EVALUATION OF ANTIBIOTIC SUSCEPTIBILITY PATTERNS OF UROPATHOGENS CIRCULATING IN HYDERABAD, PAKISTAN

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ABSTRACT

OBJECTIVE: to evaluate the antibiotic susceptibility of uropathogens circulating in the Hyderabad region.

METHODOLOGY: A single midstream urine sample was collected by clean catch method from 119 outdoor and indoor patients attending various diagnostic centers across Hyderabad, during July 2012 to December 2012. Duplicate samples from the same patient were excluded. In vitro antimicrobial sensitivity tests were carried out using Kirby-Bauer disc diffusion technique.

RESULTS: Predominant isolate found in the present study was E. coli (57.14%), followed by Pseudomonas aureginosa (6.12%), Klebsiella pneumonia (4.08%), and Proteus mirabilis (4.08%). Antibiotic susceptibility testing demonstrated varying patterns of susceptibilities against tested antibiotics. All E. coli isolates showed highest sensitivity against Amikacin (100%) followed by Fosfomycin (96.4%), Nitrofurantion (89.2%), and Amoxacillin plus Clavulanate, (82.1%). Amikacin showed 100% sensitivity against E. coli, P. aureginosa, K. pneumonia & P. mirabilis. Importantly, Amoxicillin plus Clavulanate showed comparable sensitivity patterns against E. coli, K. pneumoniae, P. mirabilis, and Enterococcus species, the most common uropathogens in the region. Furthermore, it was observed that 64.29% of the E. coli isolates were resistant to Co trimaxazole, which has previously been used as an antibiotic of choice for treatment of uropathogens.

CONCLUSION: The commonest uropathogens in Hyderabad was E. coli and Pseudomonas aureginosa. Amikacin with highest sensitivity against multiple uropathogens, can be prescribed as the drug of choice in empirical treatment of UTIs. Furthermore, proper knowledge of susceptibility pattern of uropathogens is crucial in order to discourage the indiscriminate use of antibiotics as well as in formulating effective empiric therapy.

KEY WORDS: Antibiotic resistance, Uropathogens, Empirical Treatment, UTI.

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INTRODUCTION

Urinary tract infections (UTIs) are one of the commonest infectious diseases of humans affecting at least 250 million people annually worldwide. UTIs are defined by the presence of a growth of more than 10^5 colony forming units (CFU) of bacteria per ml of urine for asymptomatic individual and much lower for symptomatic individuals (~10^3CFU/ml). E. coli has been reported as a most common etiologic agent[1]. High risk groups include neonates, preschool girls, sexually active women, and elderly women and men. Bacteriological investigations of UTI are not complete without an antibiotic sensitivity test of the isolated organisms. Microorganisms causing UTI vary in their susceptibility to antimicrobials from place to place and time to time. It is important to take preventive measures as detection and treatment are costly for both patients and healthcare systems[2]. Moreover, emergence of antibiotic resistance, allergic reaction to pharmaceuticals, alteration of normal gut flora, and failure to prevent recurrent infections document the need for effective prevention. In women and children, non-complicated UTIs account for the highest number of infection observed. UTI may occur in the lower urinary tract or may involve both lower and upper urinary tract which is characterized by a syndrome involving; dysuria, frequency, urgency, and occasional supra-pubic tenderness. UTIs are often treated with broad-spectrum antibiotics. Fluoroquinolone are preferred as initial agents for empiric therapy of UTI in an area where resistance is likely to be a great concern. This is because they have high bacteriological and clinical cure rates, as well as low rates of resistance, among most common uropathogens[3,4]. The extensive and misuse of antimicrobial agents have invariably resulted in the development of antibiotic resistance, which in recent years, has become a major public health problem world-wide[5].

Resistant bacteria emerge under the selective pressure of antibiotics. In hospitals, due to large-scale usage of antibiotics, bacteria frequently become resistant to several antibiotics which cause serious problems for the treatment of patients with infections by these microorganisms. The use of antibiotics has an influence in the spread of antimicrobial resistance among bacteria[6-9]. The local data about the antimicrobial resistance of uropathogens should be available for proper therapeutic interventions of UTI. There are a few studies on the drug resistance and pattern of antibiotic sensitivity of bacterial pathogens among urinary tract infections in Pakistani population[10-13]. Since the surveillance studies are important tools to guide antibiotic selection, the current study was conducted in order to assess the in vitro antibiotic susceptibility patterns of uropathogens circulating in Hyderabad region of Pakistan to assist doctors/clinicians in selection of empirical therapy for effective management of UTI.

METHODOLOGY

Sample collection and processing

A single midstream urine sample was collected by clean catch method from each of total 119 outdoor and indoor patients attending various diagnostic centers across Hyderabad, during July 2012 to December 2012. The samples were collected in sterile plastic bottles and processed immediately following collection. Only those patients who were suspected UTI by a physician were

TABLE I: DISTRIBUTION OF MALE AND FEMALE SUBJECTS AMONG TOTAL URINE SAMPLES

Urine Culture	Male		Female		Total	
	Frequency	%age	Frequency	%age	Frequency	%age
Culture Positive	12	10.08	37	31.09	49	41.18
Culture Negative	44	36.97	26	21.85	70	58.82
Total	56	47.06	63	52.94	119	100

TABLE II: AGE AND SEX WISE DISTRIBUTION OF TOTAL AND CULTURE POSITIVE URINE SAMPLES

Age (years)	Total Male		Male Culture Positive		Total Female		Female Culture Positive	
	Frequency	%age	Frequency	%age	Frequency	%age	Frequency	%age
0-10	8	6.72	0	0.00	2	1.68	1	0.84
11-20	2	1.68	2	1.68	3	2.52	1	0.84
21-30	8	6.72	2	1.68	17	14.28	8	6.72
31-40	8	6.72	2	1.68	12	10.08	4	3.36
41-50	7	5.88	1	0.84	3	2.52	4	3.36
51-60	6	5.04	1	0.84	11	9.24	7	5.88
Above 60	17	14.28	4	3.36	15	12.60	12	10.08
Total	56	47.04	12	10.08	63	52.92	37	31.09

TABLE III: DISTRIBUTION OF TOTAL MICROBIAL ISOLATES STUDIED IN THIS STUDY

Organism		Frequency (n=49)	%age
Gram-negative (n=35)	*E. coli*	28	57.14
	P. aureginosa	3	6.12
	K. pneumoniae	2	4.08
	P. mirabilis	2	4.08
Gram-positive (n=6)	*Enterococcus species*	4	8.16
	Streptococcus species	2	4.08
Others (n=8)	*Candida species*	2	4.08
	Mixed cultures	6	12.24

TABLE IV: ANTIBIOTIC SUSCEPTIBILITY PATTERN OF BACTERIAL ISOLATES OF URINE

Organism	E. coli (n=28)		K. pneumoniae (n=2)		P. mirabilis (n=2)		P. aureginosa (n=3)		Enterococcus Species (n=4)		Streptococcus Species (n=2)	
Antibiotics	**S %**	**R %**	**S %**	**R %**	**S %**	**R %**	**S %**	**R %**	**S %**	**R %**	**S %**	**R %**
Amoxicillin/Clavulanate	82.14	17.86	100	0	100	0	—	—	75	25	—	—
Ampicillin	21.43	78.57	0	100	50	50	—	—	75	25	—	—
Nitrofurantoin	89.28	10.72	100	0	0	100	—	—	75	25	—	—
Cefuroxime	46.43	53.57	100	0	100	0	—	—	—	—	—	—
Fosfomycin	96.43	3.57	100	0	50	50	—	—	—	—	—	—
Nalidixic Acid	25	75	100	0	100	0	—	—	—	—	—	—
Co-trimoxazole	35.71	64.29	100	0	50	50	—	—	—	—	—	—
Cefexime	53.57	46.43	100	0	100	0	—	—	—	—	—	—
Cefotaxime	50	50	100	0	—	—	—	—	—	—	—	—
Amikacin	100	0	100	0	100	0	100	0	—	—	—	—
Aztreonam	57.14	42.86	100	0	100	0	100	0	—	—	—	—
Ofloxacin	50	50	100	0	100	0	100	0	75	25	0	100
Gentamicin	67.86	32.14	100	0	100	0	100	0	100	0	—	—
Ceftazidime	—	—	—	—	—	—	100	0	—	—	—	—
Piperacillin/Tazobactam	—	—	—	—	—	—	100	0	—	—	—	—
Imipenem	—	—	—	—	—	—	100	0	—	—	—	—
Tetracycline	—	—	—	—		—	—	—	0	100	—	—
Vancomycin	—	—	—	—	—	—	—	—	100	0	100	0
Ceftriaxone	—	—	—	—	—	—	—	—	—	—	100	0

TABLE V: MULTI-DRUG RESISTANCE PROFILE OF E. COLIUROPATHOGENS ISOLATED IN THIS STUDY

Resistance Patterns of E. coli	No. of isolates	No. of antibiotics
1. AMP	2	1
2. NA	2	
3. SXT	1	
4. AMP, NA	1	2
5. AMP, SXT	1	
7. FM, NA, SXT	1	3
8. AMP, NA, SXT	2	
6. AMC, AMP, ATM, CFX	1	4
9. AMP, NA, SXT, OFX	2	
10. AMP, CN, SXT, OFX	1	
11. AMP, CXM, NA,SXT, CFM, OFX, CFX	1	7
12. AMP, ATM, CN, NA,SXT, CFM, OFX, CFX	2	8
13. AMP, ATM, CN, CXM, NA, CFM, OFX, CFX	1	
14. AMP, ATM, CN, CXM, NA,SXT, OFX, CFX	1	
15. AMP, ATM, CXM, NA,SXT, CFM, OFX, CFX	1	
16. AMC, AMP, ATM, CXM, NA, SXT, CFM, TZP, CFX	1	9
17. AMP, ATM, CN, CXM, NA,SXT, CFM, OFX, CFX	1	
18. AMP, ATM, CN, CXM, F, NA, SXT, CFM, OFX, CFX	1	10
19. AMC, AMP, ATM, CN, CXM, NA,SXT, CFM, OFX, TZP, CFX	1	11
20. AMC, AMP, ATM, CXM, F, NA,SXT, CFM, OFX, TZP, CFX	1	
21. AMC, AMP, ATM, CN, CXM, F, NA,CFM, OFX, TZP, CFX	1	

included in this study. Duplicate sample from same patient were excluded.

Isolation and identification of bacterial isolates of UTI

The samples were inoculated on Cystine-lactose-electrolyte-deficient (CLED) media and Blood agar media and the plates were incubated overnight at 37°C. Samples that demonstrated pure growth of a bacterial isolate in a count of $\geq 10^5$ CFU/ml of urine following overnight incubation were considered as indication of significant bacteriuria[14]. The isolates were initially characterized on the basis of their gram staining reaction, morphology, growth and biochemical characteristics i.e. fermentation of lactose, ability to produce indole, reaction on triple sugar iron (TSI) medium, observation of hemolysis on blood agar, citrate utilization and motility of organism.

Antimicrobial susceptibility testing

Antibiotic susceptibility test was carried out following the method of Kirby-Bauer disk diffusion method[15]. Mueller-Hinton agar was used as the growth medium in all the antibiotic disk (Oxoid, UK) susceptibility tests. The sizes of the zones of inhibition of growth were measured and interpreted by referring to guidelines of Clinical and Laboratory Standards Institute (CLSI, 2007) and the isolates were reported as being susceptible (S) or resistant (R) to the agents that were tested. The antibiotic disks used in present study included: Amoxicillin/ Clavulanate (AMC, 20/10μg), Ampicillin (AMP, 10μg), Amikacin (AK, 30μg), Aztreonam (ATM, 30μg), Gentamicin (CN, 10μg), Ceftriaxone (CRO, 30μg), Cefuroxime (CXM, 30μg), Nitrofurantoin (F, 300μg), Fosfomycin (FM 200μg), Nalidixic Acid, (NA, 30μg), Cotrimoxazole (SXT, 1.25/23.75μg), Cefexime (CFM 5μg), Ofloxacin (OFX, 5μg), Ceftazidime (OFX, 30μg), Piperacillin/Tazobactam (TZP, 100/10μg), Cefotaxime (CFX, 30μg), Imipenem (IMP, 10μg), Tetracycline (TE, 30μg), Vancomycin (VA, 30μg).

RESULTS

Urine culture results

A total of 119 urine samples were collected over a time period of six months and investigated for bacteriological profiling followed by sensitivity to various commonly used antibiotics. The positivity of samples appeared to be 41.18% (n=49) that included both bacterial and fungal growth, whereas 58.82% (n=70) of the samples yielded no growth, thus were sterile. Women accounted for 31.09 % (n=37) of all positive patients (table 1). Demographic data with respect to age and gender of all patients is listed in table II. We observed the association of increased age with UTIs since higher incidences of bacteriuria, were seen in patients of older age i-e 60 years and above. However no incident of UTI was found among male infants. Among the 49 patients of bacteriuria, E. coli was the most frequent and predominant isolate accounting 57.14% (n=28), whilst the remainder.42.86 % (n=21) isolates represented all other bacterial and fungal flora such as P.mirabilis, P. aureginosa, Enterobacter species, Enterococcus species and Candida species (Table III). We also found mixed pathogens from 12. 24% (n=06) of total patients.

Antibiotic susceptibility patterns of UTI isolates

In vitro activity of various antibiotics tested against all bacterial isolates of UTI is listed in (Table IV), and the results are reported as susceptible (S) and resistant (R) isolates. In the present study, a change in trends of susceptibility of isolates to Co-trimoxazole has been observed. β-lactam antibiotics are commonly used in the treatment of UTIs. E. coli isolates showed higher level of sensitivity against Amoxicillin plus clavulanate (82.14%) as compared to that of Ampicillin. Only 17.86% of the isolates were found to be resistant to the antibiotic. Similarly, K. pneumoniae isolates were also sensitive to the former while showed resistance against the later antibiotic. Nitrofurantoin showed a good activity against E. coli isolates of UTIs as only 10.72% of the isolates exhibited resistance. Fosfomycin remained effective against the isolates of UTIs. Our results demonstrated that all isolates of E. coli (the leading uropathogen) were sensitive to Amikacin. The susceptibility patterns of Gram-positive isolates of UTIs showed that the Enterococcus species were highly susceptible (100%) to Gentamicin. They were also sensitive (75%) to Ofloxacin while the Streptococcus species were (100%) resistant to the Ofloxacin. However, isolates of the Streptococcus species showed susceptibility to Vancomycin, and Ceftriaxone. Similarly, the susceptibility rate of Enterococcus species to Vancomycin was 100% suggesting that the VRE challenge does not prevail in this region.

Patterns of multi-drug resistance among E. coli uropathogens

In the present study, we observed 21 different trends of resistance among the E. coli isolates (Table 5). E. coli demonstrated highest resistant (78.57%) to Ampicillin and least resistance was observed against Fosfomycin (3.57%) and Nitrofurantoin (10.72%). A change in pattern of resistant to Co-trimoxazole was evident, since 64% of the E. coli isolates resisted the antibiotic. Among all E. coli isolates, 28.57% (n=8) were resistant to all cephalosporin used in this study suggesting the presence of ESBL producers, however, no further confirmatory phenotypic tests were conducted for presence of ESBL, which should always be taken in account while devising therapeutic strategies for uropathogens. Only 7.14% (n=2) E. coli isolates were sensitive to all antibiotics tested in this study, and 17.86% (n=5) were sensitive to only one of three different types of antibiotics. The rest of 75% (n=21) isolates showed resistance against multiple antibiotics ranging from 2 to 11 different antibiotics (Table V) and thus were reported as multi-drug resistant E. coli.

DISCUSSION

UTIs impose a huge burden on healthcare systems due to high prevalence of infection in both community and nosocomial settings. UTIs are caused by variety of pathogens including E. coli, K. pneumonia and P. aureginosa. Continuous surveillance of antibiotic susceptibility patterns of uropathogens at local level is crucial in dealing with emerging problems of antibiotic resistance and provides assistance in managing effective initial therapy. In the present study, E. coli was predominant amongst all isolates, and the second commonest causative agent was P. aureginosa. These findings are in agreement with the published data from other regions indicating that E. coli, a Gram-negative bacilli, remained most frequent isolate among UTI patients[16-18], The prevalence of uropathogenic E. coli was found 57% of total uropathogens isolated in the present study; however a recent study carried out in other region of Pakistan reported 73% prevalence of E. coli [11]. Antibiotic resistance represents a global challenge to public health. The intensive use and misuse of antibiotics have been responsible for emergence of antibiotic resistance together with selection and spread of the antibiotic resistant strains of bacterial pathogen, including uropathogens[12]. Knowledge of the local resistance and surveillance studies to monitor emerging trend of resistance through susceptibility testing of uropathogens, particularly E.coli is recommended[19]. This study provides the current scenario of antibiotic resistance pattern in Hyderabad, Pakistan.

Furthermore, understanding the current patterns of antibiotic susceptibility of uropathogens is of great importance in formulating effective strategies to overcome the therapeutic difficulties caused by multi-resistant bacteria and in selection of appropriate empirical therapy for UTI. The findings of present study demonstrated that E. coli, leading isolate of UTIs, exhibited a low degree of susceptibility (35.7%) to Cotrimoxazole which indicates that it should no more be chosen for treating UTIs. Although this antibiotic has previously been used as drug of choice for empirical treatment of UTIs, resistance against Co-trimoxazole has been documented recently acrossvarious other regions [20-22]. The current study also indicates that there is an increase in the resistance for antibiotics such as Cefuraxime, Ceftazidime and Cefotaxime, which suggest that many of the isolates could be ESBL producers. We tested susceptibility of Imipenem against P. aureginosa only and found that the all isolates of P. aureginosa were sensitive to the antibiotic. Carbapenemsare considered as the final therapeutic option for any infection to prevent the occurrence of carbapenems resistance. Hence they should notbe given for empirical treatment. The pattern of Nitrofurantoin susceptibility appeared to be satisfactory in our study as it showed very good activity against uropathogens of the region. Nitrofurantoin were not tested against P. aureginosa because they possess intrinsic resistance to the antibiotic, thus, testing sensitivity of Pseudomonas against Nitrofurantoin is of no use. It is shown in our study that Nitrofurantoin has strong activity against E. coli isolates (89.28%). Hence Nitrofurantoin can be opted as the drug of choice for empirical therapyin UTI. In contrast to a recent study by Bano et al., carried out from other region of Pakistan[10], our results demonstrated that all isolates of E.coli (the leading uropathogen) were sensitive to Amikacin. Our results are supported by a previous study wherein sensitivity level of E. coli to Amikacin remained 100%[23] Amikacin also demonstrated highest efficacy against all other uropathogens that were isolated in this study. Previous studies from other regions have also reported efficacy of Amikacin against uropathogens.[13,24] While noticing the susceptibility patterns of Gram-positive isolates of UTIs, it was observed that the Enterococcus species were highly susceptible (100%) to Gentamicin, which is in contrast to a recent study.[25]

Owing to high potency Amikacin against all gram negative uropathogens, it should be prescribed as the drug of choice in empirical treatment of UTI. However, in view of the increasing trends of developing antibiotic resistance by bacteria, the antibiotic therapy should only be prescribed based on the antimicrobial sensitivity reports of the isolates. This would not only help in the rational use of antibiotics but also would result in curbing the propagation of antimicrobial resistant strains in the community as well as in the hospital environment. Furthermore, it should be the responsibility of health care workers to play their role in prevention of the spread of antimicrobial resistance. Strict measures should be undertaken to reduce the problem of antimicrobial resistance such as promotion of the careful use of antibiotics and taking hygienic measures. Physicians should also rationally prescribe the antibiotics as per the results of the culture and sensitivity tests. In conclusion, the findings of the present study provide invaluable information on the current trends of antibiotic resistance, which will definitely lead to the rational selection of antibiotics for empiric treatment of UTIs.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

SAA: Concept and design, drafting the manuscript & final approval of the version to be published

HWA: drafting the manuscript, final approval of the version to be published

OMA & MSA: acquisition, analysis and interpretation of data, final approval of the version to be published

FW: critical revision, final approval of the version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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