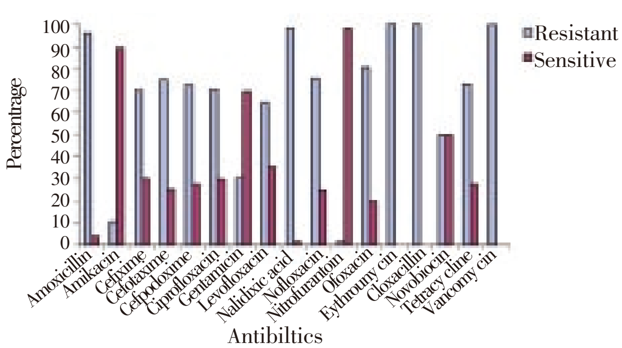

Figure 4. Shows common antibiotic resistant pattern of UPEC isolated from rural Indian teaching hospital.

The major Gram positive uropathogenic isolates *Staphylococcus* sp., (n=39) showed resistance in the order of nitrofurantoin (0%)≤novobiocin (8.7%)≤amikacin (11.1%)≤ gentamicin (18.8%)≤vancomycin (20%)≤cefpodoxime (25.0%) ≤cefixime (31.2%)≤tetracycline (33.3%)≤cefotaxime (38.1%) ≤erythromycin (41.7%)≤ciprofloxacin (46.9)≤levofloxacin (47.4%)≤cloxacillin (59.1%)≤nalidixic acid (59.1%)≤ofloxacin (74.1%)≤norfloxacin (75.4%)≤penicillin V(79.2%)≤amoxicillin (81.8%) as presented (Table 3).The predominant uropathogenic *E.coli* is found to exhibit an dreadful resistance to number of antibiotics (Figure 4). The isolated uropathogens antibiotic resistance on the whole observed in this study is higher than the already available results from urban areas which is an alarming one.

4. Discussion

In India and some other nations, the limited controls on prescription practices, non-standardized antimicrobial manufacturing and the breakdown of infection control infrastructure due to compromised resources present a high potential for resistant pathogens emergence and their unimpeded spread[25]. Poverty, inadequate access to drugs, increased use, and misuse are major forces for the emergence and increase of this public health challenging antimicrobial resistance which hampers the clinical management of UTIs worldwide[26]. International guidelines are no longer applicable for treating community associated UTI in India, and development of specific guidelines based on local susceptibility patterns are necessary. Regional surveillance programs development are necessary to provide information for Indian CA-UTI guidelines development[16].

Since it is mandatory, the imperative sex and other socially constructed factors are also included in this study to produce principled, precise, and effective health research findings. The major causative role *E.coli* in UTI has also been observed many workers. The uropathogen profile and resistance by pattern observations of Bhargavi *et al*[12] on southeast Indian UTI isolates coincides with the present study. The study exhibited most common and higher prevalence of UTIs among rural women than men. As suggested, it may be because of clinical variables, anatomic differences, hormonal effects, and behavioral patterns[10].

Though the seasonal influences on human health have been known for more than 2000 years[27], its influence on UTI incidences throughout the world especially in India have not been appraised. To the best of our knowledge, this is the first report correlates UTI incidences with seasonal variation in India. Falagas *et al*[21] also reported the partial associations between its occurrences and meteorological parameters. They also articulated that the data available in the literature regarding the subject of this study are not conclusive.

While susceptible pathogen's appropriately targeted antimicrobials improve patients' outcome, their use at population level and overuse is associated with the bacterial resistance emergence[28]. Hence same approaches showed entirely different solutions and uropathogen responses. Timely recognition of isolates resistance to newer agents is of paramount importance, and will allow apposite treatment of affected patients and implementation of infection control procedures[29]. General practitioners put up with comparable high resistance rates should circumvent the risk of losing an effective antibiotic cure. Therefore, the choice of a rational antibiotic regime is essential[26].

The multiple drug resistance among the isolates observed in this study against the regularly used common seventeen antibiotics is very high. In addition, more number of isolates is being resistant to two or more antimicrobials. Probable major contributing factor may be the self-medication and attending medical care only at the advanced level. The interesting finding of enterococcal high amino glycosides resistance corroborates with the HILAR (high-level amino glycoside resistance) observations among South Indian setting urinary enterococcal isolates[30]. Since these proportions may lead to the drug synergism failure, routine testing of enterococcal isolates for HILAR is necessary. Investigation of prescribing patterns in many studies has revealed an increased reliance on fluoroquinolones and SxT for the empiric treatment of uncomplicated UTI. Various studies have showed the UPEC higher resistance to nalidixic acid and ciprofloxacin[31]. The reports of the study conducted at Kathmandu[32] is in controversy to present, which showed UPEC high sensitivity to amoxicillin (64%-89%), norfloxacin (65%-75%) and gentamycin (90%-93%) indicating the geographical differences. Apart from that, the main cause of this resistance could be either the more frequent and unnecessary usage of antibiotics or prescribing most recent antibiotics with newer combinations for faster recovery of infections.

Based on the present findings, we suggest that the higher sensitive antibiotics, amikacin (92.26%), and nitrofurantoin (86.22%) can be effective. A similar observation was made by Hummers-Pradier *et al*[33] who showed UPEC highest sensitivity to nitrofurantoin and its dissemination among all age groups. History has a way of repeating itself and there is no doubt that physicians will eventually need the next generation of novel agents to prevent and treat UTI[34]. Furthermore, national, state, and hospital level programs of surveillance and intervention must be strengthened to prevent the continued emergence of multi drug resistant pathogens and to limit their spread into other communities or other institutions[35,36].

The several potential limitations of this study should be taken into account while interpreting the reported findings. First, inherent limitations regarding the methodological aspects of retrospective studies should be considered[21]. Second even though no selection criterion was applied, the greater part of the patients represent economically poor background with agricultural and casual labors, hence, the findings of our study may not be representative of the whole population in the community. However, the analytical data of our study are detailed in a prospective manner.

This pilot study depicts the differential scenario in the rural environment. It also stresses the need to pursue detailed studies of this kind in rural areas which may lead to better understanding of the UTI aetiology, the magnitude of antibiotic resistance and accordingly device empirical treatment. Number of antibiotics used in the empirical treatment needs to be reevaluated. Also further research is needed regarding rapid diagnosis of UTI, accurate presumptive identification of patients with resistant pathogens, and development of new antimicrobials for drug-resistant UTI.

Conflict of interest statement

We declare that we have no conflict of interest.

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