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COMPARISON OF PATTERN OF ANTIBIOTIC THERAPY AND RECURRENCE OF URINARY TRACT INFECTIONS IN WOMEN WITH AND WITHOUT DIABETES MELLITUS

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ABSTRACT

This study was planned with the objectives of evaluating the pattern of antimicrobials used for UTI and to determine the recurrence rate of UTI in diabetic and nondiabetic women in our settings. New diagnosis of UTI is defined as a patient with no prescription for UTI in the history (for 1 year) and a first prescription for UTI in the study period. A recurrent UTI was defined as a prescription for UTI in the follow-up period (5 days after the first prescription until 30 days after the end of the first prescription) or hospitalization admission with the diagnosis of a UTI. Among 220 patients, 106(48.18%) had recurrence. Out of these patients, 74 were diabetics (74%) and the remaining were nondiabetics (26.67%). Recurrent UTI was more frequent in diabetics of above 50 years group. Duration antimicrobial therapy was significantly longer in diabetics. Most commonly used antibiotic group is cephalosporins in both diabetics as well as non-diabetics.

Key words: UTI, antibiotics, recurrence, bacterial resistance, diabetes mellitus.

INTRODUCTION

Urinary tract infection (UTI) is the most common bacterial infection encountered in clinical practice.[1] Approximately half of all women have at least one symptomatic UTI during their lifetime.[2] Relapse or reinfections are also a major concern. Many women experience relapses or reinfections of the lower urinary tract even after treatment with broad-spectrum antibiotics.[3] Diabetes has been associated with an increased risk of UTI due to various predisposing factors, such as hyperglycemia related impairment of the immune response and glucosuria.[4,5] A Dutch study showed that despite the fact that patients with diabetes more often received longer and more potent initial treatment than patients without diabetes, women with diabetes more often had recurrences of UTIs.[6] Despite guidelines/recommendations for the optimal selection of an antimicrobial agent and duration of therapy for UTI, studies demonstrate a wide variation in prescribing practice.[7,8] In clinical practice, empirical therapy is prescribed either without a urine culture and susceptibility testing or before such result is known. Clinical trials demonstrating the optimal antibiotic therapy for UTIs in diabetic patients are scanty. Current antibiotic recommendations for UTIs based on the expert's opinion. Since the resistance patterns of microbial causing uncomplicated UTI vary considerably between regions and countries, a specific treatment recommendation may not be universally suitable for all regions or countries.[6,9] With the increase in the incidence of type 2 diabetes mellitus, there is a chance for increased risk of UTI among these patients adding economical burden.[10] High rates of irrational antibiotic prescription for UTI

in these patients may lead to the development of bacterial resistance to most valuable antibiotics. Since the pattern of bacterial resistance varies in different regions, there is a need to gather data on pattern of antibiotic use and response to therapy in UTIs in different regional settings. This study was planned with the objectives of evaluating the pattern of antimicrobials used for UTI and to determine the recurrence rate of UTI in diabetic and nondiabetic women in our settings.

MATERIALS AND METHODS

This retrospective medical record based study was conducted at a tertiary care teaching hospital in South India. The study was conducted after getting approval from the Institutional ethics committee. All women aged ≥18 years with and without diabetes with at-least one episode of UTI were included in the study.

The following patients were excluded from the study:

- Pregnancy
- Patients with known anatomical abnormalities, indwelling urinary catheter
- Patients on antiretroviral therapy, immune suppressive drugs, chemotherapy during UTI and in the last 1 year
- Patients receiving a first prescription with duration of >30 days.
- Patients with a second prescription within 5 days after their first prescription
- Women with complicated UTI [defined as pyelonephritis or as infections with an invasive systemic presentation)[19]

Data was collected from the medical record department for the period of 2010 January to December 2014. All diagnoses were coded according ICD-10 which enabled us to identify patients with UTIs. The entry date into the study was the day that the patient received her first prescription for UTI. The history period was 1 year before study inclusion. Patients with diabetes were defined by prescription of one or more antidiabetic agents in the history.

New diagnosis of UTI is defined as a patient with no prescription for UTI in the history (for 1 year) and a first prescription for UTI in the study period. A recurrent UTI was defined as a prescription for UTI in the follow-up period (5 days after the first prescription until 30 days after the end of the first prescription) or hospitalization admission with the diagnosis of a UTI. These recurrences could be relapses (second infection with the same organism) or reinfections (second infection with a different organism). Hence, recurrent UTI is considered if there is prescription for UTI within 6 to 30 days of the 1st episode.

Statistical Analysis: The clinical characteristics of the study population were calculated as proportions or means (±SD). The pattern of antibiotic prescription was presented as a categorical variable for first or recurrent episodes of UTI. Antibiotic use and the recurrence rate were compared between women with and without diabetes. Analyses were done with a chi square test for categorical variables and student 't' test for continuous variables. Subgroup analyses were done by categorizing the patients into different age strata. A *P*-value <0.05 was considered to indicate statistical significance.

RESULTS

A total of 220 patients was included in the study. Among them, 120 were nondiabetics and 100 were diabetics. The mean age of diabetics was 58.51±12.11 years, whereas in nondiabetics 39.19±14.44 years. In diabetics, majority of the patients were above 60 years, whereas in diabetics majority were between 31-40 year(table 1). Table 2 shows the distribution of patients with recurrent UTIs. Among 220 patients, 106(48.18%) had recurrence. Out of these patients, 74 were diabetics (74%) and the remaining were nondiabetics (26.67%). Recurrent UTI was more frequent in diabetics of above 50 years group. In nondiabetics also, recurrence was more in patients above the age of 60 years.

The urine culture reports were negative in 78% of diabetic patients and 95% of nondiabetics. The positive urine cultures showed *E.coli* in most cases (table 3). Most commonly used antibiotic group is cephalosporins in both diabetics as well as non-diabetic. There was statistically significant difference between the two groups in the use of cephalosporins, fluroquinolones, carbapenems and nitrafurantoin. The use of cephalosporins and carbapenems was more in diabetics compared to nondiabetics. Similarly, fluroquinolones and nitrofurantoin was more often used in nondiabetics than diabetics.

Among the diabetics, 20 patients received a combination of two antibiotics, whereas 26 (21.7%) of nondiabetic patients received a combination of two antibiotics. Fluroquinolones were used in the combination only in nondiabetic patients, whereas carbapenems, clindamycin and azithromycin were used as a combination, only in diabetic patients.

Table 5 shows the type of cephalosporins used. Cefaperazone in combination with sulbactum was the most commonly used cephalosporin followed by cefotaxime in both the groups.
Table 6 shows the type of penicillins and fluroquinolones used. Ciprofloxacin is the most commonly used fluroquinolones followed by ofloxacin and norfloxacin. Among the penicillins, piperacillin in combination with tazobactum was most commonly used.

Duration antimicrobial therapy was 6.62±3.36 days in non diabetics whereas it is 8.14±3.53 days in diabetic women, the difference being statistically very significant ($p<0.001$, student 't' test). The patients who had recurrent UTI have received a longer duration of antimicrobial therapy compared to those who did not have recurrent UTI (7.82±3.6 days *vs* 6.83± 3.37 days), the difference is statistically significant ($p=0.037$). When duration of therapy was compared between two groups after categorizing as short (>5 days) and long(>5days), a higher proportion of diabetic women received long duration of therapy when compared to their nondiabetic counterparts (80% vs 61.7%), the difference being statistically significant ($p=0.003$, X^2 test).

Table 7 shows the comparison of glycaemic parameters in diabetic with and without recurrent UTI. Though the HbA1c and postprandial blood sugar were higher in patients with recurrent UTI, the differences were statistically not significant. The fasting blood sugar was higher in patients without recurrent UTI, but again the difference was statistically not significant.

DISCUSSION

Urinary tract infection is one of the common infections seen in women, especially in the presence of diabetes mellitus. Most often uncomplicated UTI is treated empirically without the evidence of susceptibility of causative agent to antibiotics used. The present study was aimed at comparing the pattern of antibiotic use and the recurrence rate among women with and without diabetes mellitus.

The present study showed that the prevalence of UTI is more in the age group of 20-40yeras in nondiabetics whereas in diabetics, the majority of patients with UTI were above 50 years. This observed difference, obviously due to the fact that the UTI is more common in sexually active age group and the number of diabetic patients in this age group is much less compared to nondiabetic group. In the age group of above 40 years, there were more diabetics than nondiabetics, suggesting a higher prevalence of UTI in diabetic women. Epidemiological studies have shown that UTI is more common in diabetic females than their nondiabetic counterpart.[11] High glucose levels in the renal parenchyma favours the growth and multiplication of microorganisms. Impairment in the immune system also contributes to the growth of microorganism. Autonomic neuropathy leading to dysfunctional bladder voiding and retention of urine enhances the risk of UTI due decreased physical clearance of microorganism through micturition.[12]

Geerlings SE, et al suggested to consider UTI as a complication in women with diabetes based on the higher prevalence asymptomatic bacteriruria in diabetic women observed in their studies.[13] Similar observations were seen in another study conducted in Iranian population. The authors of this study recommended routine urine culture for diabetic women even when there is no urinary symptom.[14]

The diagnosis of UTI is primarily based on signs and symptoms rather than isolated laboratory findings. Urine cultures may not be useful for acute uncomplicated cystitis, but recommended for patients with uncomplicated pyelonephritis and complicated UTI. [15] In accordance with this fact, our findings also shown that in the majority of the patients of both groups, the urine culture was negative and the diagnosis of UTI is based on clinical symptoms and the routine urine analysis. Hence, most of the patients received empirical antimicrobial treatment.

The most commonly used antimicrobials were cephalosporins in both diabetics and nondiabetics. Fluroquinolones are less commonly used in diabetics when compared to their nondiabetic counterparts. As a general rule, treatment of UTI in diabetic patients is similar to that of UTI in non-diabetic patients. The antibiotic choice should be guided by local susceptibility patterns of uropathogens. Nitrofurantoin, cotrimoxazole, fosphomycin are used as first line agents for acute cystitis;cirpfloxacin, ofloxacin,gentamicin, cefuroxime are used for uncomplicated pyelonephritis;ciprofloxacin, oofloxacin, gentamicin,amikacin, piperacillin-tazobactum, ertapenem used for complicated pyelonephritis. [16]

The present study showed that the selection of antimicrobials was largely according to the guidelines. However, cefoperazone was the most commonly used cephalosporin against the recommended cephalosporin i.e, cefuroxime. Around 20% of our patients in both the groups, received a

combination of two antibiotics. The most appropriate antibiotic should be selected for the empirical treatment of UTI. The empiric prescribing of broad spectrum agent or use of combination of antibiotic to broaden the spectrum should be avoided to reduce the selection of resistant bacteria. Moreover, critically important antibiotics,such as carbapenems, aminoglycosides should be restricted to the most severe infections and always be preceded by a susceptibility test. In our study, 6% of diabetics received these antibiotics. Due to the increasing prevalence of antibiotic- resistant bacteria, particularly the extended spectrum beta-lactamase producing gram-negative bacteria, it is crucial to avoid antibiotic overprescribing.

The majority of our patients were on parenteral antibiotics. Pyelonephritis in diabetic patients may be treated with oral antibiotics in patients with mild–moderate symptoms, with no alterations in gastrointestinal absorption. However, diabetic patients with severe symptoms, hemodynamic instability, metabolic disturbances should be hospitalized for initial intravenous antibiotic therapy and those with severe sepsis or known to be having a UTI with resistant bacteria should receive broad-spectrum coverage. Treatment should be modified when culture results are available. [12]

Our study showed that diabetic women had received a longer duration of antimicrobial therapy for their UTI when compared to nondiabetic women. The recommended duration of antibiotic treatment for UTI is similar to that of non-diabetic patients (upto 7 days for uncomplicated UTIs and 10-14 days for complicated UTIs). For the treatment of uncomplicated cystitis, short-course regimens (single dose to 5 days) are recommended as first-line therapy and are as effective as longer antimicrobial regimens.[12,17]

Though some argue that patients with diabetes mellitus should receive longer antibiotic treatment than patients without diabetes mellitus, randomized controlled trials are lacking.[18]

Despite receiving longer duration of treatment as well as critically important antibiotics, the recurrence rate of UTI was higher in diabetics than nondiabetics. Schneeberger C, et al also reported higher recurrence rate of UTIs in diabetic women. [6] However, Raz R, et al did not find diabetes as a risk factor for recurrent UTI in postmenopausal diabetic women.[19] Our findings did not suggest a correlation between recurrence rate of UTI and glycaemic control. Several studies did not find an association between glycaemic control and UTI in diabetics.[20,21]

CONCLUSIONS

The UTI in diabetics is more common above the age of 50 years. Parenteral cephalosporins were the most commonly used antibiotic irrespective of diabetic status. The diabetic patients received a longer duration of treatment than nondiabetics. The recurrence rate of UTI is more in diabetics. There was no correlation between glycaemic control and recurrence rate of UTI in diabetic females.

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Table 1 Agewise distribution of patients

Age group (years)	Diabetics n(%)	Nondiabetics n(%)	Total n (%)
>20	2 (2)	4 (3.3)	6 (2.7)
21-30	0 (0)	34 (28.3)*	34 (15.5)
31-40	6 (6)	35 (29.2)*	41 (18.6)
41-50	16(16)	26 (21.7)	42 (19.1)
51-60	32 (32)	9 (7.5)*	41 (18.6)
> 60	44 (44)	12 (10)*	56 (25.5)
Total	**100**	**120**	**220**

X^2 test ***p<0.0001**

Table 2: Distribution of patients with recurrent urinary tract infections

Age group (years)	**Diabetics n(%) N=100**	**Nondiabetics n (%) N=120**	**Total n (%) N=220**
>20 (n=2, 4)	0 (0)	0 (0)	0 (0)
21-30 (n=0, 34)	0 (0)	3 (8.8)	3 (8.8)
31-40 (n=6, 35)	3 (50)	8 (22.9)	11 (26.8)
41-50 (n=16, 26)	8(50)	8 (30.8)	16 (38.1)
51-60 (n=32, 9)	27 (84.4)	4 (44.4)*	31 (75.6)
> 60 (n=44, 12)	36 (81.8)	9 (75)	45(80.4)
Total (n=100, 220)	74 (74)	32 (26.67)*	106 (48.18)

X^2 test *p<0.0001

Table 3: Urine culture reports

Patient groups	No growth n (%)	Growth of *E.coli* n (%)	Growth of *Klebsiellae* n (%)
Diabetics (n=100)	78 (78)	21 (21)*	1 (1)
Non-diabetics (n=120)	114 (95)	5 (4.2)	1 (0.8)
Total	192 (87.27)	26 (11.81)	2 (0.91)

Table 4: Pattern of antimicrobial used

Antimicrobial class	Diabetics n(%)	Non-diabetics n(%)	Total n(%)
Fluroquinolones	7 (7)	38 (31.7)**	45(20.5)
Cephalosporins	67(67)	41(34.2)*	108(49.1)
Penicillins	9 (9)	9(7.5)	18 (8.2)
Tetracyclines (doxycycline)	1 (1)	4(3.3)	5(2.3)
Carbapenems	5 (5)	0*	5 (2.3)
Cotrimoxazole	8 (8)	11 (9.2)	19 (8.6)
Aminoglycosides (amikacin)	1 (1)	0	1 (0.5)
Nitrofurantoin	1 (1)	11 (9.2)*	12 (5.5)
Macrolides (Azithromycin)	1 (1)	2 (1.7)	3 (1.4)
Clindamycin	0	4 (3.3)	4 (1.8)

Table 5: Type of cephalosporins used

Type of cephalosporins	Diabetics n(%)	Non-diabetics n(%)	Total n(%)
Cefaperazone+sulbactum	34 (34)	14 (11.7)	48(21.82)
Cefotaxime	13 (13)	10 (8.3)	23(10.46)
Ceftazidine+tazobactum	3(3)	1 (0.8)	4(1.82)
Cefuroxime	2 (2)	3(2.5)	5(2.27)
Cefixime+clavulanic acid	4 (4)	4(3.3)	8(3.64)
Ceftriaxone+tazobactum	11 (11)	7 (5.8)	18 (8.18)
Cefpodoxime+clavulanic acid	1 (1)	1 (0.8)	2 (0.91)

Table 6:Type of penicillins and fluroquinolones used

Type of penicillins/ fluroquinolones	Diabetics n(%)	Non-diabetics n(%)	Total n (%)
Amoxicillin	2 (2)	1 (0.8)	3 (1.36)
Piperacillin+tazobactum	5 (5)	6 (5)	11 (5)
Ampicillin	0	1 (0.8)	1 (0.46)
Cloxacillin	1 (1)	0	1 (0.46)
Norfloxacin	2 (2)	9 (7.5)	11 (5)
Ofloxacin	0	11 (9.2)	11 (5)
Ciprofloxacin	4 (4)	18 (15)	22 (10)
Sparfloxacin	1 (1)	0	1 (0.46)

Table 7: Comparison of glycaemic parameters in diabetic with and without recurrent UTI

Glycaemic parameters	Patients with recurrent UTI	Patients without recurrent UTI
HbA1c (%)	9.84±2.20	9.47±1.69
Fasting blood sugar (mg/dl)	170.63±79.93	205.26±68.61
Post prandial blood sugar (mg/dl)	266.42±109.92	258.50±85.58

REFERENCES

1. Platt FW, Keating KN. Int J Clin Pract. 2007;61(2):303-8.
2. Engel JD, Schaeffer AJ. Urol Clin North Am. 1998; 25(4):685-70.
3. Norinder B S, Norrby R, Palmgren A C, Hollenberg S, Eriksson U, Nord C E. Antimicrob Agents Chemother. 2006;50(4):1528-30.
4. Foxman B. Am J Med. 2002;113 Suppl 1A:5S-13S.
5. Stapleton A. Am J Med. 2002; 113 Suppl 1A:80S-84S.
6. Schneeberger C, Stolk RP, Devries JH, Schneeberger PM, Herings RM, Geerlings SE. Diabetes Care. 2008;31(7):1380-5.
7. Kahan NR, Chinitz DP, Kahan E. Journal of clinical pharmacy and therapeutics. 2004;29(1):59–63.

8. Kallen AJ, Welch HG, Sirovich BE. Archives of internal medicine. 2006; 166(6):635–9.
9. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG et al. Clin Infect Dis. 2011;52(5):e103-20.
10. Yu S, Fu AZ, Qiu Y, Engel SS, Shankar R, Brodovicz KG et al. J Diabetes Complications. 2014;28(5):621–6.
11. Patterson JE, Andriole VT. Infect Dis Clin North Am. 1995; 9 (1): 25-51.
12. Nitzan O, Elias M, Chazan B, Saliba W. Diabetes Metab Syndr Obes. 2015; 8: 129–36.
13. Geerlings SE, Stolk RP, Camps MJ, Netten PM, Hoekstra JB, Bouter KP et al. Diabetes Care. 2000;23(6):744-9.
14. Boroumand MA, Sam L, Abbasi SH, Salarifar M, Kassaian E, Forghani S. BMC Womens Health. 2006;6:4.
15. Abbo LM, Hooton TM. Antibiotics. 2014; 3:174-92.
16. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG et al. Clin Infect Dis. 2011; 52: e103–e120.
17. Hooton, T.M. Clinical practice. N Engl J Med. 2012; 366(11):1028–37.
18. Geerlings SE. Int J Antimicrob Agents. 2008;31(Suppl 1):S54–7
19. Raz R, Gennesin Y, Wasser J, Stoler Z, Rosenfeld S, Rottensterich E et al. Clin Infect Dis. 2000;30(1):152-6.
20. Boyko EJ, Fihn SD, Scholes D, Abraham L, Monsey B. Am J Epidemiol. 2005;161(6):557–64.
21. Boyko EJ, Fihn SD, Scholes D, Chen CL, Normand EH, Yarbro P. Diabetes Care. 2002;25(10):1778–83.