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Original article

Uropathogens Among Diabetic Patients At Zagazig University Hospital's Outpatient Clinics: Prevalence And Their Antibiotic Susceptibility Patterns

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ABSTRACT

Background: The incidence of diabetes mellitus is increasing worldwide; it has some major effects on the genitourinary system, which makes diabetic patients more liable to urinary tract infection. Despite, all these problems, antibiotics are prescribed empirically which may adversely affect antibiotic resistance so far. Therefore, the aim of this study was to identify the etiologic agents of UTI and their antibiotic susceptibility pattern among diabetic patients attending diabetic clinic of Zagazig University Hospitals.
Material and Methods: A cross-sectional study was conducted in a total of 195 diabetic patients who suffered change from June 2017 to June 2018. Demographic and clinical data were collected. Clean catch mid-stream urine samples were collected and processed for identification of uropathogen.
Results: E. coli was the commonest isolated uropathogen followed by Klebsiella pneumoniae. All the isolated bacteria were resistant to ceftriaxone but sensitive to ciprofloxacin. Gram-negative isolates demonstrated high level of sensitive to amikacin in 188 (96.4%) patients, imipenem and meropenem in 5 (2.6%) and ceftazidime in 187 (95.9%) patients. Gram-positive bacteria showed sensitive to amoxicillin-clavulanate, linezolid and vancomycin in 7 (3.6%) patients. Multidrug resistance was observed in about 30% of the isolated uropathogens.
Conclusion: Pathogens are mostly resistant to antibiotics including ceftriaxzone and ampicillin with few exceptions including nitrofurantoin and sulfamethoxazole-trimethoprim.
Keywords: Urinary tract infection, Diabetes mellitus, Antibiotic resistance, Bacteriuria.

1- INTRODUCTION

The prevalence of diabetes mellitus (DM) is alarmingly increasing allover the world. It became a serious public health problem, especially in the developing countries. [1]

DM was associated with an increased incidence of Urinary tract infection (UTI). Urinary tract infections are generally asymptomatic in DM patients before development of symptomatic UTI. Females are more commonly affected with UTI than males In addition; the prevalence of asymptomatic bacteriuria is higher among women with type II diabetes, which leads to serious complications especially if glycemic control is poor. [2]

The problem is challenging in low-income countries because of high prevalence of infection, irrational uses of the antibiotics, over-the-counter availability of antibiotics and poor infection prevention practices. Hence, the emerging prevalence of antibiotic resistance and DM is a cause of concern for health care providers. [3]

A study of the prevalence of the different strains of UTI pathogens and their antibiotic susceptibility patterns are of primary importance in the treatment process. Therefore, the aim of this study is to determine the prevalence of different kinds of uropathogens in diabetic patients and their sensitivity and resistance pattern to antibiotics .

2- MATERIALS AND METHODS

This is a cross-sectional study that included 195 diabetic patients with signs and symptoms of urinary tract infection; community acquired UTI and not patients having these symptoms after hopitalization. They were selected from patients attending the Internal Medicine outpatient clinic of Zagazig University Hospitals in the period between June 2017 and June 2018.

All included patients were diagnosed with diabetes mellitus according to American Diabetes Association (ADA) criteria. [4]

Patients were excluded if they were treated with antibiotics within the preceding 2 weeks, known anatomic and neurologic urinary tract abnormalities, pregnant women, patients with poor urine flow (oliguria not due to dehydration, or urinary retention; urine output less than 1 ml/kg/hour) and patients with abdominal or bladder mass or pelvic mass. Also, cases of being previously hospitalizd or done previous urological procedures have been excluded.

Patients were subjected to thorough history taking regarding age, sex, body mass index, full diabetes history (diabetes duration, diabetes type, and Macro/microvascular complications), previous UTI and antibiotics use. Routine investigations included serum creatinine, blood urea nitrogen (BUN), HbA1C%, CRP, CBC and performing a pelvi-abdominal ultrasound. Full clinical examination was performed.

Microbiological methods

Clean-catch mid-stream urine samples (5–10 mL) were obtained from each patient in a sterile screw-capped wide-mouth container after informing them about proper urine collection method.. The containers were labeled with a unique sample number, date and time of collection. Urine samples were directly inoculated on blood agar, mannitol salt agar and MacConkey agar plate.

Specific organisms will produce colored colonies, depending the interaction between the enzymes they produce and the substrates in the medium, allowing identification of the most relevant urinary Enterobacteriaceae and Enterococci. In addition to MacConkey or chromogenic media, a more universal blood agar plate was inoculated allowing the detection of Gram-positive and fastidious bacteria. All culture media were incubated at 35–37 °C for at least 18 h. MacConkey agar and chromogenic agar plates were incubated overnight. To enhance growth of gram-positive bacteria, blood agar media were incubated under aerobic atmosphere with 5–10% CO2.

Urine cultures were plated using calibrated loops for the semiquantitative method.

Inhibition zones were measured to the nearest millimeter and then compared to the standards of the 28th edition of the Clinical and Laboratory Standards Institute. [5]

Ethical

Written Informed consent was taken from the patient to participate in the study. Approval for performing the study was obtained from Internal Medicine Department and Microbiology and Immunology Department, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 24.0 for windows (SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data. Independent T test and Mann Whitney test were used to calculate

difference between quantitative variables in two groups for parametric and non-parametric variables respectively. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, p <0.001 indicates highly significant difference while, P> 0.05 indicates Non-significant difference.

3- RESULTS

Cases have been divided according to gender, type of diabetes mellitus, history of UTI and antibiotic usage, and the results of the routine investigations.

The demographic features of the patients are described (Table 1).

Table 1. The demographic features of the patients

		All studied patients (n=195)
Age (years) Mean ±SD		48.81 ± 11.97
Sex	Female	116 (59.5%)
	Male	79 (40.5%)
Systolic blood pressure Mean ±SD		123.08 ± 11.2
Diastolic blood pressure Mean ±SD		78.05 ± 7.75
DM type	**I**	71 (36.4%)
	II	124 (63.6%)
Duration of DM (years) Mean ±SD Median (Range)		10.16 ± 5.14 9 (1 - 22)
History of UTI (%)		20 (10.3%)
History of Antibiotics use (%)		17 (8.7%)

Table 2. Patients' characteristics between the groups.

		Good control diabetic Group (N=60)	*Poor control diabetic Group (N=135)*	*P*	*History of UTI (n=20)*	*No History of UTI (n=175)*	*P*
Age (years) Mean ± SD		49.12 ± 12.81	48.67 ± 11.62	.812	51.15 ± 9.89	48.54 ± 12.18	.357
Female n (%)		39 (65%)	77 (57%)	.296	11 (55%)	105 (60%)	.666
BMI (kg/m^2) Mean ± SD		27.17 ± 2.4	27.96 ± 2.48	.255	28.07 ± 3.59	25.73 ± 3.08	.205
DM type	***I***	25 (41.7%)	46 (34.1%)	.309	4 (20%)	67 (38.3%)	.107
	II	35 (58.3%)	89 (65.9%)		16 (80%)	108 (61.7%)	
Duration of DM (yrs) Mean ± SD		6.48 ± 3.46	13.6 ± 4.35	**<0.001**	14.5 ± 7.78	9.98 ± 5.04	.226
History of UTI n (%)		1 (1.7%)	19 (14.1%)	**.009**			
History of Antibiotics use n (%)		0 (0%)	17 (12.6%)	**.004**	16 (80%)	1 (0.6%)	**<0.001**
Creatinine (mg/dL) Mean ± SD		.993 ± 1.01	.913 ± .245	.387	.93 ± .249	.939 ± .622	.950
BUN (mg/dL) Mean ± SD		11.16 ± 2.87	11.37 ± 2.94	.642	11.88 ± 2.19	11.24 ± 2.98	.355
HbA1c (%) Mean ± SD		7.66 ± .751	10.9 ± 1.56	**<0.001**	10.73 ± 1.42	9.8 ± 2.07	.055
CRP (mg/L) Mean ± SD		8.02 ± 2.36	15.74 ± 3.39	**<0.001**	19.93 ± 5.94	11.37 ± 4.37	**.002**

Test of significance <0.05

Table 3. Gram negative organisms' antibiotic susceptibility and resistance

Antibiotics	*Escherichia coli (n=108)*			*Klebsiella pneumonia (n=75)*			*Pseudomonas (n=4)*			*Acinetobacter (n=1)*		
	Sensitive	*Intermediate*	*Resistant*	*Sensitive*	*Intermediate*	*Resistant*	*Sensitive*	*Intermediate*	*Resistant*	*Sensitive*	*Intermediate*	*Resistant*
Amikacin	108 (100 %)	--	--	75 (100%)	--	--	4 (100 %)	--	--	1 (100 %)	--	--
Amoxicillin + Clavulanate	107 (99.1 %)	--	1 (0.9%)	75 (100%)	--	--	--	--	--	--	--	--
Ampicillin	47 (43.5 %)	6 (5.6%)	55 (50.9 %)	14(21. 3%)	6 (8%)	53 (70.7 %)	--	1 (25%)	3 (75%)	--	--	1 (100 %)
Cefoxitin	108 (100 %)	--	--	73 (97.3%)	2 (2.7%)	--	--	--	--	--	--	--
Ceftazidime	108 (100 %)	--	--	74 (98.7%)	1 (1.3%)	--	4 (100 %)	--	--	1 (100 %)	--	--
Ceftriaxone	--	--	108 (100 %)	--	--	75 (100 %)	--	--	--	--	--	--
Ciprofloxacin	108 (100 %)	--	--	75 (100%)	--	--	4 (100 %)	--	--	1 (100 %)	--	--
Gentamycin	90 (83.3 %)	6 (5.6%)	12 (11.1 %)	59 (78.7%)	13 (17.3%)	3 (4%)	4 (100 %)	--	--	1 (100 %)	--	--
Nitrofurantoin	94 (87%)	7 (6.5%)	7 (6.5%)	63 (84%)	7 (9.3%)	5 (6.7%)	--	--	--	--	--	--
Sulfamethoxazole-trimethoprim	108 (100 %)	--	--	74 (98.7%)	1 (1.3%)	--	--	--	--	1 (100 %)	--	--
Aztreonam	--	--	--	--	--	--	1 (25%)	3 (75%)	--	--	--	--
Cefepime	--	--	--	--	--	--	4 (100 %)	--	--	1 (100 %)	--	--
Imipenem	--	--	--	--	--	--	4 (100 %)	--	--	1 (100 %)	--	--
Meropenem	--	--	--	--	--	--	4 (100 %)	--	--	1 (100 %)	--	--
Tazobactam	--	--	--	--	--	--	4 (100 %)	--	--	1 (100 %)	--	--
Tetracycline	--	--	--	--	--	--	--	--	--	1 (100 %)	--	--

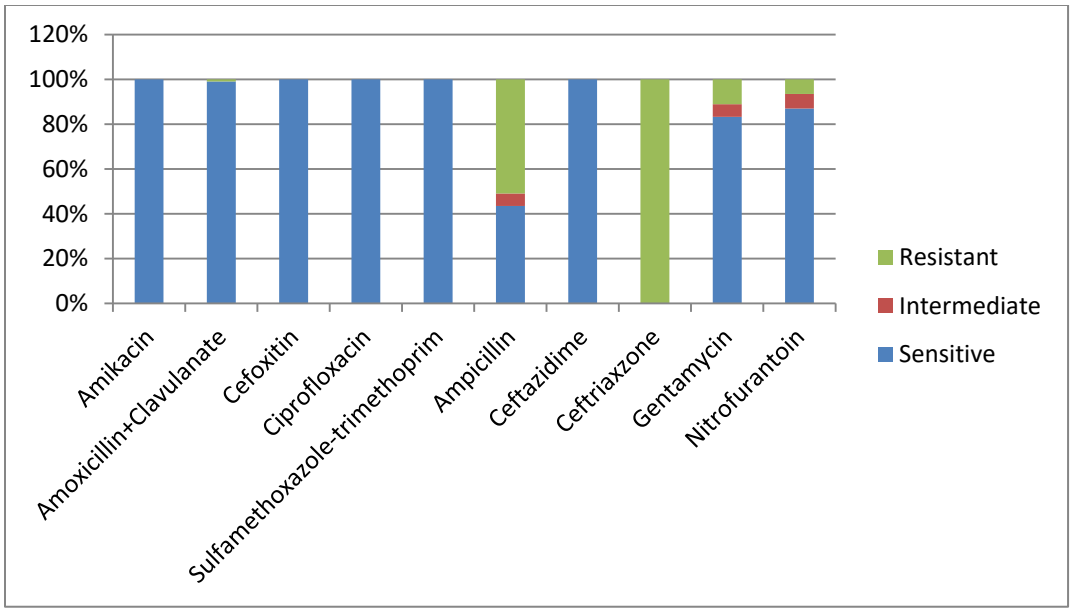

Figure 1.E. coli antibiotic susceptibility and resistance

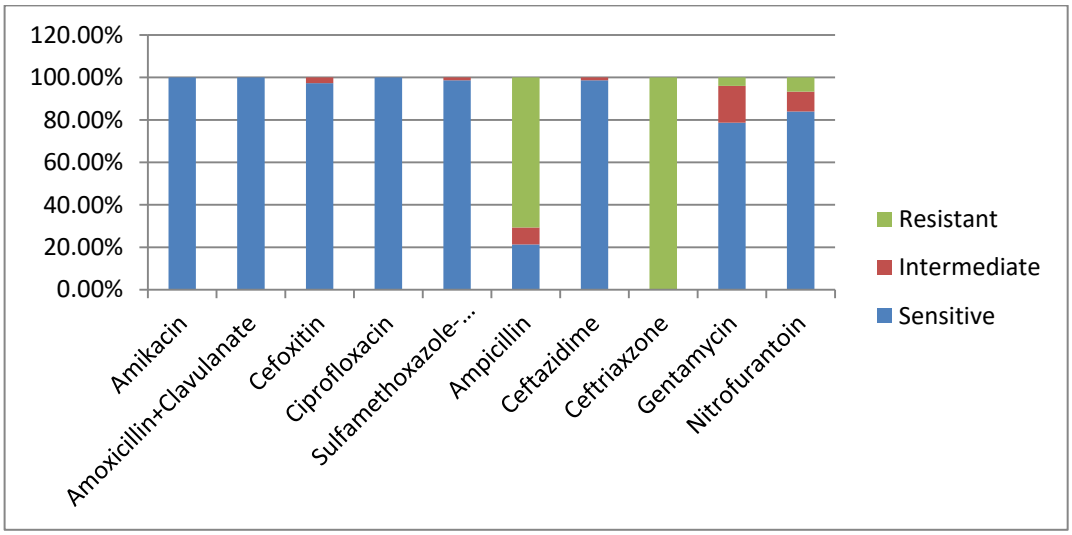

Figure 2. *Klebsiella pneumonia susceptibility and resistance*

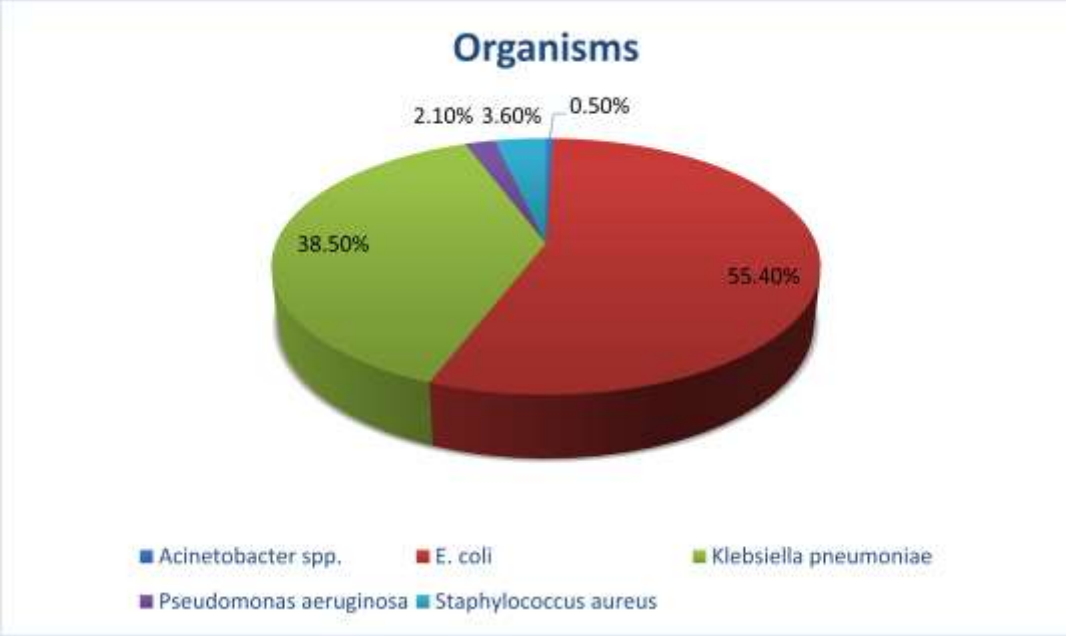

Figure (3): *Organism frequency of the studied patients.*

Figure 3 demonstrated the prevalence of each organism in the present study.
We found a high significant difference in DM duration, history of UTI and antibiotics use between well-controlled diabetic and poor controlled diabetic as summarized in table 1.
Frequency of history of antibiotics use was significantly higher in patients with history of UTI compared to patients without history of UTI antibiotics use as summarized in table 1.

5-DISCUSSION

UTI is one of the commonest infectious diseases, especially among females of all ages, and affect nearly 10% of US women per year. [6]

It is well proved that the prevalence of UTI increases with age, and this increase is seen in both men and women. [7]

The prevalence of UTI among the diabetic patients was observed by several studies. [8]

Regarding female diabetic patients was 59.5%, which was higher compared to male 40.5%. This is in agreement with the other reports stating high prevalence of UTI in females.[9]

The current study delineated that the occurrence of UTI in diabetics was observed more frequently in subjects of a mean age of just above 48 years. Gram-negative bacteria were the commonest isolated organisms in this study, and previous studies have proven this by reporting similar findings. [10] [11] [12]

Current clinical treatments are guided by proposals for both diagnosis and treatment of UTIs in adults. [8]

Although the easy access to antimicrobial agents, UTI became increasingly difficult to treat, this is due to increasing resistance to these agents. Furthermore, patients with UTI are more likely to experience treatment failure and complications, since they are mostly caused by Gram-negative bacilli resistant to more than one antimicrobial drugs.

Several important risk factors, as engagement in sexual activity by the adult group and increasing age of the diebetics make them vulnerable to UTI. The present study revealed that Escherichia coli (55.4%) were the most prevalent pathogens followed by Klebsiella pneumonia (38.5%) and

Staphylococcus aureus (3.6%). These findings are close in results to other studies' results that indicated that Gram-negative bacterium; particularly Escherichia coli remains the commonest pathogen in patients with UTI. [13]

In an another study from Nepal, it was found that E. coli was commonest organism (54.5%), followed by S. aureus (17.3%), Enterococcus species (9.4%) and Klebsiella species (7.5%). [14]

The antibiotic susceptibility pattern of the etiological agents in this study revealed that most isolates were resistant to ceftriaxzone and ampicillin, which are relatively cheaper drugs and this finding is similar to that of a previous study. [14]

Amikacin has been shown to have promising results for UTI in diabetics. Most isolates were resistant to ampicillin. Gram-negative bacteria were generally resistant to cephalosporins (cefotaxime and ceftriaxone), while Gram-positive cocci were proved susceptible to these antibiotic choices. [15]

In this research, Gram-negative bacilli are more sensitive to ofloxacin and ciprofloxacin than the Gram-positive cocci. However in another research, the Gram-positive cocci were highly sensitive to ofloxacin than the Gram-negative bacilli, while the Gram-negative bacilli were more sensitive than Gram-positive cocci to ciprofloxacin. [12]

Majority of the Gram-positive isolates and Escherichia coli were sensitive to nitrofurantoin. The most prevalent pathogen, Escherichia coli was sensitive to amikacin, gentamicin, nitrofurantoin and other antibiotics used except for ceftriaxzone and 50.9% were not responding to ampicillin.

Urinary tract infections are usually treated empirically and culture & susceptibility test are often requested only when the cases fail to improve after the administration of one or more antibiotics. This trend elevates the drug resistance patterns.

The responsible bacteria especially P. aeruginosa, Acinetobacter spp. and Enterococcus that are very deft at developing resistance by exploiting various mechanisms can be hard to manage.

Klebsiella affected patients were 100% resistant to ceftriaxzone and 70.7% resistant to ampicillin. Gentamycin and Nitrofurantoin resistance was seen in 4% and 6.7% respectively.

Ampicillin and clindamycin both showed 14.3% resistance in Staphyloccocus aureus caused UTI.

Moreover, ampicillin showed 75% resistance in Pseudomonas.

Finally, ampicillin showed 100% resistance regarding the Acinetobacter spp. organism.

Unfortunately, multidrug resistance is an increasing concern, and this issue is usually attributed to the haphazard use of broad-spectrum antibiotics. To try to limit this, programs that target inappropriate use of antibiotics are set up, in order to decrease the prevalence of drug-resistant organisms.

Moreover, strict adherence to guidelines in the process of treatment, will decrease the spread of drug-resistant organisms.

CONCLUSION

The importance of this research is targeting the usual pathogens affecting diabetic patients with UTI and their anitbiotic resistance patterns. As a result, physicians and pharmacists can use the suitable antibiotic. In this research, the used antibiotics have included: amoxicillin, ciprofloxacin, cephalosporins (1st generation, 2nd generation, 3rd generation in some cases) and ceftriaxone are mostly resistant to pathogens.

Multidrug resistance to commonly used antibiotics is an alarming phenomenon. Eventually, the need for doing urine cultures and regular check of UTI among DM patients is a must.

Extension of this study to include the use of antibiotics in vivo, measuring the rate of eradication of pathogens after the antibiotic usage and clinical factors affecting the response of patients to antibiotic is needed.

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Conflicts of interest:

The authors declare that they have no competing interests.

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