https://doi.org/10.31925/farmacia.2020.2.9 **ORIGINAL ARTICLE**

PREVALENCE OF URINARY TRACT INFECTION AND ANTIMICROBIAL SUSCEPTIBILITY AMONG DIABETIC PATIENTS

DANA CARMEN ZAHA, CLAUDIA MARIA JURCA *, LUCIA GEORGETA DAINA, COSMIN MIHAI VESA, AMORIN REMUS POPA, ALEXANDRU DANIEL JURCA, MARIANA MURESAN, OTILIA MICLE

University of Oradea, Faculty of Medicine and Pharmacy, 1st December Street, 410073, Oradea, Romania

*corresponding author: claudiajurca70@yahoo.com

Manuscript received: May 2019

Abstract

The aim of this study was to characterize the prevalence of urinary tract infections (UTIs) in patients with diabetes mellitus, antimicrobial susceptibility pattern of the isolates and to explore the relationship with glycaemic balance. 1046 patients with diabetes, 84 with type 1 and 962 with type 2 diabetes were enrolled in the study. Each urine sample obtained by midstream collection was evaluated using dipstick and microscopical evaluation of the sediment, followed by uroculture. Most patients were diagnosed with type 2 diabetes, and the incidence of UTIs was 29.82%. The predominant isolates were *E. coli* and *K. pneumoniae*, followed by *E. faecalis*. The first two isolates were susceptible to cephalosporins, aminoglycosides, carbapenems, combinations with clavulanic acid or sulbactam, less to quinolones and resistant to ampicillin. Isolates strains of *E. faecalis* have shown a good sensitivity to antibiotics. No difference was noted between the samples with *E. coli, K. pneumoniae* and *E. faecalis* in terms of glycaemic balance.

Rezumat

Scopul acestui studiu a fost de a evalua prevalența infecțiilor tractului urinar la pacienți cu diabet zaharat, susceptibilitatea antimicrobiană a tulpinilor izolate și de a explora relația cu echilibrul glicemic. Au fost luați în studiu 1046 de pacienți cu diabet zaharat, 84 cu tip 1 și 962 cu tip 2. Fiecare probă de urină obținută prin recoltarea jetului mijlociu a fost evaluată biochimic precum și microscopia sedimentului, urmată de urocultură. Majoritatea pacienților au fost diagnosticați cu diabet zaharat de tip 2, iar prevalența infecției urinare a fost de 29,82%. Tulpinile izolate predominant au fost *E. coli* și *K. pneumoniae*, urmate de *E. faecalis*. Primele două au fost susceptibile la cefalosporine, aminoglicozide, carbapeneme, combinații cu acid clavulanic sau sulbactam, mai puțin la chinolone și rezistente la ampicilină. Tulpinile de *E. faecalis* au demonstrat o bună sensibilitate la antibiotice. Nu s-a observat nici o diferență între infecțiile urinare cu *E. coli, K. pneumoniae și E. faecalis* în ceea ce privește echilibrul glicemic evaluat prin valorile hemoglobinei glicozilate.

Keywords: bacteriuria; diabetes mellitus; aetiology, antimicrobials

Introduction

Diabetes mellitus (DM) has become a serious public health threat because of its complications and mortality. The association between diabetes mellitus and an increased susceptibility to infection is well-known; immunity is altered in patients with diabetes due to depressed function of polymorphonuclear leukocytes, particularly when acidosis is also present, leukocytes adherence, chemotaxis, and phagocytosis [3, 23]. The imbalance in the antioxidant systems involved in bactericidal activity is also described [1, 15]. In addition, other conditions such as bladder dysfunction (incomplete bladder emptying) caused by diabetic neuropathy also may contribute to the increased risk for urinary infections. Evidence suggest that urinary tract infection (UTI) is the most common bacterial infection among diabetic patients [7, 9, 24]. Several studies have demonstrated a higher incidence of bacteriuria in diabetic patients, more in diabetic women than in nondiabetic women [6, 14]. Metabolic co-morbidities or unhealthy lifestyle may result in poor glycaemic control and complications [11, 21, 22]. There is evidence that improving glycaemic control in patients improves immune function and prevents the appearance and progression of complications [10, 18, 21]. Recently, the use of SGLT2 inhibitors has produced concern about an increased risk of urinary tract infections in recipients of these medications because the levels of urinary glucose increased with greater doses of the medication.

The extent of involvement ranges from inconsequential lower urinary tract colonization (asymptomatic bacteriuria) to acute cystitis, complicated lower UTI (including catheter associated UTI), pyelonephritis and complicated pyelonephritis/urosepsis.

The present study was undertaken to assess the prevalence of UTIs, antimicrobial susceptibility pattern of bacterial isolates and the relationship with glycaemic balance among adult diabetic patients attending the Oradea County Emergency Clinical Hospital, Romania.

Materials and Methods

We performed a hospital-based study conducted for two years (between January 2017 and December 2018) at the Oradea County Emergency Clinical Hospital, Romania. Socio-demographic characteristics, associated factors and clinical and laboratory data were extracted from the hospital computer system and medical records of patients admitted the diabetic clinic resulting in a number of 1046 of patients presenting urinary symptoms (dysuria, suprapubic pain and/or fever at presentation). A "mid-stream" urine sample obtained under aseptic precautions in sterile containers before starting treatment with antibiotics. Specimens were transported in sterile containers and analysed within maximum two hours from their collection. Urine specimens were analysed by dipstick and microscopy, and then cultured using a calibrated loop. The standard definition of a UTI on culture is more than 100,000 colony forming units *per* mL (CFU/mL). The identification of isolates was performed using Maldi Tof and antibiotic sensitivity by Vitek-2 Compact Systems and Kirby–Bauer disk diffusion method. The isolate was classified as susceptible, intermediate, or resistant based on the Clinical Laboratory Standards Institute (CLSI) criteria [5]. *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. faecalis* ATCC 29212 were used as quality control strains to check the quality of culture media, and antimicrobial cards and disks.

Results and Discussion

The results show that among the urine samples collected from patients, 403 exhibited bacterial and yeast growth (38.52%) and 643 samples (61.47%) did not showed any bacterial growth. A number of 91 samples were excluded from the study because they showed mixed growth of bacteria or were considered colonization susceptible due to an improper collection of the sample.

The 312 patients included were classified according to the glycaemic status as can be seen in the Table I. They were between 21 and 91 years of age and the mean age was 66 years (± 12.45). A large proportion of the patients (68.95%) was found to be in the age group between 61 and 80 years. The ratio women to men is 2.62. Females with diabetes type 2 had a higher prevalence of urinary tract infection than men like the one noted by Renko *et al*. [21]. About 91.02% of type 2 and 8.97% of type 1 diabetic patients had UTIs. The HbA1c of patients with and without UTI were 9.11% (± 2.92) and 7.13% (± 1.3) respectively. 60 patients (19.23%) with UTI were having HbA1c < 7 and 252 patients (80.76%) with UTI were having HbA1c ≥ 7.

The same patients with positive cultures had higher glycosylated haemoglobin values (more than 8.5) and more frequently complications (ketoacidosis, macro-vascular or/and microvascular complications). The most common complications were cardiac and chronic obliterative arterial disease, cerebrovascular, nephropathy and neuropathy. In multivariate analysis, comparing the risk factors for the presence of urinary tract infections diagnosis in the initial group of 1046 patients with positive or negative bacterial growth, the presence of stroke in the medical history was statistically significant positively associated with UTI and male sex was statistically significant negatively associated with UTI. Therefore, diabetic patients with stroke history, especially females, are highly susceptible to UTIs. In univariate analysis the association between positive medical history for stroke and UTI persisted ($p < 0.0001$), meaning that this macro complication of diabetes mellitus is an independent predictor of UTI presence.

Table I

Characteristics of patients according the value of HbA1c

Parameters		No	HbA1c (%)		p
			< 7 (n = 60)	**≥ 7 (n = 252)**	
Gender	Male	86	11	75	
	Female	226	49	177	0.07
Age	21 - 30	2	0	2	
	31 - 40	4	0	4	
	41 - 50	21	3	18	
	51 - 60	61	6	55	
	61 - 70	106	18	88	
	71 - 80	105	28	77	
	81 - 90	13	5	8	0.35
Type of diabetes	Type 1	28	8	20	
	Type 2	284	52	232	0.18
Complications of diabetes	Ketoacidosis	24	1	23	
	Microvascular complications (retinopathy, nephropathy, neuropathy)	242	11	231	
	Macrovascular complications (ischemic cardiopathy, chronic obliterative arterial disease, cerebrovascular disease)	268	23	197	0.55

The overall isolation rate of uropathogens in this study was 29.82% which is higher than other reports. Many studies have reported an increased prevalence of asymptomatic bacteriuria in diabetic patients ranging from 8% - 26%. This difference could be due to the difference in geographic area, samples size and processing techniques. As expected, the prevalence and the distribution of Gram-negative and Gram-positive bacteria isolated from the clinical sample's different levels of glycaemia expressed as HbA1c is clearly higher in the less controlled glycaemic group (Table II).

Among our isolates, Gram-negative aerobic rods accounted for 84.61% while Gram-positive cocci accounted for the remaining 15.38% of the total pathogens. *E. coli* (55.22%), *Klebsiella pneumoniae* (19.28%) and *Enterococcus faecalis* (7.37%) were found to be more prevalent among our patients. The same distribution of etiological agents has reported by other studies [2, 4, 8, 17]. On the other hand, more than 83% of isolates were *Enterobacterales* and the most of urinary tract infections were due to Gram-negative bacteria (265 isolates; 86.60%) contrary to the study conducted by Manikandan *et al.* were *Staphylococcus aureus* was responsible for 20.5% of UTI cases [13, 16].

Table II

Values of HbA1c and the pathogens isolated from urine specimens

	HbA1c(%)		Total no. (%)
	< 7 (n = 60)	≥ 7 (n = 252)	
Gram-negative bacilli			
E. coli	43	126	169 (54.16)
Klebsiella spp.	5	54	59 (18.91)
Enterobacter (cloacae, aerogenes)	2	10	12 (3.84)
Proteus spp.	1	9	10 (3.20)
P. aeruginosa	1	5	6 (1.92)
Acinetobacter baumannii	1	3	4 (1.28)
Morganella morganii	0	2	2 (0.64)
Citrobacter spp(cloacae, freundii)	0	2	2 (0.64)
Gram-positive cocci			
Enterococcus faecalis	5	20	25 (8.01)
Streptococcus (mitis, agalactiae)	0	11	11 (3.52)
Enterococcus faecium	0	4	4 (1.28)
S. aureus	0	2	2 (0.64)
Candida spp	2	4	6 (1.92)

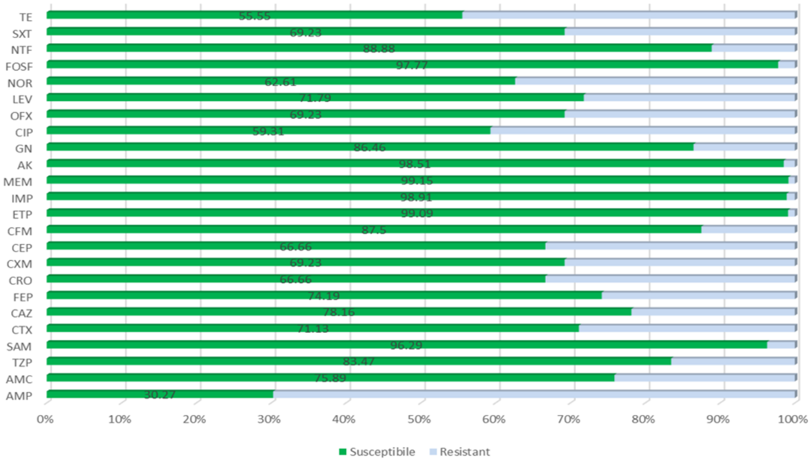

Figure 1.

The susceptibility of *E. coli*

AMP – Ampicillin, AMC – Amoxicillin/clavulanic acid, TZP – Piperacillin/Tazobactam, SAM – Ampicillin/Sulbactam, CTX – Cefotaxime, CAZ – Ceftazidime, FEP – Cefepime, CRO – Ceftriaxone, CXM – Cefuroxime, ETP – Ertapenem, IMP – Imipenem, MEM – Meropenem, AK – Amikacin, CN – Gentamicin CIP-Ciprofloxacin, LEV-Levofloxacin, NOR-Norfloxacin, FOS-Fosfomycin, NTF-Nitrofurantoin, SXT-Trimethoprim / Sulfamethoxazole

Type 2 diabetes is also a risk factor for fungal UTI, mostly caused by *Candida* species and the majority are clinically asymptomatic. In our study group, *Candida* species were present in 6 (1.92%) of the positive cultures and 4 strains in patients with HbA1c > 8.5%. Although a small number of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* strains have been identified, they are significant because of their increase resistance to antibiotics [25].

E. coli strains isolates exhibited a good sensitivity to the antibiotics, except for ampicillin (30.27%) and ciprofloxacin (59.31%). They were more susceptible to norfloxacin (62.61%), ofloxacin (69.23%), levofloxacin (71.79%) and nitrofurantoin (88.88%). The sensitivity to aminoglycosides was also good, being 98.51% for amikacin and 86.46% for gentamycin. The susceptibility of *E. coli* strains to cephalosporins was the best for ceftazidime (78.16%), cefixime (87.5%), cefepime (74.19%) and less for cefuroxime (69.23%), and ceftriaxone (66.66%) as can be seen in the Figure 1. Similarly, a lower prevalence of antimicrobial resistance to cephalosporins and quinolones and a higher haemoglobin A1c level was described in diabetic patients with *E. coli* urosepsis [24]. Extended-spectrum beta-lactamases *Escherichia coli* isolates were identified in 18.40%, a single strain producing carbapenems and 27.16% had resistance to quinolones when it tested at least two.

In the current study, *Klebsiella pneumonia* showed resistance against commonly used antibiotics: cephalosporins, combinations (amoxicillin/clavulanic acid, piperacillin/tazobactam), quinolones and gentamycin, but were susceptible to fosfomycin, carbapenems, amikacin (Figure 2). Although reports shown higher carbapenem resistance in Romania, in the present study the susceptibility rate for the tested *K. pneumoniae* was 75.67 - 79.54% lower than in *E. coli*. Unfortunately, a number of 18 strains were producing extended-spectrum beta-lactamases *K. pneumoniae*, and 4 were carbapenemase producing.

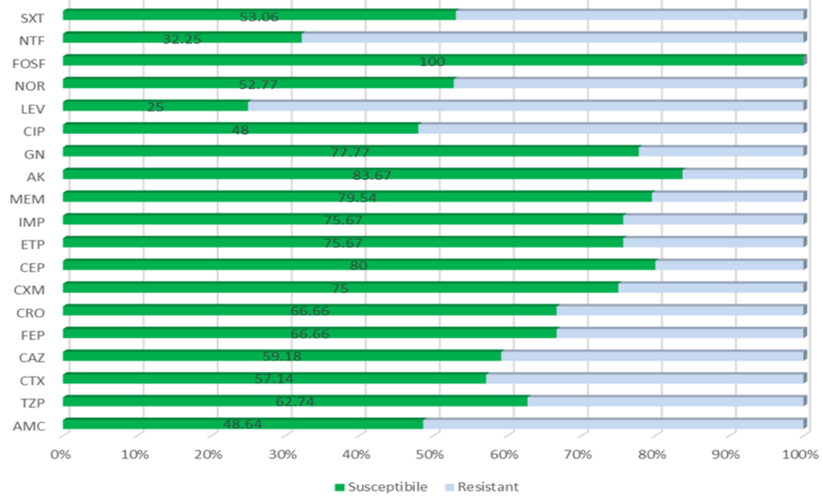

Figure 2.

The susceptibility of *Klebsiella pneumoniae*

AMP – Ampicillin, AMC – Amoxicillin/clavulanic acid, TZP – Piperacillin/Tazobactam, SAM – Ampicillin/Sulbactam, CTX – Cefotaxime, CAZ – Ceftazidime, FEP – Cefepime, CRO – Ceftriaxone, CXM – Cefuroxime, ETP – Ertapenem, IMP – Imipenem, MEM – Meropenem, AK – Amikacin, CN – Gentamicin CIP-Ciprofloxacin, LEV-Levofloxacin, NOR-Norfloxacin, FOS-Fosfomycin, NTF-Nitrofurantoin, SXT-Trimethoprim / Sulfamethoxazole

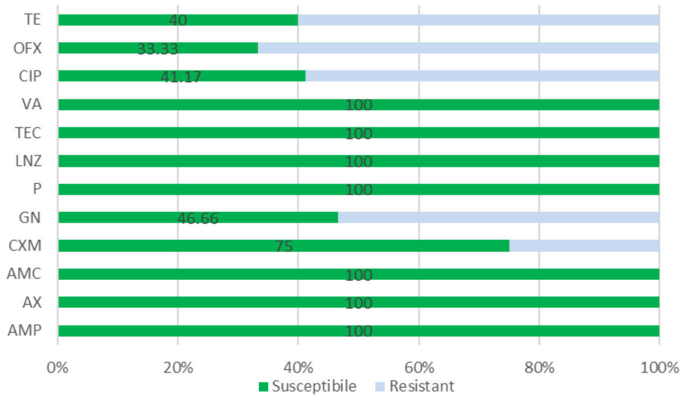

Figure 3.

The susceptibility of *Enterococcus faecalis* strains

AMP – Ampicillin, AX-Amoxicillin, AMC – Amoxicillin/clavulanic acid, CXM – Cefuroxime, CN – Gentamycin, P – Penicillin, ERY – Erythromycin, LNZ – Linezolid, TEC – Teicoplanin, VA – Vancomycin, CIP – Ciprofloxacin, OFX – Ofloxacin, MXF – Moxifloxacin, TE – Tetracycline

The third etiological agent for the patients included in our study was *Enterococcus faecalis* (7.37%). These isolates showed a higher level of sensitivity to ampicillin, amoxicillin, amoxicillin-clavulanic acid, cefuroxime, penicillin, linezolid, teicoplanin, and resistant to gentamycin, quinolones, tetracycline. No strain of *E. faecalis* showed vancomycin resistance. In a study from India amongst the Gram-positive isolates, *Enterococcus faecalis* was the most commonly isolated organism with 3.2% resistance to vancomycin [16].

Conclusions

The successful treatment of UTI in diabetic patients depends on the proper identification of the bacteria responsible and the selection of effective antimicrobial agents against them. More important is the increase in resistance to some antimicrobial agents. Appropriate antibiotic therapy with effective diabetic management is special in diabetic patients with bacteriuria because of the higher incidence of complications and involvement of upper urinary tract. Resistance to antimicrobial agents is growing and represents a challenge in the treatment of infectious diseases today. In addition to the rational use of antibiotics, natural compounds might offer favourable alternatives based on their antioxidant and disinfectant properties solutions can also be considered auxiliary medical therapies [12, 19]. This study is important for clinicians in order to facilitate the empiric treatment of patients and management of patients with symptoms of UTIs and help those responsible to formulate antibiotic prescription policies.

Conflict of interest

The authors declare no conflict of interest.

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