ORIGINAL ARTICLE

Urinary tract infections in postmenopausal women with type 2 diabetes: clinical correlates and quinolone susceptibility

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KEY WORDS

antibiotics, diabetes mellitus, menopause, pyelonephritis, urinary tract infections

ABSTRACT

INTRODUCTION Diabetes mellitus and the postmenopausal period are associated with increased risk of urinary tract infections (UTIs) in women. However, data on UTIs in postmenopausal diabetic women are scarce.

OBJECTIVES The aim of this study was to determine the prevalence of UTIs in postmenopausal women with type 2 diabetes mellitus, identify the potential risk factors, describe the causative pathogens, and assess their susceptibility to quinolones.

PATIENTS AND METHODS Patients were interviewed, examined, and had their hospital records analyzed. An uncontaminated midstream urine sample was collected and cultured in selective or enriched media. Colony-forming units were counted and susceptibility to quinolones was assessed. Univariate and multivariate logistic regression models were built.

RESULTS Forty women were included in this prospective cross-sectional study; their median age was 64 years (range, 52–84 years). UTIs occurred in 37.5% of the patients. The major implicated pathogens were *Escherichia coli* (66.7%) and enterococci (20%; most often *Enterococcus faecalis*). Most of the pathogens (93.8%) were susceptible to all tested quinolones. Patients with UTIs had a significantly lower glomerular filtration rate ($P = 0.008$) and higher comorbidity index ($P = 0.01$) compared with patients with sterile urine. Microangiopathic complications, including retinopathy and nephropathy, were identified as independent risk factor for UTIs (adjusted odds ratio, 3.5; 95% CI, 1.2–5.5; $P = 0.006$). The other clinical correlates of UTIs were urinary incontinence, hyperlipidemia, and microalbuminuria.

CONCLUSIONS Postmenopausal diabetic patients with microangiopathy are at high risk of UTIs and therefore should be educated and vigilantly monitored. Attention should also be paid to urinary incontinence, hyperlipidemia, and microalbuminuria as other risk factors for UTIs. Quinolones are an attractive treatment option in this group of patients in Poland.

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INTRODUCTION According to the International Diabetes Federation, 415 million adults worldwide have diabetes. Its global prevalence is expected to rise from 8.8% today to 10.4% in 2030.[1] In 90% of cases, type 2 diabetes mellitus is diagnosed. The most common of all complications caused by bacteria in type 2 diabetes are urinary tract infections (UTIs).[2,3] Compared with patients without diabetes, the risk for UTIs in diabetes is increased 3-fold[4] and for pyelonephritis—4-fold.[5]

Not only UTIs in diabetes are more frequent, but also their course is more often complicated.[6,7] They may lead to acute papillary necrosis, emphysematous pyelonephritis, bacteremia with metastatic localization to other sites,[8,9] and also increased morbidity.[3] It was shown that both the female anatomy and postmenopausal status predispose to UTIs in diabetes.[10] Also antihyperglycemic sodium-glucose cotransporter-2 inhibitors, which are currently widely used, may increase the risk of such complications.[11] However, many questions concerning the pathogenesis and the best therapeutic management of this condition are still unanswered, and the results of the very few previous studies remain conflicting.[10,12] Therefore, in our study, we aimed to: 1) determine the prevalence of UTIs; 2) identify the causative pathogens; 3) assess their antimicrobial susceptibility, and 4) establish the risk factors for UTIs in this population. This was to inform the reevaluation of guidelines for treatment and prevention of this complication of diabetes.

PATIENTS AND METHODS

Setting, inclusion, and exclusion criteria We prospectively analyzed consecutive postmenopausal inpatients and outpatients of the Department of Internal Medicine, Metabolic Disorders and Hypertension at Poznan University of Medical Sciences, Poznań, Poland. In all of them, type 2 diabetes was diagnosed according to the criteria of the World Health Organization Expert Committee on the Diagnosis and Classification of Diabetes Mellitus revised in 2013.[13] The exclusion criteria were as follows: antibiotic therapy in the last 3 months, asymptomatic bacteriuria, renal insufficiency, anatomic genitourinary abnormalities, and catheterization.

Ethical approval The study was approved by the Bioethical Committee at Poznan University of Medical Sciences and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Study design and methods We performed the clinical evaluation of patients and bacteriological examination of their urine samples. Patients were interviewed using a structured questionnaire regarding the age, the course of diabetes, its treatment and complications, comorbidities, clinical symptoms of UTI, and the list of risk factors for UTI. Comorbidities were medically confirmed or self-reported; the Charlson comorbidity index was calculated.[14] The lifestyle-related risk factors included, among others, smoking, physical inactivity, and the lack of implementation of dietary guidelines.

A standard physical examination was conducted and the medical records were analyzed. Blood was drawn on inclusion in the study. An uncontaminated midstream urine sample was collected by each woman and then cultured in selective or enriched media. The patients were adequately instructed to collect their urine samples.

In a quantitative bacteriological study, the colony-forming units (CFUs) were counted. Antimicrobial susceptibility or resistance was tested by the Kirby–Bauer disk diffusion susceptibility test and evaluated in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.[15]

Study parameters A lower UTI (acute cystitis) was defined as the presence of a positive urine culture accompanied by urinary symptoms related to the bladder or kidneys[16] and included the occurrence of 10^3 CFUs/ml or more of a urinary pathogen in a specimen. The symptoms of UTI were defined as the presence of complaints of dysuria, frequency of urination, urgency of urination, and/or abdominal discomfort.[6] An upper UTI (pyelonephritis) was defined as the above complaints and/or presence of fever (>38.3°C) and flank or low back pain.[17] Hereinafter, UTI refers to both lower and upper UTI.

Statistical analysis To compare differences between the groups, we used the χ^2 test or Fisher exact test, as appropriate, for categorical variables. Interval data were compared with the use of the Mann–Whitney test, unpaired samples *t* test, or unpaired samples *t* test with the Welch's *t* test, as appropriate. The Levene's test was used to verify the homogeneity of variances of the continuous data in the 2 study groups.

To evaluate the potential risk factors that might influence the occurrence of UTIs in postmenopausal patients with type 2 diabetes, we performed univariate logistic regression analyses. They were followed by a backward stepwise multiparametric logistic regression including all variables with a *P* value of less than 0.20 in the univariate analysis. There were no missing data in the study.

A *P* value of less than 0.05 was regarded as significant. Statistical analyses were performed with StatSoft Statistica v10.0 (Statsoft Inc., Tulsa, Oklahoma, United States) and GraphPad InStat v3.02 software (GraphPad Software, San Diego, California, United States).

RESULTS

A total of 52 women agreed to take part in the study, of whom 40 were enrolled. The reasons for exclusion were as follows: antibiotic therapy in the last 3 months (n = 5), asymptomatic bacteriuria (growth of $\geq 10^5$ CFUs/ml in a specimen and absence of symptoms[18]; n = 3), renal insufficiency (glomerular filtration rate <60 ml/min/1.73 m^2; n = 2), hydroureteronephrosis (n = 1), and catheterization (n = 1).

The median age at diagnosis of type 2 diabetes was 64 years (range, 52–84 years) and the median follow-up for type 2 diabetes was 6.5 years (range, 0–26 years). All patients were treated by oral hypoglycemic agents or insulin (or both). Clinical evaluation and bacteriological examination

TABLE 1 Antimicrobial susceptibility and resistance of pathogens identified as the cause of urinary tract infection in the study group

	Susceptibility, %	Resistance, %
Norfloxacin	100	0
Ciprofloxacin	100	0
Ofloxacin	93.75	6.25
Levofloxacin	100	0
Moxifloxacin	100	0
Pefloxacin	100	0
All	93.75	6.25

TABLE 2 Characteristics of the study groups

Parameter	Patients with UTI	Patients without bacteriuria	*P* value[a]
No. (%) of patients	15 (37.5)	25 (62.5)	–
Age, y	64 (52–73)	65 (50–84)	0.07
Time since diagnosis, y	6 (1–27)	12 (1–24)	0.29
Time from the last menstrual period, y	9 (1–19)	11 (1–25)	0.17
BMI, kg/m^2	33.7 (21.8–43.1)	32.7 (23.1–45.4)	0.62
Fasting plasma glucose, mmol/l	7.5 (4.9–11.3)	7.3 (5.4–15.5)	0.59
HbA_{1c}, %	7.2 (6.0–9.1)	7.5 (6.5–10.4)	0.66
White blood cells, G/l	8.9 (4.8–22.0)	7.1 (6.2–8.5)	0.20
GFR[b], ml/min/1.73 m^2	89.5 (60.1–126.3)	143.4 (93.7–175.5)	0.008
Serum creatinine, mmol/l	78.7 (54–113)	68 (51–122)	0.23
Charlson comorbidity index,	2.9 (1–6)	1.9 (1–4)	0.01

Median values (ranges) are shown unless otherwise indicated.

a Mann–Whitney test, unpaired samples *t* test or unpaired samples Welch-corrected *t* test, as appropriate

b estimated using the Cockroft–Gault equation

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range; others, see **TABLE 1**

revealed that 37.5% of the patients (n = 15) met the diagnostic criteria for UTI. Thirty percent (n = 12) had a lower UTI and 7.5% (n = 3) presented the symptoms of pyelonephritis.

The predominant causative pathogen in diabetic patients with UTI was *Escherichia coli* (*E. coli*; 66.7%). The second most common group of microorganisms found in urine samples were enterococci (most often *Enterococcus faecalis*), which occurred in 20% of the patients. Other pathogens found in urine samples were *Proteus mirabilis* (6.7%) and *Streptococcus agalactiae* (6.7%).

TABLE 1 summarizes the results of antimicrobial susceptibility testing, which demonstrated that 93.75% of the pathogens were susceptible to all tested quinolones. No antimicrobial resistance was reported for ciprofloxacin, norfloxacin, levofloxacin, moxifloxacin, and pefloxacin. The resistance for ofloxacin was observed in 6.25% of patients.

To assess the homogeneity of the groups and evaluate the possible risk factors of UTIs, we compared patients diagnosed with UTI with those without bacteriuria (**TABLE 2**). The groups did not differ in age, median duration of diabetes, the time from the last menstrual period, or glycated hemoglobin levels. However, the glomerular filtration rate, estimated using the Cockroft–Gault equation, was significantly lower in patients with UTI when compared with those without bacteriuria (89.5 vs 143.4 ml/min/1.73 m^2, respectively; $P = 0.008$). The Charlson comorbidity index also differed between the groups ($P = 0.02$), with higher values in patients with UTI.

Our analyses revealed possible risk factors for UTI in postmenopausal women with diabetes (**TABLE 3**). The most significant factor was microangiopathy (risk ratio, 4.9; 95% CI, 1.6–14.7; $P = 0.0009$) with its various manifestations: both retinopathy (RR, 2.4; 95% CI, 1.1–5.1; $P = 0.04$) and nephropathy (RR, 3.5; 95% CI, 1.8–6.7; $P = 0.002$).

The patients with urinary incontinence presented a 2.7-fold higher risk of UTI (95% CI, 1.1–6.5; $P = 0.02$). Accordingly, microalbuminuria was associated with 3.1-fold higher risk of UTI (95% CI, 1.9–4.9; $P = 0.04$), while in hyperlipidemia, the risk was 3.9-fold higher (95% CI, 1.0–15.0; $P = 0.02$).

Nevertheless, no significant increase in the risk of UTI was observed for insufficient control of glycemia, measured with hemoglobin A_{1c} (HbA_{1c}). We found no significant correlation between different lifestyle-related risk factors and the presence of UTI and the time from the last menstrual period. Neither diabetes duration nor the type of the treatment was associated with the occurrence of UTI.

Multivariate logistic regression confirmed that the presence of any microangiopathy was the factor most closely associated with UTI (odds ratio, 3.5; 95% CI, 1.2–5.5; $P = 0.0064$) of all included factors (retinopathy, nephropathy, urinary incontinence, microalbuminuria, and hyperlipidemia).

DISCUSSION

The results of our study confirm that UTIs and bacteriuria are common in postmenopausal women with type 2 diabetes, and occur in every 1 in 3 patients. They also indicate that UTIs tend to occur simultaneously with microangiopathy and that in Poland the causative bacteria are most often susceptible to quinolones. This is one of the very few studies conducted on this topic to date.

The prevalence of UTI observed in postmenopausal women with type 2 diabetes in our study is similar to[19-21] or higher[12,22] than that previously reported for type 2 diabetes in general. Apart from the postmenopausal status, the differences in patients' comorbidities and other factors, such as age, may explain the discrepancy. Postmenopausal estrogen loss is known to dysregulate the mechanisms of immunity that should protect against *E. coli* adhesion to vaginal cells.[23] The estrogen loss also makes the walls of the urinary tract thinner and reduces its ability to resist bacteria. As to the diabetes itself, the postmenopausal status may result in other problems

TABLE 3 Clinical characteristics and risk factors for urinary tract infections in the study group

Characteristic or risk factor		Patients with UTI (n = 15), n (%)	Patients without bacteriuria (n = 25), n (%)	RR (95% CI)	*P* value
Duration of diabetes ≥5 years		7 (47)	16 (64)	0.6 (0.3–1.4)	0.34
Age >60 years		9 (60)	21 (84)	0.5 (0.2–1.1)	0.13
Time from the last menstrual period ≥5 years		11 (73)	20 (80)	1.2 (0.6–2.2)	0.71
Obesity[a]		11 (73)	16 (64)	1.3 (0.5–3.4)	0.73
Urinary incontinence[b]		10 (67)	7 (28)	2.7 (1.1–6.5)	0.02
Diabetes therapy	Oral medication without insulin	9 (60)	14 (56)	1.1 (0.5–2.5)	1.0
	Insulin therapy (oral medication)	6 (40)	11 (44)	0.9 (0.4–2.1)	1.0
Microangiopathy		12 (80)	6 (24)	4.9 (1.6–14.7)	0.0009
Retinopathy		8 (53)	5 (20)	2.4 (1.1–5.1)	0.04
Nephropathy		7 (47)	1 (4)	3.5 (1.8–6.7)	0.002
Diabetic foot		1 (7)	1 (4)	1.4 (0.3–5.7)	1.0
Hyperlipidemia[c]		13 (87)	12 (48)	3.9 (1.0–15.0)	0.02
Coronary artery disease		9 (60)	11 (44)	1.5 (0.7–3.4)	0.51
Hypertension		15 (100)	22 (88)	–	0.28
Stroke		3 (20)	1 (4)	2.3 (1.1–4.7)	0.14
Myocardial infarction		2 (13)	3 (12)	1.1 (0.3–3.4)	1.0
Ischemic heart disease		8 (53)	6 (24)	2.1 (1.0–4.6)	0.09
HbA_{1c} >7%[d]		10 (67)	15 (60)	1.2 (0.5–2.8)	0.75
Lifestyle-related risk factor	Smoking[e]	7 (47)	9 (36)	1.3 (0.6–2.9)	0.53
	Physical inactivity	5 (33)	4 (16)	1.7 (0.8–3.7)	0.26
	Noncompliance to nutritional treatment[c]	6 (40)	8 (32)	1.2 (0.6–2.8)	0.73
Glucosuria		1 (7)	1 (4)	1.4 (0.3–5.7)	1.0
Microalbuminuria[f]		3 (20)	0	3.1 (1.9–4.9)	0.04
Pyuria[g]		3 (20)	1 (4)	2.3 (1.1–4.7)	0.14

a defined as body mass index ≥30 kg/m²; **b** defined as any involuntary leakage of urine; **c** self-reported; **d** glycosylated hemoglobin; **e** currently or in the past; **f** defined as albumin urine excretion in the range 30–300 mg/l; **g** defined as >5 leukocytes/mm³

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; RR, risk ratio

relevant to UTI etiology, such as neuropathy that leads to incomplete voiding of the bladder as well as glucosuria.[24]

One of the advantages of our study is that we attempted to establish the risk factors for UTI in a relatively homogenous group of postmenopausal diabetic patients. Women with urinary incontinence were found to have a 2.7-fold greater risk of UTI than those without it. Urologic factors were previously reported as independent risk factors for UTI[25] and recurrent UTI in postmenopausal women.[26] They are distinct from other risk factors for UTI, which predominate in premenopausal women, and considering the pathophysiology, their effect on an increase in the risk of UTI is likely to be additive.[27] This may be influenced by the growing prevalence of urinary incontinence due to aging,[28] obesity, and a history of hysterectomy.[29] Nevertheless, in our study, the age above 60 years was not a risk factor for UTI. On the contrary, the risk seemed to be higher for younger women, although the difference was not significant. This could be explained by a possible higher sexual activity (which is a risk factor for UTI) among younger women.[6]

We found no significant correlations between the occurrence of UTI and the duration of diabetes, type of antidiabetic treatment, serum glucose concentration, and the level of diabetic control measured with HbA_{1c} concentrations. The lack of the latter correlation was reported previously.[10] Nevertheless, microangiopathy, retinopathy, and nephropathy were the most significant risk factors for UTI (as confirmed in multivariate logistic regression) and increased its risk 4.9-fold, 2.4-fold, and 3.5-fold, respectively.

An association with the duration of diabetes might not have been found due to the frequently insidious onset of type 2 diabetes.[30] The duration of the preclinical stage has been estimated by extrapolation from the prevalence of complications at clinical diagnosis to range from 7 to 12 years

before clinical diagnosis.[31] Therefore, the presence of long-standing diabetic microangiopathic complications and their association with the occurrence of UTI likely reflect an unrecognized longer disease duration.[31]

Our results suggest a possible role for low glomerular filtration rates and microalbuminuria in the development of UTI. Albuminuria, which reflects kidney damage, might increase vulnerability to bacterial infections.[32] If impaired renal function increases the risk of UTI, a vicious cycle develops whereby a growing renal insufficiency and recurrent UTIs reciprocally contribute to each other. However, glucosuria, although considered to contribute to the growth of pathogenic microorganisms,[33] was not found to be a risk factor for UTI in our study. This may be due to the variability of renal threshold for glucosuria in different individuals and also in the same person at different times.[34]

Our study was observational and as such cannot prove causation. It might also be that patients with more frequent UTIs show a faster progression of renal disease. This, however, would not explain the relationship between retinopathy and UTIs.

Another clinical correlate of UTI found in our study is hyperlipidemia. This phenomenon was not reported in previous studies and remains unexplained; it may be related to renal disease, which may be reflected by the concentration of urinary liver-type fatty acid-binding protein.

We did not observe the impact of lifestyle-associated risk factors, such as smoking, physical inactivity, and the lack of adherence to nutritional treatment, on the occurrence of UTIs. Obesity was not found to correlate with the prevalence of UTI in our group of postmenopausal women, although it was reported as a risk factor for UTI in men.[35]

No significant increase in the risk of UTI was seen in association with hypertension, stroke, or myocardial infarction in patients' medical history. This might result from the high overall frequency of hypertension and low number of patients who had cardiovascular events. However, an important correlation was found between the extent of comorbidities expressed by the Charlson comorbidity index[14] and the presence of UTI. The results of this assessment were significantly higher in the group of patients with UTI, which indicates comorbidities as an important risk factor for UTI. The quantitative measurement of comorbidities provides a new, useful tool that allows patient risk stratification and was so far underrated. This, in turn, may aid prophylaxis planning or treatment decision making, also in the case of postmenopausal patients with diabetes and UTI. We consider an objective approach with regard to comorbidities as particularly valuable.

The most common UTI pathogen in our study was *E. coli*, followed by other Gram-negative bacteria, and enterococci. This pathogen profile and the antimicrobial susceptibility pattern resemble the ones found in nondiabetic patients and agrees with findings from previous research.[12,36]

The growing antimicrobial resistance remains a considerable concern in contemporary medicine.[37-39] Since quinolones replaced trimethoprim/sulfamethoxazole as the recommended first-line treatment, the rates of uropathogen resistance to fluoroquinolones were reported to exceed 10% to 25% in a few countries. This renders their empirical use problematic[40] and raises the question of whether the loss of the antimicrobial potential of quinolones is vitally important.

We reported an antibiotic susceptibility of 87.5% to all tested quinolones and a 100% susceptibility to ciprofloxacin, moxifloxacin, pefloxacin, and levofloxacin. The good results of the latter may arise from its pharmacokinetics and pharmacodynamics.[41] The results from research on antimicrobial resistance, with an excellent outcome for ciprofloxacin, along with previous reports,[42] encourage maintaining quinolones as recommended treatment for UTIs. A 7-day quinolone regimen is the current standard.[43,44] The place of antimicrobial testing, however, is also prominent and should not be neglected. Moreover, as probiotic supplementation might improve metabolic control and modify cardiometabolic risk factors in patients with type 2 diabetes,[45] its use should be highly encouraged during the treatment of UTI. Supportive local short-term nonhormonal and hormonal treatment should be considered.[46]

In our study, we took numerous precautions to minimize potential bias. We used the EUCAST criteria to assess antimicrobial resistance and prevent misclassification. We used the gold standard of analysis, which allows the reproducibility of the study and generalizability of the findings.[47] The latter, however, may not be possible for other ethnic groups because our population was uniformly Caucasian. Furthermore, the phenomenon of local antimicrobial resistance is known. It makes the results of antimicrobial resistance testing in our study generalizable to the Polish and some other European populations.

Our study has also some limitations. There was no control group of postmenopausal women without diabetes and the studied group was small. Moreover, we excluded patients with features potentially interfering with the results. The exclusion limits the generalizability of the results to a large subgroup of postmenopausal diabetic patients, but on the other hand, the homogeneity of the study sample was necessitated by the regression analyses. We believe that precise exclusion criteria increase the reliability of the results, even if this reduces the study sample. Moreover, the size of the studied groups was sufficient to detect differences equaling a parameter's standard deviation assuming that $\alpha = 0.05$ and $\beta = 0.2$.[48] Furthermore, we did not study susceptibility for antimicrobials other than fluoroquinolones: although further assessments could provide interesting data, we aimed to verify the efficacy of the gold standard antibiotics. Finally, the question

remains whether the risk factors for UTIs such as urinary incontinence, lower glomerular filtration rate, and microalbuminuria are the causes of UTIs rather than its sequelae or the consequences of past disease. It is difficult to construct a methodology that could allow definite conclusions, but a careful study of the past medical history and past laboratory findings might provide an insight.

We believe that the results of our study are important for establishing risk factors for UTIs. Appropriate categorization of at-risk groups may help prevent serious renal complications of UTIs through prompt investigation and treatment[8] and, in this manner, reduce disease-related costs.[49] The increased and targeted vigilance may also contribute to preventing further rise of antimicrobial resistance.

In patients with type 2 diabetes and risk factors for UTI, especially microangiopathic complications, which are an important concern in the course and management of diabetes,[50] we would recommend education of patients about UTI symptoms, careful follow-up of patients, and—if required—secondary prophylaxis. The Charlson comorbidity index may facilitate this process. In fact, when the risk of UTIs and their high prevalence are considered, a routine urinalysis and/or culture can be recommended for diabetic postmenopausal women even when there are no urinary symptoms. The current recommendations discourage the treatment of asymptomatic bacteriuria in diabetic patients,[24] yet this group, especially prone to developing symptomatic infection, should be further monitored.

Consequently, the approach to the problem of UTIs in postmenopausal women should be integrated, focused on prophylaxis, and take into account the many possibilities on 3 levels: 1) risk stratification, vigilance, and early treatment; 2) prevention of diabetes-related risk factors; and 3) adequate control of risk factors resulting from postmenopausal anatomic and hormonal changes.

In summary, we showed that 1 in every 3 postmenopausal diabetic women has UTI. We identified the causative pathogens and the clinical correlates of UTI. The most prominent of these was microangiopathy, which also proved to be an independent risk factor for UTI. The susceptibility of the identified strains to quinolones was excellent. Stepping-up the prevention and early detection of UTIs in this group of women seems to be the best way to prevent future complications.

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Contribution statement MB, AC-C, PF-S, AP, and MC conceived the idea of the study, contributed to the design of the research, and were involved in data collection. MB analyzed and interpreted the data, performed statistical analyses, and prepared the tables. MB, AC-C, JKN, ES-C, and MR wrote the manuscript. All authors edited and approved the final version of the manuscript.

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