Bulletin of the *Transilvania* University of Braşov.
Series VI: Medical Sciences • Vol. 16(65) No. 2 – 2023
https://doi.org/10.31926/but.ms.2023.65.16.2.2

ASSESSMENT OF THE ETIOLOGICAL SPECTRUM OF URINARY INFECTIONS IN DIABETIC PATIENTS AND OF THE RESISTANCE PATTERNS OF THE UROPATHOGENIC GERMS INVOLVED

Mihaela E. IDOMIR[1,2*]

Abstract: *The aim of the retrospective - descriptive study consisted in the analysis of the spectrum of urinary infections and antimicrobial resistance of the uropathogenic bacteria involved in diabetic patients. The etiological spectrum was wide, being dominated by Escherichia coli (67,68%), Klebsiella sp. (14,14%), Proteus sp. (7,07%), Enterococcus sp. (6,31%). Enterobacteriaceae had higher percentages of resistance to trimethoprim-sulphamethoxazol, quinolones and cephalosporines, antibiotics frequently used in the therapy of urinary infections but also of other infections in diabetics. Over 50% of Enterococcus strains were resistant to fluoroquinolones. The detection of the carbapenem resistant strains (imipenem – 8% and meropenem – 10,2%) is worrying. Colistin, carbapenems and amikacin were most effective in vitro against Gram negative bacilli and linezolid, vancomycin and teicoplanin, in the case of Gram positive cocci. The study results reveal the importance of monitoring the etiological spectrum and the resistance to antibiotics of the germs involved in urinary infections in diabetic patients, for the initiation of an effective therapy and the optimal management of the cases.*

Key words*: urinary infections, antimicrobial resistance, diabetes mellitus*

1. Introduction

Diabetes is a major public health problem that affects, globally, around 425 million people, with a tendency to increase of the number of cases to over 600 million in 2045.

There is serious evidence that microbes play an important role in diabetes mellitus, being suspected of being both triggering factors of the disease and agents of various infections that appear as a result of metabolic alterations.

Many clinical studies have shown that infections have a higher frequency and often have a worse or prolonged evolution in diabetics, being associated with higher rates of morbidity and mortality compared

[1] Transilvania University of Brasov, Faculty of Medicine
[2] Clinical County Emergency Hospital Brasov
*corresponding author: mihaela.idomir@unitbv.ro

to the general population and with increased costs of medical care. [1],[2],[3]

Infections can represent the first form of clinical manifestation of diabetes mellitus or can be triggering factors of some serious complications of the disease such as keto-acidosis or hypoglycemia.

Uncontrolled diabetes mellitus leads to metabolic alterations, hyperglycemia being associated with dysfunctions of the anti-infective defense (affecting the functions of the macrophages and polymorfonuclear neutronphils – chemotaxis, phagocytosis, changing the microenvironment – the pH, viscosity and biochemical parameters of the blood – and the inflammatory response, depression of the antioxidant system and humeral and cellular response – decrease in the production of Ig A and Ig G, alteration of some categories of T lymphocytes and complement components), micro-/ macro – angiopathies (decrease in tissue irrigation and absorption of antibiotics), neuropathies, gastro-intestinal and urinary tract motility disorder [1], [2], [3].

Diabetes mellitus was associated with an increased incidence of skin and soft tissues (inclusive diabetic foot), respiratory, blood, head and neck, genitourinary, neurological and gastrointestinal infections, osteomyelitis and arthritis [2], [3], 4], [5], [6].

Cinical studies also reveal higher risks in diabetics compared to other categories, for the hospitalization for skin and soft tissue infections, CNS infections, emphysematous pyelonephritis or colecistitis, liver or renal abscesses and for the admission to the Intensive Care Unit ward [5], [7].

The etiology of these infections is varied, involving bacteria, viruses, fungi, parasites, eventually prioni, some species with higher frequencies than in other patients such as Chlamydophila pneumoniae, Haemophilus influenzae, Streptococcus pneumoniae, coronavirus 2, hepatitis virus B, influenzae virus A. [2]

Diabetes is a major risk factor for urinary tract infection (UTI), this being one of the most common infectious diseases in diabetic patients that can cause renal failure if geting complicated. Many studies show that the frequency of urinary infections is significantly higher in diabetics compared to the non-diabetic population. [6],[8],[9],[10],[11],[12]

Diabetes mellitus is also associated with more severe complications or relapses of UTI, including longer hospitalizations and an increased mortality.

These infections can be associated with therapeutic difficulties due to multiple bacterial resistances to antibiotics (extended spectrum β-lactamase, positive Enterobacteriaceae, fluoroquinolone-resistant or carbapenem-resistant Enterobacteriaceae, vancomycin-resistant enterococci) [13],[14].

Many studies have shown that community-acquired and healthcare-associated UTI in diabetic patients have similar etiology. More frequently cases occur peri-/post surgery, at elderly patients or at those with indwelling urinary catheters or ureteric stents. [6]

2. Material and methods

The study group consisted of 396 diabetic patients hospitalized in the Diabetes and Nutritional Diseases ward of the Clinical County Emergency Hospital of Brasov in the period 1.01.2018 - 31.12.2022, who had positive urine bacterial cultures with etiopathogenic significance.

Only urine samples considered appropriate from the point of view of collection and transport to the laboratory have been processed. The calibrated loops method (10 μl loops) was used for the quantitative uroculture. Values > 100,000 CFU/ml were considered significant for urinary infection

but also urine samples with values between 1000 and 100,000 CFU/ml, obtained from diabetic patients that have been treated with antibiotics or catheterized were also processed, in order to be interpreted in a clinical context.

The culture media used were Columbia Agar with 5% sheep blood, Mac Conkey selective-differential medium and Brilliance UTI Agar (Oxoid, U.K.). The identification of the isolated germs to the bacterial genus or species level was based on chemical tests (Bile esculine Agar, TSI Agar, Urea Agar, Citrate Simmons Agar) and antigenic tests (STREPTOCOCCAL GROUPING KIT, STAPHYTEC PLUS KIT, Oxoid, U.K.).

Bacterial sensitivity to antibiotics was tested using the Kirby-Bauer diffusimetric method, interpreted based on the CLSI 2018-2022 (Clinical & Laboratory Standards Institute) guideline and confirmed with the VITEK 2 COMPACT automated system.

The aim of the study was the evaluation of the etiological spectrum of urinary tract infections in patients with diabetes and of the resistance patterns, in order to optimize the empiric antibiotical therapy as well as the prospective management of these cases.

3. Results and discussions

Initially it was analyzed the etiological spectrum of urinary infections in diabetic patients during the 5-year studied period (Figure 1).

The etiological spectrum of urinary tract infections in diabetics was dominated by Escherichia coli (67.68%), followed by Klebsiella sp. (14.14%), Proteus sp. (7.07%) and Enterococcus sp. (6.31%).

With lower frequencies, Enterobacter sp., non-fermentative Gram-negative bacilli (P. aeruginosa, Acinetobacter sp.) and Gram-positive cocci were also isolated.

The dynamic evaluation of the spectrum of germs did not reveal any aspects of interest, these germs having a relatively constant presence in the studied years, with slightly lower values in the pandemic years, probably due to the reduction in the number of hospitalizations.

All E. coli strains were sensitive to colistin, tested carbapenems (imipenem, merope-nem) and fosfomycin. The sensitivity was also high to the tested aminoglycosides (amikacin - 98.84%, gentamicin - 90.8%). Higher percentages of resistant strains were observed to ampicillin (56.42%), nalidixic acid (32.3%), ciprofloxacin (30.56%) and norfloxacin (28.25%), trimethoprim-sulfa-methoxazole (28.24%).

Klebsiella sp. had higher levels of resistance to antibiotics, especially to those frequently used in the therapy of urinary infections like trimethoprim-sulfamethoxazole (34.62%), tested quinolones (nalidixic acid – 31.91%, ciprofloxacin – 25%), tested cephalosporines (ceftriaxone – 29.09%, ceftazidime – 27.27%), amoxicillin-clavulanic acid (23.21%).

The sensitivity to colistin was 100%, most of the isolated strains being also sensitive to carbapenems (imipenem - 92%, meropenem - 89.8%) and aminoglycosides (amikacin - 90.38%, gentamicin - 84.31%).

The presence of CRE (Carbapenem Resistant Enterobacteriaceae) strains (imipenem–8%, meropenem–10.2%)of Klebsiella species (CRK = Carbapenem Resistant Klebsiella) it is worrying.

The uropathogens strains of Proteus sp. had high sensitivity to amikacin (100%), meropenem (95.7%) and the cephalosporins (ceftazidime, ceftriaxone - 91.7%). Higher rates of resistance have being observed to ampicillin (62.5%), nalidixic acid (52.2%),

trimethoprim-sulfamethoxazole (48%), amoxicillin-clavulanat (36%), ciprofloxacin (26.7%).

All Enterococcus strains were sensitive to linezolid, vancomycin and teicoplanin, the backup antibiotics for infections with Gram-positive cocci, but more than half were resistant to quinolones (ciprofloxacin – 56.52%, levofloxacin – 51.85%).

Some resistance phenotypes, that limit the therapeutic options, were detected, like ESBL (Extended Spectrum Beta-Lactamase) producing strains at Enterobacteriaceae (E. coli – 38 strains out of 268, Klebsiella sp. – 8 strains out of 56, Proteus sp. – 3 strains out of 25), CRE (Carbapenem Resistant Enterobacteriaceae) at Klebsiella sp. (8 strains), HLAR (High Level Aminoglycoside Resistance) at Enterococcus sp. (13 strains out of 28) and MRSA (Methicillin Resistant Staphylococcus aureus - 2 strains out of 5).

No VRE (Vancomycin Resistance Enterococci) were detected during the retrospective (5 years) study.

The number of strains from the other isolated bacterial genera (P. aeruginosa, Acinetobacter sp., Enterobacter sp., Group B Streptococcus sp., Staphylococcus aureus) was small during the study, therefore the analysis of antibiotic resistance patterns was not of interest.

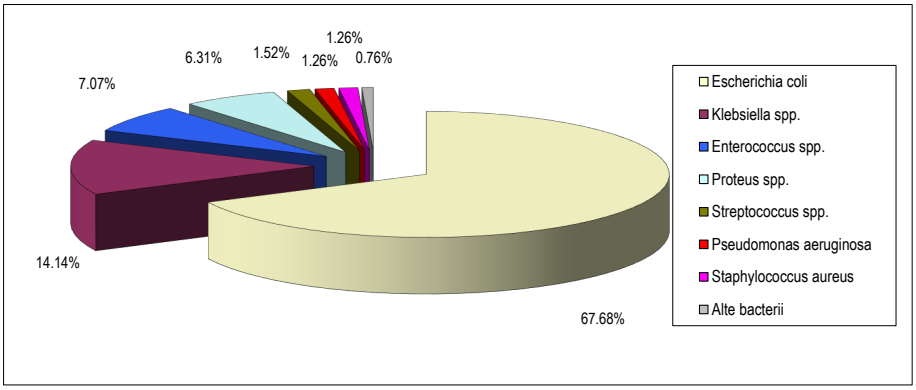

Fig. 1. *The etiological spectrum of urinary infections in diabetic patients in the period 2018-2022*

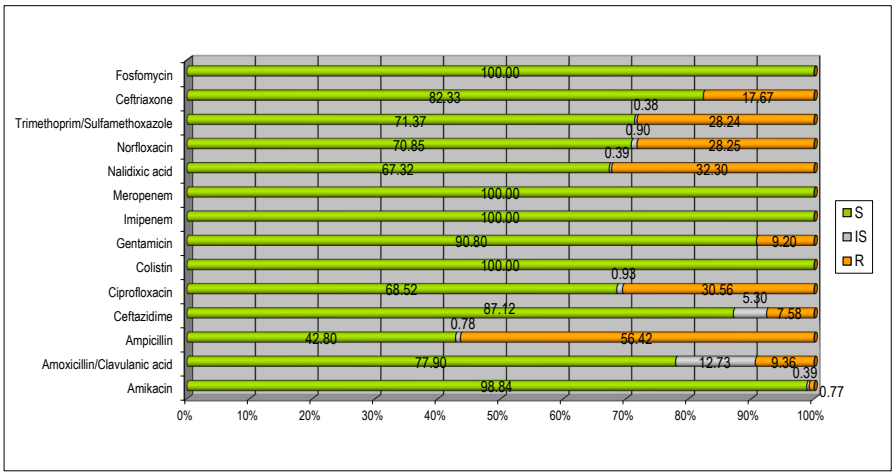

Fig. 2. *Susceptibility to antibiotics of E. coli isolated from urine in the period 2018-2022*

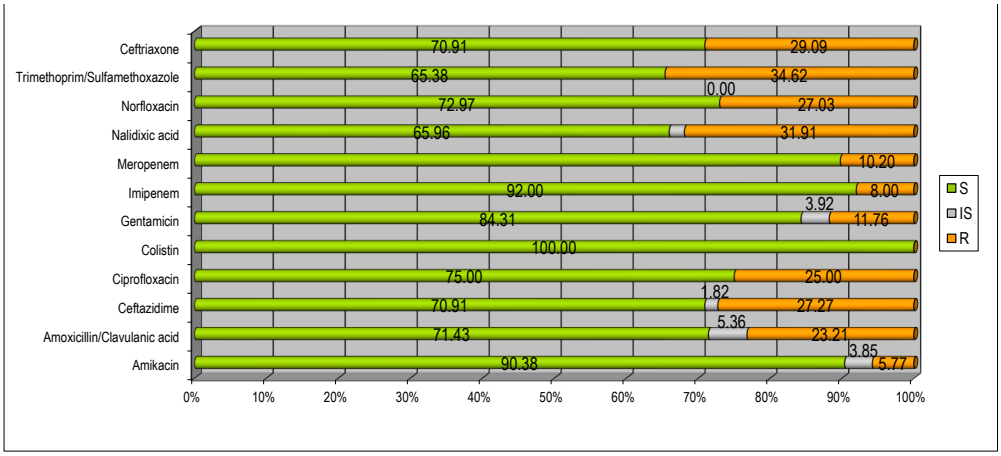

Fig. 3. *Susceptibility to antibiotics of Klebsiells sp. isolated from urine in the period 2018-2022*

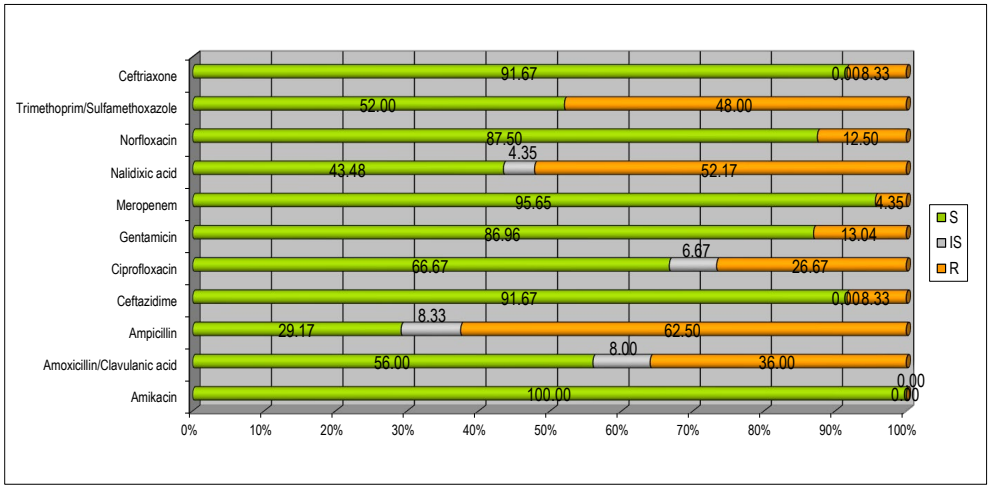

Fig. 4. *Susceptibility to antibiotics of Proteus sp. isolated from urine in the period 2018-2022*

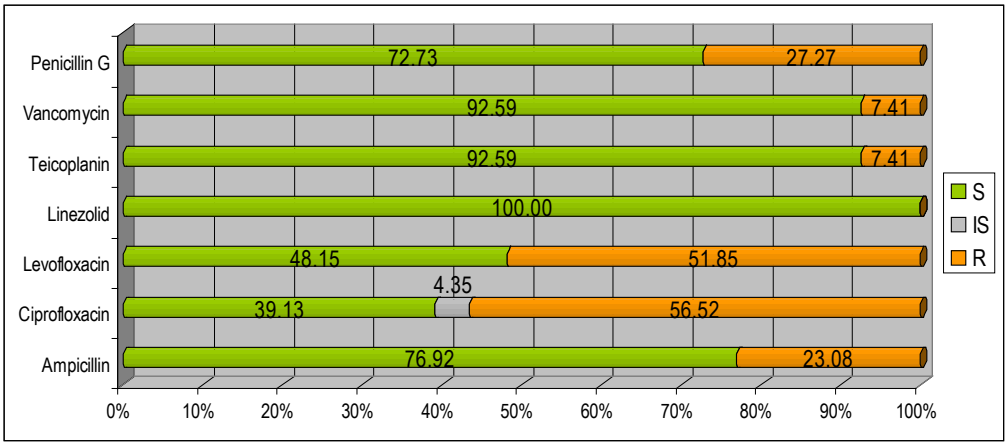

Fig. 5. *Susceptibility to antibiotics of Enterococcus sp. isolated from urine in the period 2018-2022*

The results regarding the categories of isolated uropathogens from diabetics are

consistent with other published studies, the etiological spectrum being dominated by Gram negative bacilli, especially by E. coli, but also by Klebsiella sp. and Proteus sp. It is worth noting the involvement of Enterococcus sp. in the ICU in diabetics, an aspect also reported in other studies, especially in the groups of hospitalized patients [6], [7], [8], [9], [15].

With lower frequencies there were isolated strains of P. aeruginosa, Acinetobacter sp., Enterobacter sp., Streptococcus group B and Staphylococcus aureus, bacterial species that have been involved in UTI in diabetics and that have been reported in other previously carried out studies, in the same medical unit or in other hospitals [7], [16], [17], [18].

A study previously carried out also in the Clinical County Emergency Hospital Brasov shows that the most frequent infections in diabetic patients were urinary infections and their etiological spectrum was relatively constant, being dominated by Escherichia coli (70.8%) but has also included other Gram-negative bacilli, Gram-positive cocci and yeasts.

Conclusions

1. The etiological spectrum of urinary tract infections in diabetics was wide including Gram negative fermentative and non-fermentative bacilli and Gram positive cocci, being dominated by E. coli (67.68%), Klebsiella sp. (14.14%), Proteus sp. (7.07%) and Enterococcus sp. (6.31%).
2. In the case of Enterobacteriaceae, higher rates of resistance to trimethoprim-sulfamethoxazole, to quinolones and tested cephalosporins were obtained, antibiotics widely used in the therapy of urinary tract infections and other infections of diabetic patients.
3. In Klebsiella sp., rates of resistance were relatively high to some antibiotics, the presence of the CRE strains being worrying (imipenem – 8% resistant strains, meropenem – 10.2% resistant strains).
4. Enterococcus strains were sensitive to the backup antibiotics used in Gram-positive cocci infections (linezolid, vancomycin, teicoplanin) but more than 50% were resistant to tested fluoro-quinolones.
5. Knowledge of the resistance patterns still allows the judicious use, for some urinary tract infections, of fosfomycin, cephalosporins of the third generation and fluoroquinolones.
6. The results show the importance of monitoring the etiological spectrum and of the resistance to antibiotics in case of UTI in diabetics, in the context of the wide etiological spectrum and the risk of relapses or evolution with complications of these cases.

References

1. Casqueiro J., Casqueiro J., Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian Journal of Endocrinology and Metabolism*, 2012; 16(7): 27.
2. Chávez-Reyes J., Escárcega-González C.E., Chavira-Suárez E., León-Buitimea A., Vázquez-León, P., Morones-Ramírez, J., Villalón, C.M., Quintanar-Stephano A., Marichal-Cancino B. Susceptibility for some infectious

diseases in patients with diabetes: the key role of glycemia. *Frontiers in Public Health*, 2021, 9.

3. Toniolo A., Cassani G., Puggioni A., Rossi A., Colombo A., Onodera T., Ferrannini E. The diabetes pandemic and associated infections: Suggestions for clinical microbiology. *Reviews and Research in Medical Microbiology*. 2019; 30(1): 1–17.
4. Abu-Ashour W., Twells L., Valcour J., Randell A., Donnan J., Howse P., Gamble J.M. The association between diabetes mellitus and incident infections: A systematic review and meta-analysis of observational studies. *BMJ Open Diabetes Research and Care*. 2017; 5(1).
5. Kim E.J., Ha K.H., Kim D.J., Choi Y.H., Diabetes and the risk of infection: A national cohort study. *Diabetes and Metabolism Journal*. 2019; 43(6): 804–814.
6. Paudel S., John P.P., Poorbaghi S.L., Randis T.M., Kulkarni R. Systematic Review of Literature Examining Bacterial Urinary Tract Infections in Diabetes. *Journal of Diabetes Research*, 2022.
7. Jagadeesan, S., Tripathi, B., Patel, P., Muthathal S. Urinary tract infection and Diabetes Mellitus—Etio-clinical profile and antibiogram: A North Indian perspective. *Journal of Family Medicine and Primary Care*. 2022; 11(5): 1902.
8. Ramrakhia S., Raja K., Dev K., Kumar A., Kumar V., Kumar B., Ramrakhia S. Comparison of incidence of urinary tract infection in diabetic vs non-Diabetic and associated pathogens. *Cureus,* 2020; 12(9).
9. Akash M., Rehman K., et al. Diabetes-associated infections: development of antimicrobial resistance and possible treatment strategies. *Archives of micro-biology*. 2020; 202(5): 953–965. doi: 10.1007/s00203-020-01818-x.
10. Tegegne K., Wagaw G.B., Gebeyehu N.A., Yirdaw L.T., Shewangashaw N.E, Kassaw M.W. Prevalence of urinary tract infections and risk factors among diabetic patients in Ethiopia, a systematic review and meta-analysis. *PLOS ONE*. 2023; 18(1), e0278028.
11. Walelgn B., Abdu M., Kumar P. *The occurrence of urinary tract infection and determinant factors among diabetic patients at Dessie Referral Hospital, South Wollo, Northeast*, 2021, Ethiopia, SAGE Open Medicine, 9.
12. Papp S.B., Zimmern P.E. Recurrent urinary tract infections and type 2 diabetes mellitus: a systematic review predominantly in women. *Frontiers in Urology.* 2023; vol.3, https://doi.org/ 10.3389/fruro.2023.127533.
13. Jadeja B., Khokhar N. and Shrimali G. *Risk factors for extended-spectrum* β-lactamases- and carbapenem-resistant Enterobacteriaceae in patients with urinary tract infection from a tertiary care hospital*. National journal of physiology, pharmacy and pharmacology*. 2023; 13(6): 1. doi: 10.5455/ njppp.2023. 13.04212202302052023.
14. Nitzn O., Elias M., Chazan B., Saliba W. Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. *Diabetes, metabolic syndrome and obesity: targets and therapy*. 2015; 8: 129-126. doi: 10.2147/dmso. s51792.
15. Al Qurabiy H.., Abbas I., Hamaddia A.T.A. et al. *Urinary tract infection in patients with diabetes mellitus and* the role of parental genetics in the

emergence of the disease. *Journal of medicine and life*. 2022; 15(8): 955–962. doi: 10.25122/jml-2021-0331.

16. Asghar M. S., Akram M., Singh M., et al. Characteristics of asymptomatic bacteriuria in diabetes mellitus patients: A retrospective observational study. *Cureus*. 2021; 13(2). doi: 10.7759/ cureus.13562.
17. Confedereat L.G., Condurache M.I., Alexa R., Dragostin O. Particularities of urinary tract infections in diabetic patients: a concise review. *Medicina,* 2023; 59*(*10): 1747;https://doi.org/ 10.3390/medicina59101747
18. Idomir M., Pascu A., Bășescu A. Studiu asupra infecțiilor la diabetici. *Acta Medica Transilvanica*. 2008; vol. II, nr. 3, p. 70.