

CAUSATIVE AGENTS OF URINARY TRACT INFECTION IN DIABETIC PATIENTS AND THEIR PATTERN OF ANTIBIOTIC SUSCEPTIBILITY

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ABSTRACT

OBJECTIVES: To determine the etiologic agents of urinary tract infection (UTI) and their antibiotic susceptibility patterns among diabetic patients.

METHODS: This cross-sectional observational study was conducted from 1st August 2016 to 28th Feb 2017 at Cantonment General Hospital Rawalpindi, Pakistan. A consecutive non-probability sampling technique was used to screen diabetic patients for urinary tract infections (UTIs) irrespective of their symptoms. Subjects from both genders and aged more than 18 years were included. Urine cultures were taken and uropathogens were isolated and tested for drug susceptibility following standard laboratory procedures.

RESULTS: Out of 209 diabetic patients, 106 (50.7%) had culture positive UTI, 77/106 (72.6%) were females. Mean age of patients with UTI was 49.9 ± 9.80 years. Ninety-eight (93.5%) had type 2 diabetes and with a mean duration of 8.25 ± 3.78 years. Mean HbA1c level was $9.63 \pm 2.00\%$. Thirty-five (33%) patients had HbA1c > 11%, 52 (49.1%) patients had HbA1c values ranging between 7-11% and 19 (17.8%) patients had HbA1c level of <7%. *Escherichia coli* (*E. coli*) was the most common uropathogen (80%) followed by *Enterobacter* (7.6%), *Citrobacter* (6.7%), *morganella* (4.8%) and *pseudomonas* (1%). No gram positive bacteria were isolated. Fosfomycin was 100% sensitive against all uropathogens. Meropenem, piperacillin-Tazobactum and cefoperazone-salbactum were 91.4%, 88.6% and 86.7% sensitive respectively, whereas amikacin was 72.4% sensitive. Chloramphenicol, doxycycline and amoxicillin/culvunate showed sensitivity of 66.7%, 61% and 40% respectively. Cephalosporins and quinolones were least sensitive classes.

CONCLUSION: *E. coli* were the most common uropathogens in diabetics. Fosfomycin, Meropenem, piperacillin-Tazobactum and cefoperazone-salbactum had good sensitivity profile against uropathogens in diabetics.

KEY WORDS: Diabetes Mellitus (MeSH); Urinary Tract Infections (MeSH); Antibiotics (MeSH).

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INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infections worldwide which ranges from uncomplicated cystitis to bacteremia with relevant morbidities.¹ Diabetes mellitus is a known risk factor for UTI.² The exact reason for it is unclear; however, impaired immune system and inadequate bladder emptying predispose diabetics to UTI.³⁻⁵ Moreover, glycosuric state creates a good culture medium for the growth of

pathogenic microorganisms relating poor glycemic control to increase the risk of UTI.⁶ UTI in diabetics is asymptomatic initially and females are effected more than men leading to serious complications if not treated in time and adequately.^{2,7,8}

Several studies have shown that *Escherichia coli* (*E. coli*), *Klebsiella*, *Proteus*, Group B *Streptococcus*, coagulase-negative *Staphylococci* (*CoNS*), *S. aureus*, *Enterococcus*, *Enterobacter*, *Citrobacter*, *Serratia*, *pseudomonas*

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aeruginosa and *candida* have been isolated among patients of diabetes Mellitus with a varying frequency in different regions.^{2,7-13} Increasing antimicrobial resistance has been observed for common uropathogens in the Asia-Pacific as well as in global studies.⁹⁻¹² It leads to prolonged hospital stays and higher medical costs because of inappropriate antibiotic treatment.¹

This is one of the biggest challenges in low-income countries like us, due to high infection rates in poorly controlled diabetics, irrational use of antibiotics, over-the counter availability of antibiotics and poor infection prevention practices. Empirical antibiotic treatment should be prescribed according to local epidemiologic data and antibiotic susceptibility results.

Uropathogens vary in their susceptibility to antibiotics from place to place and time to time, hence constant screening of trends and susceptibility pattern of predominant organisms against antimicrobials is essential. This study was planned to determine the etiologic agents of UTI and their antibiotic susceptibility patterns among diabetic patients at Cantonment General Hospital Rawalpindi, Pakistan.

METHODS

This cross-sectional observational study was conducted from 1st August 2016 to 28th Feb 2017 at Cantonment General Hospital Rawalpindi, a teaching hospital affiliated with Yusra Medical College, Islamabad, Pakistan.

After taking ethical approval from Hospital ethical committee, all the diabetic patients of both genders who were aged more than 18 years were screened for UTI irrespective of their symptoms. Sampling technique was consecutive non-probability and total number of patients was 209. A well written informed

consent was taken from the patients. Patients with culture positive UTI were included in the study. Patients who had taken antibiotics within the preceding 2 weeks and the patients known to have anatomical and neurologic urinary tract abnormalities were excluded from the study. More over pregnant ladies with diabetes were also not included.

Mid-stream urine sample was taken in a sterile container for urine culture and sensitivity. Uropathogen was grown on cysteine lactose electrolyte deficient (CLED) media incubated at 37°C for 24 hours.⁵⁻⁷ CLED media plates were available in hospital Laboratory.

On the next day, the bacterial growth was controlled, and total colony count was calculated. Urine culture was considered significant bacteriuria (SB) when for a single isolated uropathogen colony forming units (CFUs) were $\geq 10^5$ /mL of voided urine.^{5-7,10} The grown organisms were gram stained and were characterized as per the standard microbiological procedures.⁶ Antibiotic susceptibility testing was performed on neutral agar.

The isolates were tested for amoxicillin-clavulanic acid (20/10µg), ceftriaxone (30µg), ciprofloxacin (5µg), norfloxacin (10µg), amikacin (30µg), doxycycline (30µg), fosfomycin (200µg), gentamicin (10µg), piperacillin-tazobactum (75/10µg), meropenem (10µg), cefoperazone-salbactam (75/15µg), ceftazidime (30µg), cefepime (30µg), aztreonam (30µg), and chloram-

phenicol (30µg). The sensitivity plates were incubated aerobically at 37°C for 24 hrs, and the zone of inhibition was recorded.⁵⁻⁷ The result was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guideline as susceptible (S), intermediate (I) or resistant (R).

Data was entered and analyzed using SPSS version 20. Descriptive statistic was calculated for both qualitative and quantitative variables. For qualitative variables percentages and frequencies were calculated. For quantitative variables mean \pm SD was calculated. Student t test and chi square test were employed to look for statistical difference where ever indicated. P value ≤ 0.05 was taken significant.

RESULTS

Two hundred and nine already diagnosed diabetic patients visiting medical OPD were screened for UTI. Out of 209 patients, 106 (50.7%) patients had culture proven UTI, which were analyzed further for demographic features, causative organism of UTI and antibiotic susceptibility.

Mean age of patients with UTI was 49.9 ± 9.80 years. Period prevalence of culture positive UTI in our study population was 50.7% (n=106). Out of 106 patients with UTI, 77 (72.6%) were females. Ninety-eight (93.3%) patients had type 2 diabetes with mean duration of 8.25 ± 3.78 years. Mean HbA1c level was 9.63 ± 2.00 . Thirty-five (33%)

TABLE I: DRUG SUSCEPTIBILITY OF EACH ORGANISM IN DIABETIC PATIENTS WITH URINARY TRACT INFECTIONS

Drugs	Organisms				
	E coli Sensitivity	Enterobacter Sensitivity	Citrobacter Sensitivity	Morganella Sensitivity	Pseudomonas Sensitivity
Amikacin	73%	57.1%	62.5%	80%	100%
Gentamicin	29.8%	42.9%	37.5%	20%	0%
Doxycyclin	61.9%	57.1%	62.5%	40%	100%
Fosfomycin	100%	100%	100%	100%	100%
Norfloxacin	11.9%	14.3%	50%	80%	100%
Ciprofloxacin	13.1%	28.6%	50%	100%	100%
Amoxiclave/culvunate	39.5%	57.1%	25%	60%	0%
Piperacillin/sulbactam	89.5%	57.1%	100%	100%	100%
Meropenem	95.2%	71.4%	100%	100%	100%
Aztreonam	13.1%	14.3%	37.5%	20%	0%
Ceftriaxone	11.9%	14.3%	25%	100%	0%
Cefoperazone/sulbactam	88.1%	71.4%	87.5%	80%	100%
Ceftazidime	34.9%	28.6%	50%	100%	100%
Cefepime	11.9%	14.3%	25%	100%	0%
Chloramphenicol	71.4%	57.1%	50%	20%	100%

patients had HbA1c >11% depicting poor control of diabetes, 52 (49.1%) patients had HbA1c values ranging between 7-11% and 19 (17.8%) patients had well controlled diabetes with HbA1c level of <7%.

E coli was the most commonly isolated uropathogen accounting for 80% (n= 84) of all cases of which 20% was Extended Spectrum Beta Lactamase ESBL. Percentage distributions of organisms are given in figure I.

Fosfomycin showed 100% drug sensitivity to all uropathogens. Meropenum, piperacillin-Tazobactum and cefoperazone-salbactum showed high sensitivities of 91.4%, 88.6% and 86.7% respectively followed by amikacin that was 72.4% sensitive. Chloramphenicol, doxycycline and amoxicillin-culvunate showed sensitivity of 66.7%, 61% and 40% respectively. Cephalosporins and quinolones turned out to be the less sensitive classes. Organism wise drug susceptibility is shown in table I.

DISCUSSION

Our study showed that on routine screening, significant number of diabetics had UTI. Period prevalence of culture proven UTI was 50.7%. It is relatively high as compared to other studies showing 43%, 34% and 35% respectively.^{9,11,12} Reason for this can be geographic variation, ethnicity and also that our study population had poorly controlled diabetes that make them prone to develop UTI.

Females are more prone to get UTI and same is true for diabetics which is also supported this fact.^{9,12,14} Our patients were relatively younger as compared to other studies,^{3,11} the reason for this can be early diagnosis of diabetes, ethnic variation and attitude of general population for seeking medical attention.

Most common organism isolated in culture was E coli followed by citrobacter, enterobacter and morganella. In our study the E coli was found quite high (80%) but in other relevant studies E coli were isolated in 41.5% (n=49),⁹ 48% (n=49),¹⁰ 58.3% (n=252),¹¹ 64.5% (n=31).¹² Rest of the organisms i.e. citrobacter, enterobacter, morganella and

pseudomonas were isolated in few cases, which corroborates the findings of other authors who reported less frequent isolation of these organisms in urine specimens of diabetic patients.⁹⁻¹²

20% of E coli in our study were extended spectrum beta-lactamases (ESBL) that supports the fact that diabetics, especially with poor control, are more prone to get ESBL positive UTI.^{10,15}

We didn't report any gram positive organism or candida in any of the urine specimen, where as in a study, staphylococcus was just next to E coli in causing UTI in diabetics followed by candida and streptococcus.¹⁰ Even a study from India has revealed staphylococcus as a second predominant isolate¹⁶ which is absolutely absent in our findings. In this regard our study was supported by a study done in Khatmandu that also showed no gram positive organism isolated in urine of diabetic patients.¹¹ Other studies showed less rate of gram positive and candida isolation in diabetic UTIs.^{9,12}

There is wide variety of organisms being isolated at different frequencies in different studies, the reason being regional differences, diagnostic tools and expertise, geographic distribution of organisms, difference in sample size and patient related factors like previous UTIs, catheterization, diabetic control etc.

Regarding antibiotic susceptibility pattern, we found that our 100% organisms isolated in our study were sensitive to fosfomycin. This is never observed in any of the study before, may

be due to the fact that the drug isn't being used commonly for UTI. Meropenem was next to fosfomycin giving more than 90% sensitivity that was consistent with other studies.^{3,4,10}

Cefoperazone-salbactum and piperacillin-tazobactum were highly sensitive against all organisms in our study, high sensitivity of cefoperazone-salbactum is supported by one of the other study.³ Regarding piperacillin-tazobactum previous studies have shown less sensitivity as compared to ours.³

Amikacin was moderately sensitive in our study population as documented in other study as well⁹ but many studies have shown it highly sensitive to uropathogens.^{3,12}

Amoxicillin-culvunate and quinolones demonstrated very high resistance profile against uropathogens. It is similar to other studies,^{4,9,10,12} but contrary to the study conducted in Ethiopia in 2016, that showed more than 80% sensitivity to norfloxacin and ciprofloxacin.² The reason for this difference can be a small sample size of 11 in that study along with racial difference.

Regarding cephalosporins, we have documented very low sensitivity trend even with 4th generation drugs. Although many studies showed moderate sensitivity of cephalosporins^{3,4} but in our case they were the least sensitive drugs. The probable explanation to this difference can be the irrational and/or over the counter use of cephalosporins in our setup.

Aztreonam had very low sensitivity against organisms; this finding was also supported in the study done in India.³

As a whole all studies, including ours, highlight the increasing resistance of uropathogens to antibiotics, which can be attributed to indiscriminate misuse of antibiotics among the general population, drug abuse and over the counter availability of drugs.

There were some limitations to our study. We didn't focus on the history in terms of urinary symptoms, prior episodes of UTI or catheterization. We didn't check for antibiotic sensitivity against nitrofurantoin that can be the good option for treatment.

Our study showed high prevalence of UTIs among diabetic patients in our setup, this led us to keep our threshold low to screen diabetic patients for UTI.

It is the highly alarming situation that the broad spectrum antibiotics like ceftazidime, cefipime and aztreonam showed high rate of resistance for uropathogens in diabetes. These antibiotics are usually reserved for complicated UTIs but probably their irrational use has led to this devastating finding leaving us helpless in the situations where they are actually needed.

It's high time for physicians and pharmacists to identify the infection causing agents and the resistance pattern of antibiotics routinely at their setup to rationalize the use of antibiotics. Continued surveillance of sensitivity patterns among disease causing organisms is required to ensure appropriate recommendations for the treatment of these infections.

CONCLUSION

E coli was the most common uropathogen in diabetics, followed by Enterobacter. No gram positive organisms were isolated in our study population. Fosfomycin, Meropenem, piperacillin-Tazobactum and cefoperazone-salbactum had good sensitivity profile against uropathogens in diabetics. Broad spectrum antibiotics like ceftazidime, maxipime and aztreonam showed high rate of resistance. Amoxicillin-culvunate and quinolones, cephalosporins also showed less sensitivity against Uropathogens.

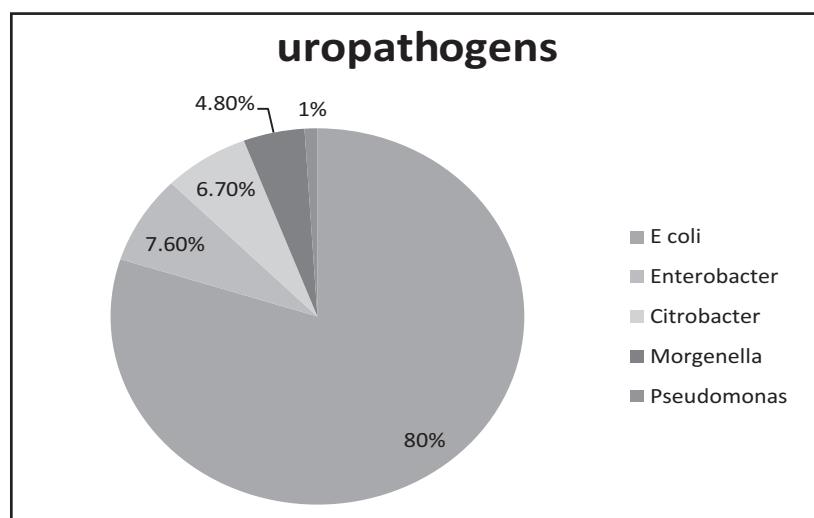


Figure 1: Organisms causing UTI among diabetic patients (n= 106)

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AUTHOR'S CONTRIBUTION

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

HB: Concept & study design; acquisition, analysis & interpretation of data; drafting the manuscript, final approval of the version to be published

KS: Acquisition of data, drafting the manuscript, final approval of the version to be published

MJ: Critical review, drafting the manuscript, final approval of the version to be published

CONFLICT OF INTEREST

Authors declared no conflict of interest

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