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Current Antibiotic Resistance Pattern of Prevalent Uropathogens in Urinary Tract Infection of Diabetic Patients in Comparison with non-Diabetics

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Abstract **Original Research Article**

Introduction: Urinary tract infections (UTIs) are a common infectious disease worldwide. Bacterial resistance to antibiotics is one of the most challenging global health problems. Regional surveillance programs are necessary to update knowledge on antimicrobial resistance patterns for empirical antibiotic treatment of the patients. This study aimed to explore the bacteriology and antibiotic resistance pattern of urological pathogens in diabetic patients compared to that in non-diabetics. ***Materials and Methods:*** A prospective study during the period from June 2021 to November 2021 in Khulna City Medical College Hospital was carried out including 347 diabetic and non-diabetic patients. Midstream clean-catch urine samples were collected from suspected UTI patients of age more than 14 years and inoculated in Mac Conkey & Blood agar media for semi-quantitative urine culture and sensitivity test. Antibiotic susceptibility test was done by Kirby-Bauer disc diffusion method following clinical laboratory science (CLS) program. ***Results:*** Among the 347 inoculated samples, Culture positive were in 286 cases. Gram-negative E. coli was isolated from 119 (overall 41.6%, 51% in diabetics and 36.5% in non-diabetic patients) samples which were the most predominant bacteria, followed by Enterococcus, Pseudomonas and Klebsiella. UTI with E. coli was significantly at a higher rate in diabetic patients and Exhibits 100% resistance to Ceftriaxone, Nalidixic acid, Cefuroxime and Cefixime. Bacteria offered a high degree of resistance against commonly used antibiotics-Amoxycillin, Ciprofloxacin, Amikacin, Gentamycin, Levofloxacin, Nalidixic acid and Nitrofurantoin ranging from 7% to 93%. ***Conclusion:*** E. coli infection is significantly predominant in UTI cases in this study and exhibits a higher rate of resistance to all antibiotics in diabetic patients than that in non-diabetics. None of the antibiotics is 100% sensitive in diabetic patients. Imipenem, meropenem and Piperacillin remain moderately sensitive while Enterococcus is sensitive to Vancomycin. In non-diabetic patients, only Meropenem, Imipenem, Piperacillin and Amikacin are 100% sensitive.

Keywords: Urinary tract infection, Comparison, Culture, Sensitivity, Resistance.

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INTRODUCTION

Urinary tract infection (UTI) is one of the most common types of infectious disease throughout the world [1]. It is a leading cause of repeated physician consultations and multidrug resistance is a problem for clinicians to select appropriate antibiotics for treatments of the patients [2, 3]. Antibiotic resistance is a major health problem for both hospital and community-acquired infections [4]. UTI is a common disease in patients with diabetes mellitus and it is usually asymptomatic at the initial stage, later it becomes symptomatic [5, 6]. The prevalence of diabetes Mellitus is increasing throughout the world, especially in the developing countries [7]. The relationship between urinary tract infection with diabetes mellitus is not definitely clear [8]. Poor glycemic control and asymptomatic infections lead to serious complications [9]. Despite the availability of international guidelines, it was observed that improper use of antibiotics is a

global health problem especially in low-income countries because of the high prevalence, availability of antibiotics and lack of knowledge regarding preventive measures [10]. Various pathogens have been isolated from urine samples of diabetic patients having urinary tract infections with varying frequencies [11]. Monitoring of pathogen resistance profile is helpful to guide proper antibiotic therapy before culture and sensitivity reports are available from the laboratory [12]. Bacterial resistance to antibiotics is one of the most challenging global health problems encountered in modern medical practice and it has been estimated that by 2050, 10 million lives per year will be at risk from antibiotic-resistant infections [13]. In September 2016, 193 countries agreed to emphasize reducing antimicrobial resistance at the United Nations General Assembly following a worldwide campaign by the UK Government [14]. Urinary tract infection is a major public health problem in terms of morbidity and treatment cost which affects 150 million people each year worldwide [15, 16]. It also represents the most common antibiotic-resistant infection in primary health care centres [17, 18]. Updated information on the spectrum of uropathogens with their antibiotic resistance pattern from regional research is essential for better patient management [19]. Altered composition of urine in a diabetic patient can change the bactericidal activity and influence the ability to inhibit or support the growth of microorganisms [20]. Some studies have reported that diabetic patients have an immunologic impairment and they are at increased risk for urinary tract infection [21]. Higher rates of multidrug resistance in UTIs n diabetic patients were found with a varying range between 59.8% and 71.7% [22]. Bladder emptying time and higher glucose concentration in the urine influence the growth of pathogenic microorganisms, and in addition to these, expression of different virulence factors is important for the development of UTI [23], so there may be a difference between resistance patterns in UTIs of diabetic patients and that of non-diabetics. We have been encouraged to explore the antibiotic resistance pattern of isolated organisms from the urine of both symptomatic and asymptomatic diabetic patients and that of non-diabetic patients for comparison.

MATERIALS AND METHODS

A total of 347 patients attending the Khulna City Medical College Hospital during the period from June 2021 to November 2021 were included in this prospective cross-sectional study. This study aimed to isolate the causative agents from the urine samples of diabetic and non-diabetic patients having UTIs for the comparison of their antibiotic resistance patterns. The participants were selected from the patients presenting with the suspected UTI (dysuria, increased frequency, fever and pain in the lower abdomen) of age above 14 years. The patients presented with active menstruation, PID, tubal-ovarian disease, appendicitis, colitis, epididymitis and orchitis diagnosed either clinically or by investigations were excluded from this study. The patients on antibiotic therapy were advised to stop antibiotics for 48 hours and were included in this study. After selection according to the inclusion and exclusion criteria, informed consent was obtained from the participant and then freshly voided midstream clean-catch 10-20 ml urine samples were collected from 347 patients in a sterile screw-capped universal container. The specimen was labelled and transported to the microbiology laboratory of Khulna City 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 carried out to transfer 0.001 ml of sample on blood agar and Mac Conkey 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. After incubation of 347 samples, significant growth of uropathogens was observed in 286 cases. The plates were then examined macroscopically for bacterial growth and colony count was done using the semi-quantitative method. The number of colonies obtained was multiplied by 1000 to obtain the colony-forming units (CFU)/ml [19]. A significant growth was considered if the number of colonies was ≥ 10[5] CFU/ml [24]. Colonial appearance and morphological characteristics of isolated bacteria were noted and gram staining with biochemical tests was done for the identity 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 Muiller Hinton Agar. Interpretation of results was expressed insensitive and resistance depending upon the size of the zone of inhibition. The antibiotics used for susceptibility testing in our study were Amoxicillin, Amikacin, Cefixime, Cefuroxime, Ciprofloxacin, Levofloxacin, Piperacillin, Ceftriaxone, Gentamycin, Imipenem, Meropenem, Vancomycin, Nalidixic acid and Nitrofurantoin. All observations and results were recorded and data were summarized to present in tables and charts. The data obtained from observations were analyzed by using the computer software 'Statistical package for the social sciences (SPSS Inc; Chicago, IL, USA)'.

RESULTS

A total of 347 urine samples were collected from the participants and processed in the laboratory to isolate the organisms for sensitivity tests. Among the samples, 286(82%) cases yielded culture-positive growth and the study aimed to compare the resistance pattern of uropathogens in diabetics to that in non-diabetics, for this purpose sensitivity tests to antibiotics were done with these culture-positive cases. Among these 286 samples, 170 cases were non-diabetic and 116 cases were diabetic patients. The majority of the patients were in the age group 54 to 73 years (121/42.3%), followed by the age group 34 to 53 years

(71/24.8%) and the age group 14 to 33 years (48/16.7%), The least number of patients were in the group of above 74 years (46/16%), (Table-1). A high prevalence of culture-positive infections was observed in male non-diabetic patients in the age group of 54 to 73 years (75%). Among the 286 culture-positive samples, growth of E. Coli was found in the highest number of cases 119(41.6%), followed by enterococcus 77(26.9%), Pseudomonas 43(15%), and Klebsiella 38(13.3%) cases (Table-2). Candida was found in only 1 urine sample. E. coli growth was predominant in diabetic patients 60(52%), and on the other hand, 59(34.7%) non-diabetic cases yielded E. Coli growth. Among 116 diabetic patients, 59 showed growth of E. Coli (51%), 28 cases were infected by Enterococcus (24%), pseudomonas was in 17(15%) and in 12(10%) cases Klebsiella was found (Table-3). Predominant E. Coli showed 100% resistance against Ceftriaxone, Cefuroxime, and Cefixime. A higher rate of resistance showed against Ciprofloxacin (93%), Levofloxacin (89%), Amoxicillin (79%), Gentamycin (55%), and Amikacin (55%). Low resistance to Meropenem (7%), Imipenem (7%), and Piperacillin (17%). Enterococcus showed 100% resistance against Ceftriaxone, Cefuroxime, Gentamycin, Cefixime, Nalidixic acid, Ciprofloxacin, Levofloxacin and Meropenem. High resistance was observed against Amikacin (85%), Imipenem (78%), Amoxicillin (71%), Piperacillin (50%), Nitrofurantoin (42%), and low resistance to only Vancomycin. Among the urine samples from 170 non-diabetic patients, 62(36.5%) cases showed growth of E. Coli, 48(28.2%) showed Enterococcus, Pseudomonas and Klebsiella were found in 26(15.3%) cases each, Staphylococcus in 6(3.5%), and Proteus in 2(1.2%), (Table-4). E. Coli showed high resistance against Nalidixic acid (90%), Ciprofloxacin (58%), Levofloxacin (61%), Ceftriaxone (61%), Cefixime (70%), Cefuroxime (58%), and Amoxicillin (41%). Low resistance was found against Gentamycin (9%), Amikacin (6%), Piperacillin (6%), Meropenem (9%), Imipenem (9%), and Nitrofurantoin (22%). Gram-positive Enterococcus showed high resistance against Nalidixic acid (96%), Cefixime (83%), Ciprofloxacin (79%), Cefuroxime (75%), Levofloxacin (70%), Ceftriaxone (70%), and low resistance against Imipenem (16%), Amoxicillin (29%), Vancomycin (37%), and Amikacin (42%). The predominant organism in urine samples of diabetic patients was E. Coli 59(51%), followed by Enterococcus 28(24%), Pseudomonas 17(14.7%), and Klebsiella 12(10.3%), (Table-5). Predominant E. Coli didn't show 100% sensitivity to any drug and high sensitivity to Meropenem (93%), Imipenem (93%), and Piperacillin (82%) were observed. Enterococcus was also found in 28 cases and it was not 100% susceptible to any drug. It showed high sensitivity to Vancomycin (78%). Pseudomonas showed the highest sensitivity to Piperacillin and Imipenem (50% each), and Klebsiella showed the highest sensitivity to Imipenem and Piperacillin (66% each). Gram-negative E. Coli was found in 62/ (36.5%) non-diabetic patients, followed by Enterococcus (48/28.2%), Pseudomonas and Klebsiella (26/15.3% each), Staphylococcus (6/3.5%) and Proteus (2/1.2%), (Table-6). Predominant E. Coli showed 100% susceptibility only to Piperacillin. High sensitivity to Imipenem (93%), Amikacin (93%), Meropenem (90%), and Gentamycin (90%). Gram-positive Enterococcus showed high sensitivity to Piperacillin (91%), and Imipenem (83%), Pseudomonas was 100% sensitive to Piperacillin, and Meropenem and Imipenem. Enterococcus was moderately sensitive to only Vancomycin.

Table-1: Distribution of the culture-positive patients according to different age groups and categories. (n=286)

Age	Diabetic male	Diabetic female	Non-diabetic male	Non-diabetic female	Total
14-33	0	2	2	44	48
34-53	6	21	5	39	71
54-73	12	39	27	43	121
74 and above	25	11	2	8	46
Total	43	73	36	134	286

Table-2: Microbial uropathogens isolated from the urine of different categories of patients. (n=286)

Microorganisms	Diabetic male	Diabetic female	Non-diabetic male	Non-diabetic female	Total (%)
E.Coli	17	43	16	43	119(41.6%)
Pseudomonas	12	5	0	26	43(15%)
Enterococcus	7	20	15	35	77(26.9%)
Klebsiella	6	5	5	22	38(13.28%)
Staphylcoccus	0	0	0	6	06(2.1%)
Proteus	0	0	0	2	02(0.6%)
Candida	1	0	0	0	01(0.3%)

Table-3: Resistance pattern of microorganisms isolated from the urine of diabetic patients to different antibiotics. (n=116)

Microorganisms	Amoxicillin (%)	CTX (%)	Cefuroxime (%)	Cefixime (%)	Gentamycin (%)	Nalidixic Acid (%)	Ciprofloxacin (%)	Levofloxacin (%)	Piperacillin (%)	Nitrofurantoin (%)	Meropenem (%)	Amikacin (%)	Imipenem (%)	Vancomycin (%)	No. of. Growth
E.Coli	79	100	100	100	55	100	93	89	17	34	7	55	7	-	59
Enterococcus	71	100	100	100	100	100	100	100	50	42	100	89	78	21	28
Pseudomonas	75	100	100	87	62	100	87	87	50	62	62	75	50	-	17
Klebsiella	100	100	100	66	50	66	100	83	33	83	50	83	33	-	12
Total Patient															116

Table-4: Resistance pattern of microorganisms isolated from the urine of non-diabetic patients to antibiotics. (n=170)

Microorganisms	Amoxicillin (%)	CTX (%)	Cefuroxime (%)	Cefixime (%)	Gentamycin (%)	Nalidixic Acid (%)	Ciprofloxacin (%)	Levofloxacin (%)	Piperacillin (%)	Nitrofurantoin (%)	Meropenem (%)	Amikacin (%)	Imipenem (%)	Vancomycin (%)	No. of. Growth
E. Coli	41	61	58	70	9	6	90	58	61	0	22	9	9	-	62
Enterococcus	29	70	75	83	42	42	96	79	70	8	49	20	16	37	48
Pseudomonas	53	69	76	92	7	15	76	53	58	0	38	0	0	-	26
Klebsiella	61	30	61	46	46	7	84	53	46	7	76	0	0	-	26
Staphylococcus	33	33	33	100	33	0	100	100	100	0	66	0	0	66	6
Proteus	0	0	0	0	0	0	100	0	0	0	100	0	0		2
Total Patient															170

Table-5: Drug sensitivity of microorganisms isolated from the urine of diabetic patients. (n=116)

Microorganisms	Amoxicillin (%)	CTX (%)	Cefuroxime (%)	Cefixime (%)	Gentamycin (%)	Nalidixic Acid (%)	Ciprofloxacin (%)	Levofloxacin (%)	Piperacillin (%)	Nitrofurantoin (%)	Meropenem (%)	Amikacin (%)	Imipenem (%)	Vancomycin (%)	No. of. Growth
E.Coli	20	0	0	0	44	0	6	10	82	65	93	44	93	-	59
Enterococcus	28	0	0	0	0	0	0	0	50	57	0	14	21	78	28
Pseudomonas	25	0	0	12.50	37	0	12	12	50	37	37	25	50	-	17
Klebsiella	0	0	16	33	50	33	0	12	66	12	50	16	66	-	12
Total Patients															116

Table-6: Drug sensitivity of microorganisms isolated from the urine of non-diabetic patients. (n=170)

Microorganisms	Amoxicillin (%)	CTX (%)	Cefuroxime (%)	Cefixime (%)	Gentamycin (%)	Nalidixic Acid (%)	Ciprofloxacin (%)	Levofloxacin (%)	Piperacillin (%)	Nitrofurantoin (%)	Meropenem (%)	Amikacin (%)	Imipenem (%)	Vancomycin (%)	No. of. Growth
E. Coli	58	45	41	29	90	93	9	41	38	100	77	90	93	-	62
Enterococcus	70	29	25	16	58	66	4	20	29	91	54	79	83	62	48
Pseudomonas	46	30	23	7	92	84	23	46	61	100	61	100	100	-	26
Klebsiella	38	69	38	93	53	92	15	46	53	92	23	100	100	-	26
Staphylococcus	66	66	66	0	66	100	0	0	0	100	33	100	100	-	6
Proteus	100	100	100	100	100	100	0	100	100	100	0	100	100	-	2
Total Patient															170

DISCUSSION

This study aimed to compare the antibiotic resistance pattern of uropathogens in diabetic patients to that in non-diabetics having UTIs. The urine samples from 347 participants were processed in the laboratory and 286 samples yielded growth of microorganisms and subsequent sensitivity tests were done. In our study among 286 culture-positive urine samples, 51% of diabetic patients had been infected by E. Coli, on the other hand, 36.5% of urine samples from non-diabetic patients yielded growth of E. Coli (Table-3, 4). Bacterial pathogens causing UTIs among diabetics exhibit a higher rate of multi-drug resistance than non-diabetics. This had also been revealed in different studies conducted in various regions like Sudan, United Arab Emirates, Ethiopia, Libya, Australia and Israel [6, 9, 13]. Findings of a study showed a multi-drug resistance of up to three antibiotic agents used and K. pneumonia resistance against ampicillin and co-trimoxazole to be at 20%, a rate which is comparable to the findings in a study done in Sudan 22.2% and resistance of P. mirabilis against ampicillin, nitrofurantoin and co-trimoxazole was found to be at 25%, while a similar study in Sudan found it to be at 33% in which four antibiotics were used [6]. While a study carried out in Ethiopia showed that over 60% of the isolated E. coli were resistant to ampicillin and most multi-drug resistant cases of E. coli had been reported among pregnant women in Ethiopia [10]. A study carried out in Australia concluded that routine use of antibiotics in primary care could be a cause of antibiotic resistance [14]. Some factors contribute to the development of antibiotic resistance in different geographical locations. The frequency of antibiotic use and adherence to prescribed doses are some of the factors that can vary from place to place. In a retrospective study done in South Africa between 2004 and 2009, P. mirabilis showed the highest resistance to ampicillin, cloxacillin, amoxicillin, tetracycline, and co-trimoxazole, erythromycin and chloramphenicol [15]. Proteus mirabilis is a common pathogen in nosocomial infections and its resistance has been on the rise in the recent past. Interestingly in our study, only two non-diabetic female patients have been found to develop infection by Proteus and they showed resistance to only Nalidixic acid and Nitrofurantoin but were 100% sensitive to all other antibiotics used in the laboratory. The frequency of antibiotic use in most countries is the reason for the increasing antibiotic resistance. Studies have also found that missing information on the resistance patterns in many developing nations contributes to the burden of hazards in the management of the patients due to antibiotic resistance. A study carried out in Indonesia concluded that there is an urgent need to have up to date findings on current antibiotic resistance patterns as this helps in interventions aimed at the management of antibiotic resistance [16]. The economic burden that comes along with antibiotic resistance was also explained. Most of the affordable antibiotics that are readily available to individuals are not effective anymore due to resistance [17]. It should be noted that even if 100% gentamycin sensitivity was recorded in non-diabetic cases, caution must be taken before they are used. Aminoglycosides should not be used in patients with chronic kidney diseases due to their nephrotoxic effect. Just like other aminoglycosides, gentamycin decreases the glomerular capillary filtration by destroying the proximal tubule cells [18]. A study in Bangladesh revealed that 80% of the cases had culture-positive patients with UTI symptoms which were much higher than a previous study in 2011 where growth was 24% cases [19]. The reason for the higher rate of culture positivity in UTI cases in this study is due to biased sampling and it should be considered that the samples were selected according to inclusion and exclusion criteria to demonstrate particularly the resistance pattern of isolated organisms. Furthermore, this study has some limitations as it is a hospital-based study that used a non-probability sampling method, selection bias may be introduced that hinders the generalization of the results to all diabetic and non-diabetic patients in the study area and also lack of resource tests evaluating HBA1c and immunologic function like cytokine production and neutrophil function could not be performed. The present study revealed that the predominant organism in diabetic patients is E. Coli and exhibits 100% resistance to Ceftriaxone, Cefixime, Cefuroxime and Nalidixic acid, on the other hand, in non-diabetic cases, prevalent uropathogen is also E. Coli but exhibits relatively lower resistance to Ceftriaxone (61%), Cefixime (70%), Cefuroxime (58%), and Nalidixic acid (90%). Enterococcus also exhibits 100% resistance to Ceftriaxone, Cefixime, Cefuroxime, Nalidixic acid, Ciprofloxacin, Levofloxacin, Gentamycin and Meropenem in diabetics, on the other hand, in non-diabetic patients, it showed relatively lower resistance to Ceftriaxone (70%), Cefixime (83%), Cefuroxime (75%), Nalidixic acid (96%), Ciprofloxacin (79%), Levofloxacin (70%), Gentamycin (42%) and Meropenem (20%). A study in southern Ethiopia on 240 diabetic patients showed that E. Coli was 100% resistant to Ampicillin, 64% resistant to Ceftriaxone, 58.8% to Gentamycin, and 100% sensitive to Nitrofurantoin [25]. In the present study, relatively lower resistance was observed to Imipenem, Meropenem and Piperacillin in both diabetic and non-diabetic patients, and considerable sensitivity was seen to Imipenem, Meropenem, Piperacillin, Nitrofurantoin and Vancomycin ranging from 12% to 93% in diabetic cases and from 23% to 100% in non-diabetic cases.

CONCLUSION AND RECOMMENDATIONS

E. Coli was the predominant microorganism isolated from the urine samples of both diabetic and non-diabetic patients. Bacteria offered a higher rate of resistance to commonly used antibiotics in diabetics than in non-diabetic patients. No antibiotic is 100%

sensitive in diabetic patients having UTI, on the other hand, only Meropenem, Imipenem, Piperacillin and Amikacin were 100% sensitive in non-diabetic patients.

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Conflict of interest

None declared

Ethical approval

The research protocol for this study and informed consent form were reviewed and approved by the ethical review committee of Khulna City Medical College. Written informed consent was then obtained from each participant and a unique identification number was assigned and all records were kept in a secured room to ensure confidentiality.

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