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Antimicrobial Susceptibility Pattern of Bacterial Isolates from Urine Samples from Female Patients Suffering from Urinary Tract Infection at Tertiary Care Center in South India

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ABSTRACT

Introduction: The frequency of bacteria affecting urinary tract and their antibiotic susceptibility pattern vary from one territory to another. This study was conducted to determine spectrum of bacterial isolates causing UTI and their antibiotic susceptibility pattern among female patients attending tertiary care center

Materials and Methods: A total of 577 female urine culture sensitivity reports (CS) were collected. The culture was done by inoculation by standard loop technique. Antibiotic susceptibility testing for identified bacteria was done by Kirby-Bauer disc diffusion method and result was interpreted as per CLSI guidelines. Data was analyzed using SPSS software.

Results: Infection rates were similar up to reproductive age group with no significant difference between gram-positive (GP) and gram-negative organisms (GN) but post reproductive age group suffered more from GN. The most commonly infecting organism was Staphylococci followed by Escherichia coli showing resistance in >50% tests to cephalosporins, penicillin and fluoroquinolones. All antibiotics are showing resistance from one or the other organisms.

Conclusion: The commonly infecting bacteria are developing resistance to regularly used antibiotics raising concerns of cross resistance and selection of antibiotics. This warrants due diligence by all stakeholders, including public-health authorities, health care providers, policymakers and even the public to prevent and control antimicrobial resistance.

Key words: Urinary tract Infection, Antimicrobial susceptibility, Bacterial infection, Bacteriuria

INTRODUCTION

Urinary Tract Infections (UTI) is one of the most common bacterial infections in female and its prevalence among females varies from 21.8 to 31.3 in various parts of India.[1,2] UTI in females present as either asymptomatic bacteriuria or symptomatic bacteriuria. Asymptomatic bacteriuria is the presence of bacteria in the urine in the absence of urinary symptoms. It is a common clinical finding that often warrants a decision to initiate antimicrobial therapy. Guidelines only recommend screening and appropriate treatment for asymptomatic bacteriuria in pregnant women and in individuals undergoing endourological procedures associated with mucosal trauma.[2]

Symptomatic urinary tract infections are divided in-

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to lower tract (cystitis) or upper tract infections (pyelonephritis) which requires antimicrobial therapy. Symptomatic bacteriuria is bacteriuria in the presence of genitourinary symptoms like dysuria, suprapubic pain or tenderness, frequency, urgency and also fever while asymptomatic bacteriuria is bacteriuria with absence of theses genitourinary signs and symptoms.[3]A urine culture with ≥ 10^5 CFU/ml is classically considered as positive for presence of bacteriuria. Inappropriate treatment of these can lead to development of antimicrobial resistance.

Developing countries like India are at higher risk of development of antimicrobial resistance (AMR) due to sub-optimal hygiene, poor infection control, lack of surveillance and antimicrobial stewardship programs. Self-medication and noncompliance to the prescribed antimicrobial regimen also contributes to the emergence of AMR. [3] AMR can have serious consequences like prolonged or failure of treatment, increased healthcare costs, increase in morbidity and mortality.[4,5] AMR kills an estimated 700 000 people all over the world every year, most from developing countries. It is estimated that by 2050, this number may increase to 10 million.[6] The consequences of AMR have a direct or indirect impact on individuals, healthcare institutions and the society at large. Patients infected by resistant pathogens have longer hospital stays, undergo additional laboratory investigations and are the source of infection that can spread to healthy people. Second-line treatments for such patients are less effective, more costly, more toxic and sometimes difficult to administer. The technical and financial challenges that are felt by health systems for effective management of these patients are colossal too.[6]

The frequency of bacteria affecting and their antibiotic susceptibility pattern vary from one geographical area to another.[5] Thus, knowing the local pattern can help in the empirical treatment of female patients thereby preventing undue adverse outcomes.

This study was conducted to determine the spectrum of bacterial isolates causing UTI among female patients attending tertiary care center; and also, to determine antibiotic susceptibility pattern of bacterial isolates.

METHODOLOGY

This retrospective study was conducted in a tertiary care center in southern India after obtaining approval from the institutional ethics committee. Permission from Central lab was obtained to collect the data. The department of microbiology received 577 urine samples of female patients presented to the hospital with any symptoms of urinary tract infection for 12 months. About 20 ml of clean catch midstream urine samples were obtained from each patient. Samples thus collected were immediately transported to the Diagnostic Microbiology Department and processed within 1 hour. In case of delay, the samples were refrigerated at 4°C. The urine specimens were first processed by routine quantitative culture and were then tested by the screening methods under consideration.

A total of 577 female urine culture sensitivity reports were collected from department's record. The culture was done by inoculation by standard loop technique on to culture media.[7] Antibiotic susceptibility testing for identified bacteria was done by Kirby-Bauer disc diffusion method[8,9] and the results were interpreted as per CLSI guidelines. [10] The data was analyzed using SPSS software.

RESULTS

The 577 urine samples data collected was divided into three groups considering age as a criteria, <15, 16-49 and >49 which represent pre reproductive, reproductive and post reproductive age group respectively. Reproductive age group constitutes 376 samples of which 63.30% showed no growth, 30.85% showed bacterial growth and 2.13% showed mixed bacterial growth. Candida infections were more commonly seen in reproductive age group, constituting about 3.72% of this age group.

Table 1: Age wise distribution of culture and sensitivity reports based on microbial growth (N=577)

Age (yrs)	Samples	Bacterial Infection (%)	Mixed bacterial growth (%)	Candida infection (%)	No growth (%)
<15	72	24 (33.33)	0 (0)	1 (1.389)	47 (65.28)
15 to 49	376	116 (30.85)	8 (2.13)	14 (3.723)	238 (63.3)
> 49	129	56 (43.41)	3 (2.33)	0 (0)	70 (54.26)
Total	577	196 (33.97)	11 (1.91)	15 (2.6)	355 (61.53)

Table 2: Age wise distribution of bacterial infection samples based on gram staining (N=196)

Age in years	Bacterial Infection	Gram Positive (%)	Gram Negative (%)
<15	24	12 (50)	12 (50)
15 to 49	116	53 (45.69)	63 (54.31)
> 49	56	15 (26.79)	41 (73.21)
Total	196	80 (40.82)	116 (59.18)

Table 3: Percentage wise distribution of bacterial isolates in positive culture in different age groups

Organism	Over all	Pre reproductive	Reproductive	Post reproductive
E.coli	27.55	20.83	23.28	39.28
Coagulase positive staphylococci	22.96	33.33	25	14.29
Klebsiellsa sps	13.27	8.33	12.07	17.86
Coagulase negative staphylococci	11.73	12.5	14.66	5.36
Enterococci	7.14	12.50	6.89	5.36
Pseudomonas	4.08	8.33	4.31	1.79
Citrobacter	3.57	0	4.31	3.57
MRSA	2.55	4.17	1.72	3.57
Epidermidis	2.04	0	2.59	1.79
Streptococci	1.53	0	1.72	1.79
proteus vulgaris	1.53	0	1.72	1.79
Diptheroids	0.51	0	0.86	0
Enterobacter	0.51	0	0	1.79

Table 4: Comparison of resistance demonstrated by Bacteria to the commonly used antibiotics amongst age groups

Antibiotic	Resistance Demonstrated (%)	Pre reproductive (%)	Reproductive (%)	Post reproductive (%)
Ampicillin	85.71	100	75	100
Ampicilin/sulbatum	53.57	37.5	56.25	58.82
Amoxicillin/calvulanate	40.26	55.56	33.33	52.94
Cefixime	75.00	60	69.56	100
Cefoxitin	50.76	37.5	45	73.33
Ceftazidime	61.11	50	53.19	77.41
Cefpodoxime	60.00	0	66.67	-
Ofloxacin	55.56	36.36	54.9	64.29
Ciprofloxacin	53.66	20	48.148	80
Norfloxacin	48.86	16.66	44	66.66
Levofloxacin	48.28	75	33.33	71.43
Cotrimoxazole	46.48	60	39.53	54.76
Erythromycin	36.36	25	33.33	-
Gentamicin	25.00	57.14	25.93	20
Amikacin	14.75	7.14	13.89	16.67
Vancomycin	13.16	10	15.69	6.67
Nitrofurantoin	7.23	0	6.79	11.11

Pre-reproductive age group had 72 samples of which 65.28% showed no growth while 33.33% showed bacterial growth. Out of 129 samples belonging to the post-reproductive age group, 43.1% of showed bacterial growth, 2.33% showed mixed growth and gram negative organisms were predominant in this age group. (Table 1and 2)

The most common infecting organisms were staphylococcal species (77 positive cases) followed by E. coli with 54 positive cases and Klebsiella with 26 cases. In the pre reproductive age group, the most commonly infecting organisms were found to be Coagulase positive staphylococci followed by Escherichia coli. The highest degree of resistance was demonstrated towards Ampicillin (100%) followed by Levofloxacin (75%) and Cotrimoxazole (60%). In women of reproductive age group, the frequently found organisms were Coagulase positive staphylococci, Escherichia coli, Coagulase negative staphylococci and Klebsiella. (Table 3)

Higher resistance was seen towards cefixime (80%), cefpodoxime (66.67%) and Ampicillin with sulbactum (56.25%). In postmenopausal women, common organisms found were Escherichia coli followed by Klebsiela and Coagulase positive staphylococci. Cefixime (100%), Ampicillin (100%), Ciprofloxacin (80%), Cefotaxime (80%) and Ceftazidime (77.42%) exhibited the most resistance in this age group. (Table 4)

Although UTI was more commonly seen in women of reproductive age, higher prevalence of antimicrobial resistance was seen in postmenopausal women. Highest percentage of resistance was towards ampicillin followed by cefixime, ceftazidime, cefpodoxime and ofloxacin. (Table 4) All organisms showed resistance to one or the other antibiotics.

DISCUSSION

Antimicrobial resistance is rising to dangerously high levels all over the world, threatening the ability of healthcare providers to treat common infections. With no urgent intervention, we would enter the post-antibiotic era where common infections and minor injuries would be catastrophic.[11] When first line antibiotics can no longer cure infection more expensive medicines would be required with prolonged hospital stay and increased healthcare costs. This will cause economic burden on families and societies. Organ transplantation, chemotherapies and

surgeries become dangerous with no effective antibiotic to prevent and treat infections. This along with the ease and frequency with which people travel, AMR becomes a global problem and a threat to modern medicine.[11]

This study provides information regarding the agents causing UTI among women attending the tertiary care centre and their antimicrobial susceptibility pattern in relation to age. 33.96% of the 577 were found to have a positive urine culture. Most commonly infecting organisms were E. coli followed by staphylococcal species which is consistent with findings from other studies.[12] Females in reproductive age group were found to be more susceptible to UTI. Factors for higher incidence among females of reproductive age group are associated with high sexual activity and a history of recurrent UTI.[13]

In our study, gram negative organisms were predominant. E.coli infection was more among females aged 15-49 where as in both extremes i.e. pre reproductive and post reproductive age group, staphylococcal species infection was more common. Also, a higher incidence of candidal infections was seen among the reproductive age groups. This correlates with numerous other reports in India like Devanand Prakash et al and Iram Shaifali et al [13,14]

In the younger age group, isolates showed higher resistance to cotrimoxazole and ampicillin whereas Nitrofurantoin, Ciprofloxacin, Imipenem and Amikacin were among those that bade less resistance. The resistance percentages are similar to a study by Ali Reza Nateghian et al in Tehran, Iran.[15] Poor empiric prescribing practices, lack of urine testing, and nonselective use of prophylaxis are the causes for resistance to antimicrobials in pediatric ages too. Selective application of antibiotic prophylaxis to patients; and use of local antiobiograms, particularly pediatric-specific antibiograms, with inpatient and outpatient data can help curb the rise of AMR. [16]

Women aged between 15-49 years were more sensitive to nitrofurantoin, amikacin, Imipenem and cefoperazone with sulbactum with less than 15% resistance. Premenopausal women showed much lesser resistance to antimicrobials than postmenopausal women which was also observed in studies in the States and Poland.[17,18] But, in this study, it was observed than women of reproductive age showed lesser resistance to cotrimoxazole than both extremes of age.

A higher prevalence of antimicrobial resistant uropathogen was seen among older females. Higher degree of resistance was seen to ciprofloxacin, cotrimoxazole, levofloxacin, ampicillin and cephalosporins. It is important to note that 73.3% of the bacteria showed resistant to Cefoxitin suggesting resistant to beta lactam antibiotics. A similar result was reported by Pawel Miotla et al.[18] Older people are more likely to get multiple organism infections when compared to youngsters, declining renal function as part of normal ageing which reduces the ability of some antimicrobials (Eg. Nitrofurantoin) from achieving therapeutic concentrations in the urinary tract and increased resistance to antimicrobials complicates treatment of UTIs by limiting therapeutic options which contributes to excess morbidity.[19,20] In older patients with UTI, empirical treatment regimen should be decided based on previous uropathogen susceptibility profile whenever available.[17] Postmenopausal women are at risk for UTIs because of physiologic and hormonal changes after menopause, which include thinning of the tissue in the vagina, trouble in completely emptying the bladder, and lower levels of the hormone estrogen-which are said to promote growth of commensal bacteria that keep infectious organisms in check. However, whether they contact a drug-resistant infection depends on their medical history, past antibiotic use, and environmental exposure.[21]

More commonalities in antimicrobial resistance pattern was seen between the pediatric and postmenopausal women as both showed 100% resistance to Ampicillin, greater than 70% to Levofloxacin, and more than 50% resistance to cotrimoxazole and amoxicillin with calvulanic acid. Resistant to beta lactam antibiotics increased from 37.5% in pre reproductive, 45% in reproductive to 73.3% in post reproductive age group. All women >15 years showed more than 50% resistance to Ofloxacin and Ampicillin with sulbactum while those aged <49 showed more 50% resistance to Ceftazidime and >60% to Cefixime. Nitrofurantoin, Imipenem and Vancomycin were the most sensitive antibiotics among all age groups showing ≤15% resistance. Higher resistance to cotrimoxazole in pediatric and postmenopausal age group and sensitivity of Nitrofurantoin was seen in a study done in the United States.[17]

For the treatment of uncomplicated UTI, clinical practice guidelines recommend the empirical use of Nitrofurantoin or Trimethorprim-sulfamethazole (Cotrimoxazole) as first line therapy.

Alternatively, fluoroquinolones like ciprofloxacin, Ofloxacin, Levofloxacin etc are used.[17] Nitrofurantoin exhibited very low resistance in all age groups and among various organisms too. While Cotrimoxazole faced more than 50% resistance from E.coli, Klebsiella species and Enterococci, Cotrimoxazole was observed to be more effective in >15 and <49 years.

Fluoroquinolones, Ciprofloxacin (53.66%), Levofloxacin (48.27%), Ofloxacin (55.55%) and Norfloxacin (48.88%) encountered quite high resistance. This high resistance to fluoroquinolones, was seen in other studies from Spain and Iran.[22,23] Fluoroquinolones are the drug of choice for empirical treatment of uncomplicated and complicated UTIs due to trimethoprim-sulfamethoxazole resistant uropathogens and its increasingly used both orally and parentarally for not just UTI but also other common infections, resulting in increased re-

sistance.[24]

In an international level, WHO recommend increased collaboration between governments, non-governmental organizations, professional groups and international agencies, International approach for control the counterfeit antimicrobials.[25] At a national level, formation of national committee to monitor impact of antibiotic resistance and provide inter-sectoral co-ordination is required which according WHO should formulate AMR policy; provide guidance on standards, regulations, training and awareness on antibiotic use and AMR.[25]

Antimicrobial Use and Antimicrobial Resistance: A Population Perspective, by Lipsitch et al., suggests that prevention of AMR in an individual suffering from infection is one of the basic method to prevent further spread of resistance to the wider community.[26] This mandates a community level of intervention, public and professional education towards rational use of antibiotics, regulatory control on OTC use of antibiotics, high standards of hygiene, use of alcohol-based hand rubs or washing hands and use of public latrines. Including pharmacist directed antibiotic stewardship programs (ASPs) as an approach to improve the utilization of antibiotics would also help. Extended pharmacist's roles are well established in developed nations like United States, United Kingdom, Canada, Australia and New Zealand which has produced notably positive outcomes in both hospital and community settings.[27]

We identified a few drawbacks to our study, which includes under presentation of culture and sensitivity of patients for whom the empirical treatment was successful, this may have led to over estimation of antimicrobial resistance. Lack of clinical information, didn't allow us to exclude patients with complicated medical histories or differentiate between hospital acquired and community acquired infections.

Keeping in mind the ever changing pattern of antimicrobial resistance it is important to constantly update the antibiograms by conducting similar studies. Combating AMR most importantly requires clinicians to judiciously select antibiotic therapy based on clinical guidelines, local resistance data and individual patient characteristics.

CONCLUSION

The commonly infecting bacteria are developing resistance to regularly used antibiotics raising concerns of cross resistance and selection of antibiotics. This warrants due diligence by all stakeholders, including public-health authorities, health care providers, policymakers and even the public to prevent and control antimicrobial resistance.Combating AMR most importantly requires clinicians to judiciously select antibiotic therapy based on clinical guidelines, local resistance data and individual patient characteristics.

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