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Antibiotic Resistance in Urinary Tract Infection in a Tertiary Care Hospital in Bangladesh-A Follow-up Study

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Abstract

Introduction: *Bacterial resistance to antibiotics is one of the most challenging global health threats. Urinary tract infections (UTIs) are a common infection. Regional surveillance programs are necessary to update knowledge on antimicrobial resistance pattern where empirical antibiotic treatment is the mainstay. The aim of this follow up study is to see the changing trends in bacteriology and antibiotic resistance pattern among urological pathogens in comparison to similar study 5 years back.* ***Materials and Methods:*** *We performed a prospective study in Comilla Medical College Hospital, Bangladesh during the period of July 2015- June 2016. Midstream clean-catch urine samples were collected from 658 suspected UTI patients with age more than 12 years and inoculated in MacConkey& Blood agar media for semi quantitative urine culture and sensitivity test. Antibiotic susceptibility pattern was done by Kirby-Bauer disc diffusion method following clinical laboratory science (CLS) program.* ***Results:*** *Culture positive were in 198 samples among 658 inoculated samples. E. coli was isolated from 171(86%) samples which was the most predominant bacteria followed by Klebsiella and Enterococcus. UTI with E. coli was significantly increased in the year 2016 in comparison to 2011. Meropenem, imipenem, amikacin, tazobactum, gentamycin nitrofurantoin, and mecillinum found resistance against 0% to 12% of the urological pathogens. Bacteria offered high degree of resistance against commonly used antibiotics - amoxycillin, amoxiclav, cephradine and cefixime ranging 60% to 86%. Comparative study of 2016 vs 2011 shows significant increased resistance for ceftriaxone, amoxiclav and reduced resistance for nalidexic acid, mecillinum and cefuroxime.* ***Conclusion:*** *E. coli infection is significantly increaseing in follow up study from 2011 to 2016 with no steady increase in resistance to all antibiotics. Imipenem, meropenem, tazobactum, amikacin and nitrofurantoin still remain more sensitive while comparative study of 2016 vs 2011 shows significant increased resistance for ceftriaxone, and amoxiclave and reduced resistance for nalidexic acid, mecillinum, cefixime and cefuroxime.*

Keywords: *Urinary tract infection, Follow up comparative study, Changing trends, Culture, Sensitivity, Resistance.*

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Introduction

Bacterial infection resistance to antibiotics is one of the most challenging global health threats faced in modern medicine. It has been estimated that by 2050, 10 million lives per year will be at risk from antibiotic-resistant infections [1]. In September 2016, 193 countries agreed to prioritize reducing antimicrobial resistance at the United Nations General Assembly following a worldwide campaign by the UK Government[2]. Urinary tract infection (UTI) is a common bacterial infection globally and is a major public health problem in terms of morbidity and treatment cost which affecting 150 million people each year worldwide[3,4]. It also represent the most common antibiotic-resistant infections in primary care setting[5,6]. It is a leading cause of repeated physician consultations and antibiotic resistance and problem for clinicians in selecting appropriate antibiotic [7, 8].

Diagnosis and treatment of UTI are mostly empirical to initiate empirical treatment with appropriate antibiotic is necessary to have current knowledge regarding causative organisms and their antibiotic resistance pattern [9]. But alarming fact is that a large number of patient do not respond to conventional antimicrobial agents [10].

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Antibiotic use affects bowel flora acquiring drug resistance and may increase risk of urinary autoinoculation with antibiotic-resistant microbes. Antimicrobial resistance is a well known important emerging clinical and public health problem. There are various reports available in last two decades about changing pattern of pathogen and their sensitivity pattern to routinely used antibiotics which makes the situation miserable [10]. An increasing antibiotic resistance among urological pathogens to commonly prescribed drugs has become a global reality. Resistance occurs in intestinal bacteria due to antibiotic therapy for treating infections outside the urinary tract [11]. The irrational use of antibiotics has an influence in the spread of antimicrobial resistance among bacteria [12, 13]. Controlling antimicrobial resistance is a major issue confronting organized health care today. Therefore this is warranted to know information about rapidly changing sensitivity pattern of micro-organisms towards antibiotics in UTI. For updated proper therapeutic interventions, periodic evaluation and regional surveillance programs is necessary with antibiotic resistance data and analysis about antimicrobial resistance to uropathogens.

The present study was undertaken to find the current urological pathogens and their antibiotic resistance pattern in a tertiary hospital in Bangladesh to compare with previous pattern of study in 2011 [14]. It will be helpful for awareness and antibiotic use in UTI in this tertiary level hospital and country level.

Materials and Methods

It was a prospective study conducted during July 2015 to June 2016 on patients attending the outpatient and inpatient departments of in department of medicine, Comilla Medical College to find out the causative agents of UTI and their antibiotic resistance pattern. All the patients included in this study were above 12 years of age, presented with the suspected UTI (dysuria, frequency, fever and pain in lower abdomen). In this study, patients presented with active menstruation, PID, tubo-ovarian disease, appendicitis, colitis, epididymitis and orchitis diagnosed either clinically or by investigations were excluded from this study. Patients on antibiotic was advised to stop antibiotic for 48 hours and were included in this study.

According to protocol, freshly voided midstream clean-catch 10-20 ml urine samples were collected from 658 patients in a sterile screw capped universal container. The specimen was labeled and transported to the microbiology laboratory of Comilla Medical College Hospital for culture within half an hour of collection. A modified semi-quantitative technique using a standard calibrated bacteriological loop of urine was performed to transfer 0.001 ml of sample on blood agar and MacConkey agar media. After allowing the urine to be absorbed into the agar, the plates were then inverted and incubated aerobically at 37°C for 24 hours. The plates were then examined macroscopically for bacterial growth. The colony count was done using semi quantitative method. Number of colonies obtained was multiplied by 1000 to obtain the colony forming units (CFU)/ml[15]. A significant growth is considered if the number of colony is ≥ 105 CFU/ml. Colonial appearance and morphological characters of isolated bacteria was noted and gram staining was done for identification of the isolated organisms. The characteristic bacteria on the culture media were aseptically isolated.

Antimicrobial sensitivity tests were carried out by disc diffusion technique using Muller Hinton Agar. Interpretation of results was expressed in sensitive and resistant depending upon the size of the zone of inhibition. The antibiotics used for susceptibility testing in our study were amoxycillin, amoxyclav, amikacin, cefixime, ceftazidime cefuroxime, cephradineciprofloxacin cotrimoxazole, cefotaxime, ceftriaxone, cephalexin, gentamycin, imipenem, meropenem, mecillinum, nalidexic acid, nitrofurantoin, and tazobactum. All the authors vouch for the completeness and accuracy of data and analyses presented.

Results

Total 658 patients urine samples were collected in 2016 and their baseline characteristics are shown below.

The table I and II, the bacterial growth was positive in 198 patients out of total 658 patients included in the study. Most of the patients were from rural community, married, sexually active, middle class, had fever, abdominal pain, dysuria and comorbid condition as diabetes mellitus, hypertension. 50% patients took antibiotics before included in study.

Table-I: Base line characteristics in patients without growth in urine culture.

	Frequency (n=460)	Percentage
Residence		
• Urban	136	30
• Rural	334	70
Education		
• Educated	303	66
• Not educated	157	34
Marital status		73
• Married	338	27
Unmarried	122	
Sexual activity		62
• Active	285	38
• Not active	175	
Economical status		
• Lower class	49	11
• Middle class	393	85
• Higher class	18	4

Dysuria		
• Present	321	68
• Absent	139	32
Urgency		
• Present	359	78
• Absent	101	22
Fever		
• Present	336	73
• Absent	124	27
Abdominal pain		
• Present	354	77
• Absent	106	23
Treated with antibiotics	221	48
• Yes	239	52
• No		
Co-morbid condition		
• DM	55	12
• HTN	15	3
• ISD	8	2
• Others	34	7

Table-II: Base line characteristics in patients with growth in urine culture.

	Frequency (n=198)	Percentage
Residence		
• Urban	66	33
• Rural	132	67
Education		
• Educated	134	68
• Not educated	64	32
Marital status		
• Married	163	82
• Unmarried	35	18
Sexual activity		
• Active	143	72
• Not active	55	28
Economical status		
• Lower class	10	5
• Middle class	180	91
• Higher class	8	4
Dysuria		
• Present	152	77
• Absent	46	23
Urgency		
• Present	175	88
• Absent	23	12
Fever		
• Present	133	67
• Absent	65	23
Abdominal pain		
• Present	150	76
• Absent	48	24
Treated with antibiotics		
• Yes	94	48
• No	104	52
Co-morbid condition	68	34
• DM	45	23
• HTN	27	14
• IHD	4	2

Among 198 culture positive samples, E. coli was ranked highest 171(86%), simultaneously growth of Klebsiella pneumonia and Enterococcus was found in 17(9.6%) and 10(5%) samples. It was also observed from table III that the maximum numbers of isolates were distributed among the females 123 (62%).

Table-III: Frequency of Isolation of organism in relation to sex of patient and their overall percentage.

SL No.	Bacterial Isolates	Frequency		
		Number (%)	Male (%)	Female (%)
01	E. coli	171 (86)	69 (35)	102 (51)
02	Klebsiella	17 (9.6)	4 (2)	13 (7)
03	Enterococcus	10 (5)	2 (1)	8(4)
	Total	**198**	**75 (38)**	**123 (62)**

UTI with E. coli was found statistically significant increase in the year 2016 with p values <0.01(table - IV).

Table- IV: Comparative study between the common isolated urological pathogenic bacteria in the year 2016 and 2011.

Name of organism	No (%) 2016	No (%) 2011	Chi-Square Value (x^2)	P. value
E. coli	171 (86)	98(75)	3.17	<0.01
Klebsiella	17 (9.6)	14(10.4)	.29	>0.1
Enterococcus	10 (5)	8(6)	.38	>0.1

Pseudomona	0	2(1.5)	.16	>0.1
Proteus	0	2 (1.5)	.16	>0.1
Staph. aureus	0	4 (3)	.47	>0.1
E. coli & Klebsiella	0	3 (2.29)	.35	>0.1

Study shows, meropenem, imipenem, amikacin, tazobactum, gentamycin, and mecillinum, were found to be most effective antibiotic against most of the urological pathogens. In vitro sensitivity of the isolates to these antibiotics was shown to be varied from 88% to100%. Table V also shows high degree of resistance against commonly used antibiotics- amoxycillin, amoxiclav, cephradine and cefixime. In vitro resistance of the isolates to these antibiotics was varied from 60% to 86%.

Table-V: In vitro antibiotics resistance pattern of the bacteria (n=198).

SL No.	Name of antibiotics	Total No Sensitive	Percentage
01	Meropenem	0	0
02	Imipenem	1	0.5
03	Amikacin	2	1
04	Tazobactum	2	1
05	Gentamycin	20	10
06	Nitrofurantoin	23	12
07	Mecillium	24	12
08	Colistin	31	16
09	Ceftazidime	84	47
10		93	47
11	Ciprofloxacin	94	48
12	Ceftriaxone	96	55
13	Nalidexic acid	190	55
14	Cephlalexine	112	57
15	Cefuroxime	114	58
16	Cefotaxime	114	58
17	Cefixime	118	60
18	Cephradine	130	66
19	Amoxiclav	149	76
20	Amoxicillin	170	86

There was statistically significant increase in resistance pattern in year 2016 in comparison to 2011 was detected for ceftriaxone, and amoxiclav with p value <0.001, which is shown in table VI. On the other hand significant reduced resistance was found for nalidexic acid, mecillinum, cefixime and cefuroxime. No statistically significant change in sensitivity pattern was shown for other antibiotics.

Table-VI: Comparative study between 2016 and 2011 of trend of antibiotic registance pattern of uropathogenic bacteria.

Antibiotic	2016 (n=198)	2011 (n=131)	Chi-Square Value (x^2)	P value
Carbapenem				
• Imipenem	1(0.5%)	0(0%)	0.04	0.83^{ns}
• Meropenem	0 (00.0%)	3(2.0%)	2.39	0.12^{ns}
Cephalosporins				
• 1st Generation				
○ Cephradine	130(66.0%)	83(63.0%)	0.18	0.67^{ns}
○ Cephlalexine	112(57.0%)	85(64.9%)	2.27	0.13^{ns}
• 2nd Generation				
○ Cefotaxime	114(58.0%)	80(61.0%)	0.38	0.52^{ns}
○ Ceftazidime	84(42.0%)	-	72.41	$<0.001^{s}$
○ Cefuroxime	84(42.0%)	82(63.0%)	12.83	$<0.001^{s}$
• 3rd generation				
○ Ceftriaxone	102(51.5%)	31(24.0%)	25.39	$<0.001^{s}$
○ Cefixime	80(40.0%)	91(70.0%)	26.37	$<0.001^{s}$
Quinolones				
• Nalidexic acid	89(45.0%)	98(75.0%)	28.65	$<0.001^{s}$
• Ciprofloxacin	104(52.0%)	86(65.5%)	5.6	0.02^{s}
Aminoglycosides				
• Amikacin	2(1.0%)	3(2.3%)	0.22	0.63^{ns}
• Gentamycin	20(10.0%)	18(14.0%)	1.02	0.31^{ns}
Penicillin				
• Amoxiclav	149(76.0%)	31(24.0%)	84.67	$<0.001^{s}$
• Amoxicillin	170	114(87.0%)	0.09	0.76^{ns}
• Mecillinum	24(12.0%)	39(30.0%)	15.86	$<0.001^{s}$
Colistin	31(16.0%)	17(13.0%)	0.45	0.50^{ns}
Nitrofurantoin	23(12.0%)	12(9.0%)	0.50	0.47^{ns}
Tazobactum	2(1.0%)	-	0.18	0.66^{ns}
Cotrimoxazole	93(47%)	81(62.0%)	6.98	0.008^{s}

Discussion

This study demonstrates the distribution and antibiotic resistance pattern of bacteria isolated from patients with suspected UTI from a tertiary care center. In our center only 31% had culture positive in patients with UTI

symptoms which was nearer to our previous study in 2011 where growth was 24%[14]. Study by B H N Yasmeen et al[16] on 2014 in Bangladesh shows 21% urine sample were positive for pathogenic organisms. Higher prevalence of UTI in females (73.57%) than in males (35.14%) which is similar to other reports[17-19]. It was due to anatomical and physical factors[20-22].

E. coli predominance isolated organism (86%) which was significantly higher (p value was <0.01) than our previous studies in 2011 where E. coli was 75%. Possible cause of this predominance of intestinal bacteria was due to antibiotic therapy for treating infections outside the urinary tract which contaminate the urinary tract[6].

Urological pathogens shows very low degree of resistance (0-1%) against meropenem, imipenem, tazobactum and amikacin which was similar to our previous study on 2011[14]. Bacteria shows higher degree of resistance against most of the remaining antibiotics used for sensitivity due to irrational consumption of most of the antibiotics during the past decade in our region[13,23,24]. Resistance to amikacin is only 2% and it is cheap, so it is wise to use it as parental empirical antibiotics in UTI. On the other hand nitrofurantoin offers resistance in 12% cases so it is a good oral antibiotic in UTI. This drug exhibited low resistance rate in the major part of the world (0–5.4%), despite of its use for many years which was because of localized action of this drug only on the urinary tract[25]. Resistance was significantly increased in resistance pattern in year 2016 for ceftriaxone, and amoxiclav possibly because random use of these antibiotics with inadequate dose and duration which is a public health concern in Bangladesh[26]. According to guideline by Infectious Diseases Society of America (IDSA) in the year 2011, an antibiotic is no longer recommended for empirical treatment of acute UTI if there is >20% resistance prevalence to that particular antibiotic[27]. The antibiotics shows resistance more than 20% are according to this guideline of IDSA, most of the antibiotics used in our study should not be used for empirical treatment of acute UTI and our standard treatment guidelines for UTI is not sufficient which requires a large scale study.

There is urgent need of constant monitoring with culture and sensitivity pattern of specific pathogens in different health care center in our country. Community awareness program should be undertaken for adherence to treatment protocol considering bacterial resistance and emerging multidrug resistant strains. It is necessary to conduct a regional research on the culture and sensitivity patterns of the bacteria. All the authors contributed equally in this study.

Conclusion

E. coli infection is significantly increasing in follow up study from 2011 to 2016 with no steady increase in resistance to all antibiotics. Imipenem, meropenem, tazobactum, amikacin and nitrofurantoin still remain more sensitive while comparative study of 2016 vs 2011 shows significant increased resistance for ceftriaxone and amoxiclave and reduced resistance for nalidexic acid, mecillinum, cefixime and cefuroxime.

Conflict of Interests: None.

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