GROSS PYURIC DIABETICS WITH UNCONTROLLED GLYCEMIA: PATTERN OF PATHOGENIC ORGANISMS AND ANTIMICROBIAL SUSCEPTIBILITY

Syed Fahim Shah[1]✉, Sohail Aziz Paracha[2]

[1]✉ Department of Medicine, KMU Institute of Medical Sciences (KIMS), DHQ Hospital KDA, Kohat, Pakistan
Email: syed.fahimdrkt@yahoo.com
[2] Department of Anatomy, KMU Institute of Medical Sciences (KIMS), DHQ Hospital KDA, Kohat, Pakistan

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ABSTRACT

OBJECTIVES: To determine the frequency of microbiologically confirmed urinary tract infection (UTI), pattern of causative organisms and their antimicrobial susceptibility in uncontrolled diabetic patients with gross pyuria.

METHODS: This study was conducted at Department of Medicine, Divisional Headquarter Hospital KDA Kohat and Qazi Medical Centre, Kohat- Pakistan, from January 2015 to December 2015. Ninty six adult diabetic patients having uncontrolled glycemia (Random blood sugar>200mg/dl) with gross pyuria (>100 pus cell/HPF on urinalysis) and not taking any antibiotic for the last 3 days were enrolled in study. Urine of patients was sent for culture and sensitivity.

RESULTS: Out of 96 patients, 88 (91.66%) were having Type 2 Diabetes Mellitus and 8 (8.33%) had Type 1 Diabetes Mellitus. Patients were ranging in age from 19-70 years with mean age of 51.156±12.54 years. Out of 96 tested urine samples, 80 (83.33%) were with positive urine culture report while in 16 (16.67%) cases no significant growth of any microorganism was obtained. Out of these 80 positive cases, E.Coli was the most frequent isolate in 68 (85%) samples followed by Proteus in 7 (8.75%) samples. Isolated E.Coli showed 100% sensitivity to Piperacillin plus Tazobactum and Imipinem but 100% resistance was observed to Naladixic Acid, Norfloxacin and Ciprofloxacin.

CONCLUSION: Diagnostic yield of urine culture and sensitivity in uncontrolled diabetic patients with gross pyuria was 83.33%. Escherichia coli were found to be the most predominant isolate, showing high drug resistance particularly to naladixic acid, ciprofloxacin and norfloxacin.

KEY WORDS: Urinary tract infection (MeSH), Bacteriuria (MeSH), Pyuria (MeSH), Diabetes Mellitus (MeSH), Culture Pattern (Non-MeSH), antibiotic sensitivity (Non-MeSH), Microbial Sensitivity Tests (MeSH).

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INTRODUCTION

Patients with diabetes mellitus (DM) are generally more susceptible to infections, especially to urinary tract infection (UTI). DM has a number of harmful effects on urinary system. The precise causative factors have not been established yet but multiple factors have been suggested to play vital role in its pathogenesis like high glucose levels in urine[1] improving the growth of the virulent organisms in the urine,[2] increased bacterial adherence to uroepithelial cells due to hyperglycemia,[3] neurogenic bladder due to diabetic neuropathy resulting in longer retention of urine resulting in increased probability of infection[4] and angiopathy resulting in impairment of host immune system.[2] Additionally advanced age has been widely accepted as a risk factor for patients with type 2 diabetes mellitus.

The reported prevalence of UTI in diabetic patients in UK is 46.9 per 1,000 person-years among diabetic patients[5] while it is 51% in Pakistan.[6] E.Coli is the most common pathogen causing urinary tract infection in diabetics.[7] Other causative organisms are proteus, Klebsiella streptococcus and staphylococcus.[8,9] In diabetic patients, UTI is mostly asymptomatic due to high pain threshold of patients and this is the reason why UTI in diabetics mostly lead to severe kidney damage and renal failure.[10] The severity of UTI can cause complications ranging from dysuria to organ damage and sometimes death due to complicated UTI (pyelonephritis).[11] Emphysematous pyelonephritis is almost exclusively an infection of diabetic patients and carries a grave prognosis; papillary necrosis complicates 21% of cases.[12] Therefore, improved control of glycemia with early detection and treatment of symptomatic UTI in diabetics is critical to prevent pyelonephritis and other related complications. The increased risk of UTI among diabetic patients, coupled with the increase in the incidence of type 2 diabetes mellitus worldwide in recent years, may impose a substantial burden on medical costs.[13]

Treatment of patients with UTI in diabetics is often started empirically without doing culture and sensitivity plus high rates of broad-spectrum antibiotics prescription especially by general practioners induce the development of

antibiotic resistant urinary pathogens[14]. This trend has resulted in an increased resistance to most of the commonly used antibiotics like penicillin, and fluoroquinolones. Furthermore, the non-compliance of patients and poor affordability are other reasons for increased antimicrobial resistance. Treatment of UTI should be based upon knowledge of the causative organisms as well as the susceptibility/ resistance pattern. Nevertheless, evolving and ongoing antimicrobial resistance occurrence necessitates regular surveillance of resistance pattern to get better future guidelines regarding evaluation and management.

The antimicrobial resistance especially to uropathogens has increased over the last few decades but this resistance pattern varies from country to country and time to time. However, much information on etiology and resistance pattern of community acquired UTI in Pakistan is not available. Hence, continued local studies are required to identify the uropathogens and their sensitivity patterns. Therefore, this study has been undertaken to determine the frequency of microbiologically confirmed UTI, pattern of causative organisms and their antimicrobial susceptibility in uncontrolled diabetic patients with gross pyuria in our set up.

METHODS

This descriptive cross sectional study was conducted at Department of Medicine, Teaching Divisional Headquarter Hospital KDA Kohat and Qazi Medical Centre, a private Centre at Kohat, Pakistan from January 2015 to December 2015. Ninety six adult diabetic patients (type one and type two DM with random blood sugar level above 200 mg/dl) having gross pyuria (>100 pus cells on urinalysis) irrespective of duration of DM were included in the study. Those patients who had used antibiotics in last 72 hours, patient with documented anatomical abnormalities of the genitourinary tract, patients with previous history of recent hospitalization or operations and pregnant ladies were excluded. Diabetes was diagnosed on basis of the WHO criteria.[15] Patients fulfilling the inclusion criteria were selected through Out Patient Department and Medical ward. Each patient had full documentation of history and physical examination. Approval from the ethical committee was taken and prior informed consent from patients was obtained. Convenient sampling technique was used for the collection of samples and urine of selected patients was sent for culture and sensitivity.

Ten ml of urine sample was centrifuged at 2000g for 5 minutes. The supernatant was discarded and a drop of the deposit was examined microscopically at high magnification for pus cells, red blood cells, epithelial cells, cast, and crystal. Gross pyuria means uncentrifuged urine showing more than 100 pus cells/mm^3 of specimen .UTI was defined as culture showing growth of 10^5 organism/mL and > 5 leucocytes /HPF. The patients were educated how to collect clean catch midstream urine in a sterile container which was later sent to hospital laboratory for culture and sensitivity where it was processed within 2 hour. Then gram staining was carried out by putting one drop of uncentrifuged well mixed urine on a glass slide free of grease. Twenty fields were examined under oil immersion lens. Significant bacteriuria was labeled when there were ≥1 bacteria per oil immersion field. A loop full of uncentrifuged urine was streaked on the surface of Maconkey medium. This was incubated at 37°C for 24 to 48 hours aerobically and then colony forming unit (CFU) was determined per ml of urine. The microorganisms' species were identified by standard biochemical tests.[16] More than one different microorganisms present in the sample of urine was considered to be contamination. Those culture reports were considered positive who had colony forming units more than 10^5/ ml of voided urine. Antibiotic sensitivity pattern was also performed on cases showing significant bacteriuria. Isolates were tested for antimicrobial sensitivity testing by the standard Kirby Bauer's disc diffusion method.[17]

Dried filter paper discs with specific concentration of antibiotics were used following the definition of the Committee of Clinical Laboratory International Standards (CLIS, 2014). Commonly used Antibiotic were tested including Piperacillin plus Tazobactum (Tazocine), Cefoperazone plus Salbactum (Sulzone), Ceftriaxone (Rocephin), Amoxicilin+ Clavulanic acid (Augmentin), Norfloxacin (Noroxin), Nalidixic Acid (Negram), Ciprofloxacin (Ciproxin), Cefotaxime (Claforan), Ceftazidime (Fortum), Amikacin (Gracil) Gentamycin and Tigecycline.

Data was collected prospectively on a structured proforma and statistical analysis was done using SPSS version 17.0.

RESULTS

Out of 96 patients 30 (31.25%) were males and 66(68.76%) were females with male to female ratio of 1:2.27. The most common affected age group was 50-60 years. The age and sex distribution of the patients is shown in Table I. Mean Glycosylated hemoglobin (HbA1c) was found to be 8.03±1.41 % in the study. The rest of the observed characteristics of the studied patients are depicted in Table II. Out of total 96 patients, 80 (83.33%) were with positive urine culture while in 16(16.67 %) cases no significant growth of any microorganism was obtained. The frequency rate of microbiologically positive UTI was 83.33% (Table III). The commonest organism isolated from urine culture was E.Coli 68(85%). The frequency of the rest of the isolated organisms is shown in figure 1. E.Coli was found to be 100% sensitive to Tazocine and Imipinem; but 100% resistant to Norfloxacin, Nalidixic acid, Ciprofloxacin. The most sensitive antibiotics for Proteus were Imipinem (90%), Cefoperazone + Salbactum (80%) and Ceftazidime (75%). Klebsiella showed maximum resistance to Norfloxacin (87%), Nalidixic acid (65.2%) and Cefixime (61%) and sensitive to Imipinem (95%), and Ceftazidime (80%) as given in table IV.

TABLE I: AGE AND SEX DISTRIBUTION OBSERVED IN DIABETICS WITH GROSS PYURIA (n=96)

Age group	Total (n=96)		Females (n=66)		Males (n=30)		Type I Diabetes Mellitus (n=8)		Type 2 Diabetes Mellitus (n=88)	
	Frequency	%age	Frequency	%age	Frequency	%age	Frequency	%age	Frequency	%age
19-29 years	12	12.5	8	12.12	4	13.33	4	50	8	9.09
30-49 years	24	25	17	25.75	7	23.33	2	25	22	
50-60 years	40	41.66	28	42.42	12	40	2	25	38	43.18
61-70 years	20	20.83	13	19.69	7	23.33	Nil	0	20	22.72

TABLE II: CHARACTERISTICS OF THE STUDY SUBJECTS (n=96)

Characteristics		Total number of patients
Age	Mean age (years ±SD)	51.156+12.54
Gender	M: F ratio	1:2.2
Type of diabetes	Type I	8 (8.33%)
	Type 2	88 (91.66)
Duration of diabetes	(years±SD)	6.62 ±3.59
Patients seen in OPD		70(72.91%)
Patients seen in ward		26(27.08%)
Lab investigations	Serum creatinine (mg /dl ±SD)	1.56 ±0.43
	Mean Hba1c (%±SD)	8.03±1.41
Therapy (number)	Insulin	30 (31.25%)
	Oral antidiabetics	50 (52.08 %)
	Insulin plus oral diabetics	16(16.66%)

TABLE III: FREQUENCY OF MICROBIOLOGICALLY CONFIRMED UTI IN DIABETICS WITH GROSS PYURIA (n=96)

Urine culture report	Type 2 Diabetes Mellitus (n=88)		Type I Diabetes Mellitus (n=8)		Total (n=96)	
	Frequency	%age	Frequency	%age	Frequency	%age
Positive	74	84.09	6	75	80	83.33
Negative	14	15.90	2	25	16	16.66

TABLE IV: OVER ALL SENSITIVITY/RESISTANCE PATTERN OF E.COLI TO VARIOUS ANTIBIOTICS

Tested Antibiotic	Sensitivity		Resistance	
	Frequency	%age	Frequency	%age
Piperacillin plus Tazobactum	80/80	100	Zero	Zero
Cefoperazone plus Salbactum	56/80	70	Zero	Zero
Ceftriaxone	15/80	18.75	65/80	81.25
Amoxicilin+Clavulanic acid	12/80	15	68/80	85
Norfloxacin	Zero	Zero	80/80	100
Nalidixic Acid	Zero	Zero	80/80	100
Ciprofloxacin	Zero	Zero	80/80	100
Moxifloxacillin	Zero	Zero	80/80	100
Cefotaxime	7/80	6.7	73/80	91.25
Ceftazidime	16/80	20	24/30	80
Gentamycin	3/80	3.76	77/80	96.25
Amikicin	45/80	53.3	35/80	30
Imipinem	77/80	96.25	—	—
Tigecycline	15/80	18.75	65/80	81.25

DISCUSSION

It has been generally observed that patients with diabetes mellitus are more susceptible to infections. Urinary tract infection results from the ascension of the fecally derived organisms from periurethral tissues to the bladder and kidneys. These adhere to the bladder receptor sites and if they possess the virulence factors for pyelonephritis they ascend the ureter in the continuous film of urine that coats the ureter to reach the kidneys. These bacteria elicit an inflammatory response stimulating release of cytokines and other pro–inflammatory substances.[18] UTI in diabetics is more common due to a combination of host and local risk factors. Urine may be inhibitory or even bactericidal in some conditions. Any change in chemical composition of urine in diabetic patients can change the capability of urine and thus facilitate the microbial growth. Moharam et al. in a recently published article showed an increased risk of UTI in diabetics having risk factors like female sex (relative risk) (RR 6.1), hypertension (RR 1.2), insulin therapy (RR 1.4), body mass index (BMI) .30 kg/m_2 (RR 1.72), and nephropathy (RR 1.42).[19]

In present study we have observed frequency of microscopically proven UTI is 80 (85%). Huma et al reported frequency of 60.82% in a study conducted in 97 diabetic pyuric patients with good glycemic control.[20] In another study Sewify M et al.[21] observed frequency rate of 78.17% in a study of 197 diabetics patients with poor glycemic control but no gross pyuria. This high figure could be explained on basis of our selection criteria that is diabetic patients with poor glycemic control and all were gross

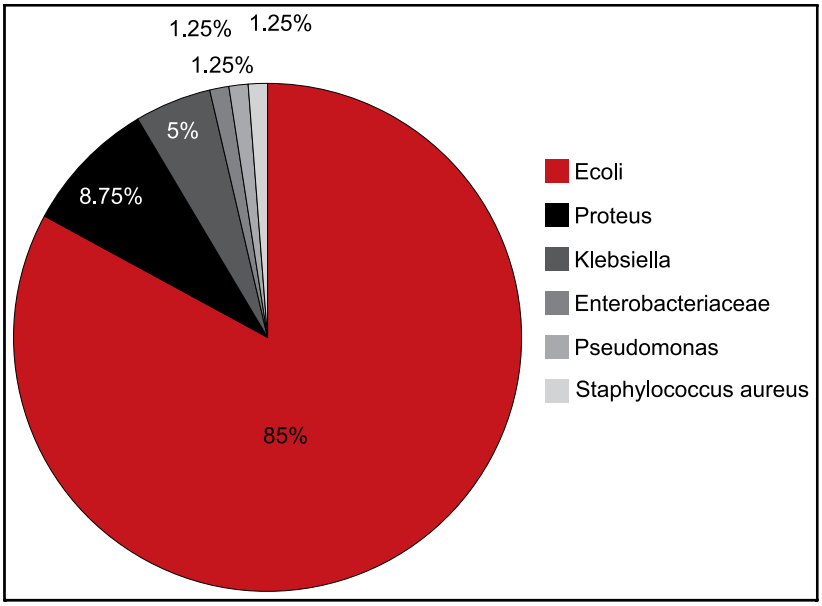

Figure 1: Pie chart showing Pattern of Uropathogens in diabetics with gross pyuria (n=80)

pyuric on urine routine examination as gross pyuria increases the chances of finding significant bacteriuria. These results highlight the importance of controlling glycaemia in diabetic patients to reduce the UTI regardless of age and gender. Furthermore about 80% of our cohort comprised of females and UTI is more prevalent in females as compared to males.

A good glycemic control helps in decreasing the frequency of urinary tract infection in diabetics. While Brauner A et al.[22] reported that the frequency of urinary tract infection in diabetic and non-diabetic females is almost equal. In his study, HbA1C was the criteria to see glycemic control, which is a very dependable tool for determining the glycemic control over the previous three months period. Therefore, improved control of glycaemia with early detection and treatment of symptomatic UTI in diabetics is critical to prevent pyelonephritis and other related complications.

The commonest organism isolated from urine culture in our study was E.Coli. It was isolated in 68 (85%) of cases. Proteus mirabilis was found in 5(8.75%), Klebsiella aerogenes in 4 (5%), pseudomonas, Staphylococcus aureus and Enterobacteracea in 1(1.25%) patient each. These results are comparable to those shown by Samreen et al[23] and Simkhada[24]. Literatures show that E.Coli is found to be the main culprit in 70 to 90% of such cases.[25,26] Furthermore, diabetics with poor glycemic control are more prone to have resistant pathogens as the cause of their UTI, including extended-spectrum β-lactamase-positive (ESBL) bacteria.[27] Infection with Proteus, Klebsiella and Staphylococcus aureus are not frequently seen apart in those with hospitalization, instrumentation, surgery, or prior antibiotic exposure. It is probable that structural changes in the urinary tract on account of previous infection could prejudice these patients such infection.

Isolated E.Coli were found to be 100% sensitive to piperacillin plus tazobactum and Imipinem; and 100% resistant to Norfloxacin, Nalidixic acid, Ciprofloxacin and Moxifloxacin. These findings are in consistent with other local and international studies.[6,23-24] Tazocine and Meronem proved to be the most effective antibiotics followed by Cefoperazone plus Salbactum and Amikacin.[28] Similar resistance to Ciprofloxacin[29], Ceftriaxone[30] and Nalidixic acid[31] has also been reported by other researchers. Nowadays the antimicrobial resistance is a serious universal issue and it has invariably been resulted from widespread use of antibiotics.[32] Furthermore, blind use of broad spectrum antibiotics by the quacks due to their low cost, easy administration for the empiric treatment of suspected infection, multiple courses of antibiotic therapy that are administered to these patients, frequently for asymptomatic or only mildly symptomatic UTI. So judicious use of antibiotics will help to reduce the antimicrobial resistance and will have favorable effect on patient centered outcome and health related expenditures.

The limitations of our study are small sample size and sampling of convenience type. Furthermore well designed studies are required to study association of UTI with glycemic control of DM in lager diabetic population. Moreover, continued surveillance of resistance rates and patterns of Uropathogens is desirable to guarantee suitable recommendations for the treatment of UTI in diabetics.

CONCLUSION

Diagnostic yield of urine culture and sensitivity in uncontrolled diabetic patients with gross pyuria was 83.33%. Escherichia coli were found to be the most predominant isolate, showing high drug resistance particularly to naladixic acid, ciprofloxacin and norfloxacin.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTION

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

SFS: Conception and design, acquisition of data, drafting the manuscript, final approval of the version to be published

SAP: Analysis and interpretation of data, drafting the manuscript, critical review, final approval of the version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.