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Original Article

Uropathogens and their antibiotic sensitivity pattern among poorly controlled diabetic Pakistani patients with Asymptomatic Bacteriuria.

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Abstract

Background: Urinary tract infections (UTIs) are common among diabetic patients, 60% of the patients with diabetes mellitus (DM) have risk of UTI and two third of them develop symptomatic or asymptomatic UTIs. The uropathogens may vary in their susceptibility to antimicrobials from place to place and time to time, therefore susceptibility pattern of predominant organisms against antimicrobials is essential. The aim of the study was to investigate the incidence of asymptomatic bacteriuria (ASB) and UTIs in clinically diagnosed diabetic patients and to determine the uropathogens responsible for ASB and UTIs as well as their antimicrobial susceptibility pattern.

Methodology: An observational, prospective study was conducted at the Islamabad Social Security Hospital, Pakistan. Total 269 patients were recruited as per the study inclusion/exclusion criteria. Fasting blood glucose (FBG), blood sedimentation rate (BSR), urine routine examination (RE), abdominal ultrasound and hemoglobin-A1c (HbA1c) were examined in all patients to exclude other causes of urosepsis.

Results: According to the study results 106 urine cultures were positive in the absence of urinary symptoms. Majority of the study subjects were around 50 years of age with an average glycosylated hemoglobin level of 8.98 g/dl. Urine culture and sensitivity test showed that E coli - Extended-spectrum beta-lactamases (ESBL) isolated in 39.63% was the most common organism sensitive to Tazobactam and Tiegecycline. E coli isolated in 32% was observed sensitive to levofloxacin, cefotaxime and tazobactam. Klebsiella (ESBL) isolated in 5.6% and found sensitive to tazobactum and amikacin. Klebsiella saprophyticus isolated in 3.77% with greater sensitivity to Tazobactum and cefixime while Enterococcus isolated in 5.6% mainly sensitive to minocycline and vancomycin. Majority of the isolated organisms were poorly sensitive or resistant to cefixime, quinolones and amoxiclav.

Conclusion: Asymptomatic bactriuria is common in type 2 diabetic patients. The growth and sensitivity of microorganism reveal resistance and poor sensitivity to commonly used oral antibiotics therefore it is mandatory to treat UTI only after isolation of microorganisms according to culture and sensitivity to prevent resistant strains.

Keywords

Diabetes Mellitus, Urinary Tract Infection, Antibiotic Susceptibility, Pakistani Population

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Introduction

Amongst the infections affecting the diabetic patients UTI's are the commonest. About 60% of diabetic patients have risk of urinary tract infections (UTI) and 2/3rd of them develop symptomatic or asymptomatic UTIs[1]. Diabetics have a unique feature, their upper urinary tract is involved bilaterally in 80% of cases and result in complications[2]. The recurrence rate of UTIs is 25-45% higher than that in non-diabetics[3]. In spite of the fact that diabetics receive prolong treatment with antibiotics[3]. Susceptibility increases with long duration of diabetes, regardless of controlled diabetes as evidenced by glycosylated hemoglobin level[4]. High urinary glucose, defective host immune factors, diabetic vascular disease and vaginal candidiasis predispose to recurrent UTI[5]. As hyper-glycaemia causes neutrophil dysfunction by affecting phagocytosis[5].

Infectious diseases are more common among diabetic patients as compared to non-diabetic counterparts, i.e. pyelonephritis, emphysematous cystitis, papillary necrosis, and renal abscess being the lethal metastatic infections among diabetics[6]. In pregnant diabetic women ASB is 2-4 times more as compared to non-diabetic pregnant females[7&8]. Unrecognized, poorly treated bactriuria in diabetic patients lead to low grade infections and result in renal damage[9]. The increasing prevalence of UTI among the pregnant diabetic females is mainly due to ureteric dilation and stasis[10-12]. Other predisposing factors may include declined immune responses and vesicoureteric reflux[10-12], which in turn increases morbidity and mortality rate both maternal and perinatal[13]. Maternal complications that increases the death risk of the fetus include anemia, pre-eclampsia, pyelonephritis and hypertension[14&15]. Such fetuses are usually born premature with low birth[15&16].

Proper screening and treatment of diabetic patients for ASB is necessary to prevent further complications of diabeties[17]. However, it is one of the biggest challenges to control UTI among the developing countries mainly in Pakistan[18]. Over-the counter availability and misuse of antibiotics, increased infection rate and poor treatment modalities further precipitate the condition, increasing the disease susceptibility[18].

Many different microorganisms can infect urinary tract of diabetic patients. Most common are gram negative bacilli (Ecoli 90%) other organisms are protease, klebsiella, entero bacter and pseudomonas[19]. These organisms result in recurrent UTI while klebsiella and protease predispose to renal stone formation[19&20]. UTI can cause poor diabetic control by increased secretion of counter insulin hormone (growth hormone, cortisol and glucagon). There is increase insulin resistance at the peripheral tissue level predisposing to hyperglycemia and aggravation on UTI[21]. Moreover, these uropathogens develop resistance against antibiotic, hence it is essential to assess the sensitivity and resistance pattern of different bacterial organisms against the antibiotics administered[18].

There is not much literature on uropathogen sensitivity and resistance pattern among pregnant diabetic females with asymptomatic bacteriuria in Pakistan. Hence, this study will help determine the increasing prevalence of bacterial uropathogens in pregnant diabetics and their resistance trends and sensitivity patterns.

Methodology

An observational, prospective, hospital based study was conducted at the Islamabad Social Security Hospital, Pakistan from January 2014 to December 2017. A total of 269 patients were recruited as per study inclusion criteria. Poorly controlled type 2 diabetic women with ASB detected on positive urine culture were included in the study sample, while catheterized patients, patients on antibiotics for last 3 months, pregnant diabetic women, recent surgery on urinary tract, and bladder dysfunction with urinary tract abnormalities immune compromised and cancer patients, patients on steroids for any reason, bed ridden patients were excluded. Mid-stream sample of urine was collected and sent for culture and sensitivity. Blood glucose random, FBG and glycosylated hemoglobin was examined for each case. Ultrasound KUB (kidney, ureter and bladder) was also performed in every patient to detect abnormalities. A single referral lab was used for clinical uniformity of results. Uropathogen identification and antibiotic sensitivity was determined on the basis of positive urine culture. The data was analyzed using SPSS ver. 22.

The study was approved by the Institutional ethics committee (IEC) and conducted in compliance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines. The IEC reviewed the progress of the study. The investigators and the participating institution agreed to maintain the confidentiality of the data. All the authors assure for the completeness and accuracy of the data and data analysis.

Results

A total of 269 females with poorly controlled diabetes were recruited during the period of January 2014 to December 2017. Strict antiseptic technique and mid-stream urinary samples were collected and subjected to culture and sensitivity to a single reference lab for accuracy of results. Around (106) 39.4% urinary samples turned out to be positive for growth of microorganisms. The details of the diabetic patient distribution with age mentioned in Table 1. According to the results the average age of type 2 diabetic patient was 50 years, i.e. 30.1% patients were between the age group of 50 to 55 years. The average Glycosylated haemoglobin (HGB) level was 8.98 and Mean duration of diabetes was 5.66 years.

Table 1: Diabetic patient distribution with age

Age in years	Duration of diabetes /years	Patients with positive urine culture N (%)	Glycosylated HGB (g/dl)
35-40	3	14(13.2)	8.7
40-45	4	19(17.9)	9.1
45-50	6	21(19.8)	8.6
50-55	8	32(30.1)	9.7
55-60	6	15(14.1)	8.6
60-65	7	5(4.7)	9.2

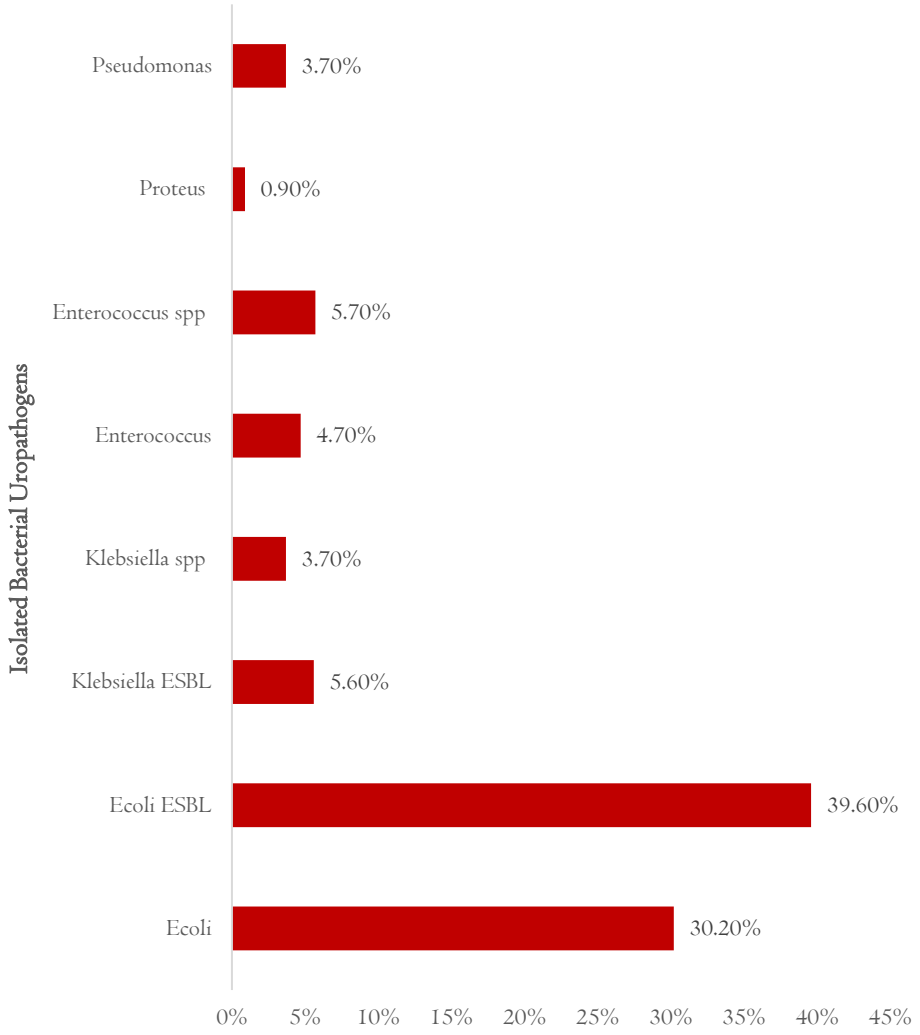

Figure 1: Bacterial uropathogens isolated from type 2 diabetic women with ASB.

Of all bacterial isolates Ecoli ESBL was the commonest i.e. 39.6% followed by Ecoli, isolated in 30.2% (32) patient. Klebsiella (ESBL) was isolated in 5.6% (6) patients while Klebsiella spp was isolated in 3.7% (4) patients.

The antimicrobial sensitivity and resistance pattern is shown in table 2. The pattern of sensitivity and resistance of many of the bacterial isolates was very much alike for many of the antibiotics. Ecoli ESBL, the commonest uropathogen was found sensitive to Fosomycin, Cefotaxime, Levofloxacin and less sensitive to Quinolones and Gentamycin. While Ecoli was found sensitive to Meropenun, Cefotaxime, Levofloxacin, and Amoxiclav and highly resistant to ciprofloxacin, Cefixime, and Ofloaxacin. Isolated Klebsiella (ESBL) was highly sensitive to Tazocin and Cefoxitin less sensitive to Ofloxacin and resistant to Cotrimoxazole, Ampicillin and Nitrofurantion. From the pattern of culture and sensitivity it is evident that the isolated uropathogens are resistant to commonly used oral medication.

Table 2: Antibiotic sensitivity and resistance pattern of isolated bacterial uropathogens

	Bacterial Isolates							
Antibiotics	EC	EC-ESBL	Klebsiella ESBL	Klebsiella spp	Entero coccus	Entero-coccus spp	Proteus	Pseudo-monas
FM	7(S)	S	R	R	S	R	R	R
GM	8(S)	R	R	R	R	R	R	R
MEM	23(S)	R	R	S	R	R	S	R
CTX	22(S)	S	R	R	R	R	R	R
TGN	7(S)	R	R	R	S	R	R	R
LEV	18(S)	4(S)	R	S	R	R	S	R
COT	17(S)	13(S)	R	R	R	R	S	R
MCN	11(S)	R	R	R	R	S	R	R
AVE	10(S)	29(S)	R	R	R	R	S	R
TN	S	9(S)	1(S)	S	R	R	R	R
NFN	S	11(S)	2(S)	R	S	S	R	R
VA	R	4(S)	R	R	R	R	R	1(S)
AK	R	7(S)	R	R	R	R	R	R
CIP	R	R	R	R	R	R	R	R
SPR	R	R	R	S	S	R	R	R
CFM	R	R	R	R	R	R	R	S
CTZ	R	R	R	R	R	S	R	R
AP	R	S	R	R	R	R	R	2(S)
CPS	R	S	S	R	R	R	R	R
CXT	R	R	S	R	R	S	R	2(S)
OLF	R	R	R	R	S	S	R	1(S)
IMI	R	R	R	R	S	S	R	1(S)
PXN	R	R	R	R	S	S	R	1(S)

*R= Drug Resistance; S= Drug Sensitivity; Numbers indicate the isolated organisms of 1 specie; EC = E-coli; ESBL = Extended-Spectrum Beta-Lactamase; Fosomycin = FM; Gentamycin = GM; Meropenum = MEM; Cefotaxime = CTX; Tiegecycline = TGN; Levofloxacin = LEV; Cotrimoxazole = COT; Minocycline = MCN; Amoxilave = AVE; Tazocin = TN; Nitrofurantion = NFN; Valcomycin = VA; Amikacin = AK; Ciprofloxacin = CIP; Sparfloxacin = SPR; Cefixime = CFM; Ceftaxidine = CTZ; Ampicillin = AP; Cefoperazone sulbactam = CPS; Cefoxitin = CXT; Ofloxacin = OLF; Imipenum = IMI; Polymyxin = PXN

Discussion

The present study showed that ASB was present in 106 out of 269 patients (39.4%) (Table 1). The geographical distribution, ethnicity and variation in screening tests play a role in detection of Uropathogens[21&22]. The prevalence of ASB may vary among different population. According to a study it was shown to be 21% in Karachi[23] while 26% in Nigeria and 19% in Bahrain as quoted in other studies[24&25]. Use of broad spectrum antibiotics for UTI in patients with ASB without culture is further induces resistance against antibiotics[26]. A recent American study performed on a health service database with more than 70000 patients with type 2 DM found that 8.2 % participants (12.9% women 3.9% men) had UTI[27&28]. Moreover UTI was found more common in both males and females with diabetes as compared to those without diabetes (9.4% vs. 5.7%) among 89790 matched pairs of patients with and without type 2 diabetes[28].

Meta-analysis of 22 studies published in 2011 show that the prevalence of ASB in diabetics is 12.2% versus 4.5% in healthy controlled. Longer duration of diabetes even with good glycemic control evident by glycosylated hemoglobin levels increases the risk of developing UTI[29]. Study conducted on Indian population showed 30% prevalence of ASB in diabetics[30]. Data from Danish study highlighted the fact that the diabetic patients were hospitalized three times more than non-diabetics[31]. According to a case controlled study in Washington, pyelonephritis was 4.1 times more frequent in pre-menopausal diabetic women than without diabetics[32].

According to our study results E coli and E coli ESBL were the most common Uropathogen isolated i.e. 30.2% and 39.6% respectively (Figure 1). Our results were consistent with the findings of other studies[23,25,33&34]. As reported by Mokube and his fellows in their study, the commonest uropathogen isolated was E coli (33%)[35]. Furthermore, E coli is resistant to most of commonly used antibiotic secondary to use of antibiotic without culture creating resistant strains. Among other organisms, Klebsiella saprophytic (ESBL) was isolated in 5.6%, Klebsiella 3.77%, Pseudomonas 3.77%, Enterococcus 5.66%, Proteus 0.94% and Candida 5.66% (Figure 1). Patton also reported similar results, that after E coli, Klebsiella and Proteus are the most common organisms isolated in urinary samples with ASB in diabetics[36].

It was apparent from our study results that E coli is most sensitive to Meropenum, Cefotaxime, Minocycline, Levofloxacin, Amoxiclav but resistant to Cotrimoxazole, Fosomycin, Gentamycin,and Teigecycline (Table 2). While ESBL E coli is highly sensitive to Tazobactem, Cefoxitn, less sensitive to Teigecycline and showed resistance towards Quinolones, Cefixime, and Cotrimoxazole. This pattern of sensitivity and resistance is consistent with findings of a study conducted on Nigerian population, according to which E coli was found to be resistant to Ampicillin, Chloramphenicol and Erythrocin[34]. Moreover, it was also observed that Klebsiella showed high sensitivity to Tazobactem, Cefoxitin and Imepenum and resistance to Nitrofurantion, Amikacin and Quinolones. Enterococcus was 100% sensitive to vancomycin, Teigecycline, and Imepenum (Table 2).

The antibiotic sensitivity and resistance pattern was quite uniform for most of the identified species, as many of them were highly resistant to the antibiotics used. This may be due to the abuse of these antibiotics and excessive drug purchasing without prescriptions[34]. Due to repeated antibiotic use the uropathogens invade through the damage peri-urethra and also infects urinary tract. Hence, this resistance pattern of different organisms toward antibiotics limits the UTI treatment options and therefore increases the challenges during disease management.

Conclusion

This study concluded that ASB was established in 39.5% of type 2 diabetics. The results clearly indicated the high resistance of bacterial isolates to commonly prescribed oral and intravenous antibiotics. However, it is recommended to use antibiotics only after culture and antibiotic sensitivity test. It not only prevents bacterial resistance but also eliminates the factor of insulin resistance which contributes to poor glycemic control.

Conflicts of Interest

None.

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