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# Diabetes Mellitus and Lower Urinary Tract Infection Management in a Single Tertiary Center

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## ABSTRACT

**Objective:** Diabetes mellitus (DM) is known to increase urinary tract infections. Due to the frequent use of antibiotics, periodic evaluations of urinary tract infection agents and antibiotic resistance in centers are crucial. The purpose of this study was to examine the distribution of bacteria isolated as lower urinary tract infection agents and the antibiotic resistance rates of these pathogens.

**Methods:** The records of 267 patients with a diagnosis of DM and a suspected of lower urinary tract infection who were hospitalized in the Gaziantep University Hospital Endocrinology Clinic between December 2019 and April 2022 were reviewed retrospectively. Urine and blood samples of the patients were analyzed.

**Results:** Of these patients, 236 (88.4%) were female. The mean age of the patients was 57.6 years, and the mean Hba1c was 10.6%. While 174 (65.16%) cultures did not grow. 80 (29.96%) bacteria and 13 (4.86%) fungi were detected in urine culture results.Twelve different bacterial species were grown in the cultures. *Escherichia coli* was the most frequently isolated bacterium from gram-negative bacteria. *Streptococcus agalactiae* was the most common gram-positive bacteria. There were 249 patients with pyuria and, 18 patients without pyuria. While 66 (26%) of the patients with pyuria had bacterial growth in the culture, 14 (77.7%) of the patients without pyuria had bacterial growth. There were 176 patients with glucosuria. Bacterial growth was observed in 56 (31.8%) of these patients' pyuria was also present in 47 patients. Bacterial growth occurred in 24 (26.4%) of 91 patients without glucosuria. In gram-negative bacteria culture, ampicillin resistance was observed in 88%. Antibiotic sensitivity were positive for colistin, meropenem, and amikacin (100%, 96%, and 94%) respectively).

**Conclusions:** Urinary tract infections are becoming more important in diabetic patients due to their frequent recurrence and increased antibiotic resistance in isolated bacteria. Cultures take at least two days to result, necessitating the initiation of empirical antibiotic therapy. We think that each center should regularly monitor the agent distribution and antibiotic resistance status in order to select the antibiotic that can be used in empirical treatment correctly.

**Keywords:** Diabetes mellitus, Glycosuria, Pyuria, Urinary tract infection

## Introduction

Diabetes mellitus (DM) is a chronic metabolic disease in which the patients cannot adequately use carbohydrates, fatty acids, and proteins due to insulin deficiency or defects in the effect of insulin.[1] Diabetes mellitus is one of the main causes of mortality and morbidity worldwide, and its prevalence was found to be 13.7% in 2010 in our country.[2] In patients with diabetes, the risk of any type of infection is high, and urinary tract infections (UTIs) are more common, more severe, and cause worse outcomes (bacteremia, renal abscess, and renal papillary necrosis) than in non-diabetic patients. The high glucose concentration in the urine provides a rich source of nutrients for bacteria and allows colonization of the urine by microorganisms. High renal parenchymal glucose levels create a favorable environment for the growth and proliferation of microorganisms that may cause renal complications.[3] In diabetic patients, impaired neutrophil function, decreased T cell–mediated immune response, and low prostaglandin E, thromboxane B2, and leukotriene B4 levels contribute to the increased risk of infection. Bladder dysfunction caused by autonomic neuropathy results in urinary retention, decreases physical bacterial clearance, and thus facilitates bacterial growth.[4] In addition, UTIs can be seen as a side effect due to the use of sodium-glucose co-transporter-2 inhibitor (SGLT-2i) drugs that cause glucosuria, which are frequently used in the treatment of DM.[5,6] It may take time to finalize the processes required to determine the antibiotic susceptibility of the microorganism causing the UTI, and this situation necessitates the initiation of empirical antibiotic therapy. To choose the empirical treatment correctly, each center should regularly monitor the distribution of the infectious agent and the antibiotic-resistance status.



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In this study, we aimed to examine the detection status of UTI organisms in the presence of glycosuria and pyuria in patients with DM and to investigate the distribution of isolated pathogens as well as their susceptibility and resistance to antibiotics.

## Material and Method

A retrospective analysis of 267 patients with a diagnosis of DM and a lower UTI who were hospitalized at the Gaziantep University Hospital Endocrinology Clinic between December 2019 and April 2022 was performed. Exclusion criteria include having an anatomical anomaly in the urinary tract, receiving immunosuppressive therapy, or having an immunosuppressive disease. The presence of pyuria, glucosuria, and bacterial strains grown in the urine culture was evaluated, as were the antibiotic sensitivities of the detected organisms. Midstream urine samples sent from hospitalized patients with a preliminary diagnosis of UTI were quantitatively inoculated on blood agar and Eosin Methylene Blue agar and incubated at 35˚C for 18-24 hours under aerobic conditions. At the same time, all urine samples were centrifuged at 2000 rpm for 5 minutes, and the sediment at the bottom was examined under a microscope.

A symptomatic UTI was defined as having at least $10^5$ microorganisms per cubic centimeter of urine and no more than 2 different species of microorganisms in a person with a fever over 38˚C and urinary symptoms (urgency, dysuria, or suprapubic tenderness). The presence of ≥10 white blood cell/$mm^3$ or ≥3 white blood cell/high-power field of unspun urine was accepted as pyuria. Asymptomatic bacteriuria was defined as the presence of ≥$10^5$ microorganisms per cubic centimeter of urine, with no more than 2 microorganism species and no fever (<38˚C) or urinary symptoms (urgency, dysuria, or suprapubic tenderness).[7]

Colonies with a bacterial count of ≥$10^3$ cfu/mL were evaluated. Isolated bacteria were identified by conventional methods. Identification of microorganisms that could not be identified by these methods, antibiotic susceptibility tests, and extended-spectrum beta-lactamase (ESBL) detection were performed using the VITEK 2 Compact (Bio Merieux-France) system identification and antibiogram cards.

Ethics Committee approval was obtained for the study from Gaziantep University Faculty of Medicine Ethics Committee, with the decision numbered 226/2022. Since this is a retrospective study, written informed consent was not obtained from the patients.

## Results

In our study, 2850 patient files were reviewed retrospectively. Patients with pyuria on urine examination or those without pyuria but with nitrite positivity or dysuria symptoms were considered to have a suspected lower UTI. There were 267 patients with a suspected UTI. Of these patients, 236 (88.4%) were female and 31 (11.6%) were male.

### MAIN POINTS

- Bacterial growth in 29.96% and fungal growth in 4.86% urine cultures was observed in diabetic patients with suspected lower urinary tract infection.
- Most common bacteria grown in the culture were gram-negative (68.7%)
- Ampicilin resistance is the most common form of antibiotic resistance in our study group.

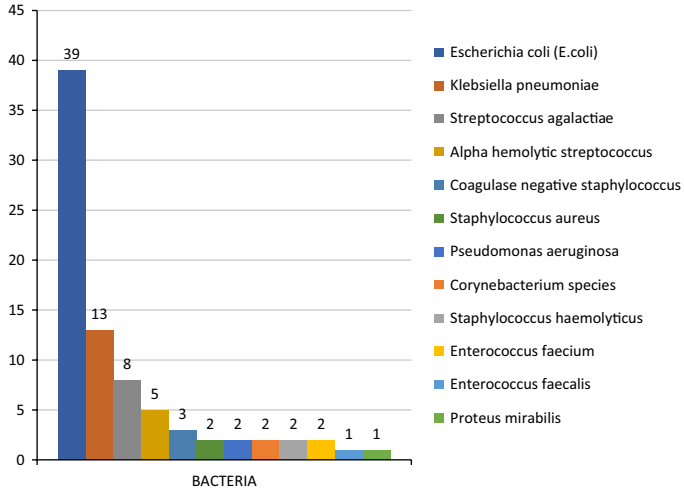


**Figure 1. Bacteria grown in culture.**

The mean age of the patients was 57.6, and the mean Hba1c was 10.6%. While bacterial growth was observed in 80 (29.96%) urine cultures and fungal growth was observed in 13 (4.86%) urine cultures, there was no growth in 174 (65.16%) urine cultures. Of the bacteria grown in the culture, 55 (68.75%) were gram-negative (-) bacteria and 25 (31.25%) were gram-positive (+) bacteria. Twelve different bacterial species were grown in the cultures. *Escherichia coli* (*E. coli*) was the most frequently isolated bacteria from gram-negative bacteria, while *Klebsiella pneumonia* grew in the second place. *Streptococcus agalactiae* was the most grown gram-positive bacteria (Figure 1).

There were 249 patients with pyuria and 18 patients without pyuria. While 66 (26%) of the patients with pyuria had bacterial growth in the culture, 14 (77.7%) of the patients without pyuria had bacterial growth. There were 176 patients with glucosuria. Bacterial growth was observed in 56 (31.8%) of these patients' pyuria was also present in 47 patients. Bacterial growth occurred in 24 (26.4%) of 91 patients without glucosuria.

In the culture antibiogram results of gram-negative bacteria, ESBL (+) 26 and ESBL (–) 24 bacteria were detected. The culture results of 5 patients were evaluated as contaminated. The highest resistance was detected against ampicillin at 88%. The most sensitive antibiotics

**Table 1. Antibiotic Sensitivity of Gram-Negative Bacteria (n= 50)**

| Antibiotic | Sensitive | Resistant |
|---|---|---|
| Amikacin | 47 (94%) | 3 (6%) |
| Amoxicillin-clavulanic acid | 25 (50%) | 25 (50%) |
| Ampicillin | 6 (12%) | 44 (88%) |
| Gentamicin | 42 (84%) | 8 (16%) |
| Colistine* | 45 (100%) | 0 (0%) |
| Meropenem | 48 (96%) | 2 (4%) |
| Piperacilin/tazobactam | 32 (64%) | 18 (36%) |
| Sefepim | 24 (48%) | 26 (52%) |
| Cefoxidine | 40 (80%) | 10 (20%) |
| Ciprofloxacin | 22(44%) | 28(56%) |
| Tigecycline | 45 (90%) | 5 (10%) |
| Trimetoprim/sulfametoxazol | 25(50%) | 25(50%) |

*Colistine did not investigate in 5 patients.

were colistin, meropenem, and amikacin (respectively 100%, 96%, and 94%) (Table 1). The culture antibiogram results of gram-positive bacteria was highly variable.

## Discussion

Urinary tract infections are the most common bacterial infections in diabetic patients, and infections are one of the most important causes of morbidity and mortality in patients with diabetes.[4] In our study, bacterial growth was observed in 29.96% of the patients whose urine cultures were examined. Similar studies in the literature show that detection rates of agent isolation range from 10.9% to 30.2%.[8-10]

Type 2 diabetes is also recognized as a risk factor for fungal-induced UTI.[3] Candiduria is usually seen in hospitalized patients, and most are asymptomatic. Patients may present with cystitis, pyelonephritis, prostatitis, epididymo-orchitis, or diffuse candidiasis. The main risk factors are DM, urinary catheters, use of broad-spectrum antibiotics, urinary obstruction, and hospitalization in intensive care units.[11] In our study, Candida species grew in 4.86% of the cultures. In the study by Zubair et al[12] the frequency of Candida species was determined at 5.61%. This result is similar to that of our study. In our study, 88.4% of the patients with UTIs were female and 11.6% were male. Most studies have concluded that UTI is more prevalent in women compared to men.[12] Zubair et al[12] reported that UTI was 87.85% in women. This has been linked to poor personal hygiene and anatomical differences that allow bacteria to enter the bladder more easily in women than in men.

Although the risk of UTI in patients with DM is higher than in other populations, the infection factors are similar.[13] Microorganisms that cause infection are most commonly from the Enterobacteriaceae family, with *E. coli* usually in the first place. In our study, *E. coli* was the most frequently isolated organism, followed by *Klebsiella pneumoniae*, *S. agalactiae*, and *Alpha hemolytic streptococcus*. In many studies conducted, it has been shown that *E. coli* is the most frequently isolated bacteria, as shown in our study.[8] Epidemiological studies have shown that adults who are not pregnant and who have diabetes have a higher risk of invasive group B Streptococcus (GBS) infections, such as skin and soft tissue infections and sepsis. The effect of diabetes on the risk of invasive GBS urogenital infections, on the other hand, is less clear.[14] In our study, *S. agalactiae* was the most isolated gram-positive bacteria. Although *S. agalactiae* is not a commonly isolated organism in UTIs, the fact that the patients in our study who had poorly controlled diabetes may have contributed to this finding. In short, immunosuppression caused by poorly managed diabetes may have contributed to this outcome. Amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole (SXT), ampicillin, fosfomycin, ciprofloxacin, and nitrofurantoin have been used frequently for the treatment of UTI. Among these, the most resistance is reported for ampicillin.[15,16] Gram-negative (–) bacteria isolated in our study were tested for antibiotic resistance, and ampicillin resistance was found to be 88%. In our study, resistance to ciprofloxacin, which is frequently preferred empirically in UTIs, was found to be 56%. Ciprofloxacin is the second most common antibiotic in the literature, and the rate in our study was found to be higher than in some studies.[8] The high rate of this resistance may be due to the frequent use of ciprofloxacin in our empirical treatments. Extended-spectrum beta-lactamase positivity rates in community- or hospital-acquired UTIs are increasing due to the use of broad-spectrum antibiotics.[15] Gram-negative bacteria were examined in our study, and the positivity of ESBL (+) was 52%. Güdücüoğlu et al[17] found ESBL positivity rates to be 29% and 49% in *E. coli* and *Klebsiella* spp. strains, while in the study of Gülcan et al.[15] ESBL positivity rates were found respectively to be 23.7% and 29.2%.[15,17] In many studies investigating antibiotic resistance rates in ESBL (+) strains, significant decreases were reported in the susceptibility rates of non-beta-lactam antibiotics such as aminoglycosides, quinolones, and SXT.[15] There was high aminoglycoside sensitivity in our study. We rarely use amikacin because of its serious toxicities, which often limit its use due to the dose and duration of therapy. The most common serious adverse effects of the aminoglycosides are ototoxicity, neuropathy, and nephrotoxicity.[18]

Hyperglycemia in patients with DM causes glucosuria. Glucosuria also predisposes to UTIs by increasing bacterial growth and disrupting phagocytosis.[19] In our study, 31.81% of glucosuria patients had organism detection. However, pyuria is also present in 26.7% of these patients. Therefore, it is necessary to consider the high rate of pyuria positivity when evaluating the relationship between glucosuria and organism detection. Bacterial growth occurred in 26.4% of patients without glucosuria. It was determined that 9 (11.25%) of 80 patients with cultured bacteria used SGLT-2 inhibitor drugs. In the cultures of the patients using SGLT-2 inhibitor drugs, 4 *Klebsiella pneumonia*, 3 *E. coli, 1 Alpha hemolytic streptococcus*, and *1 Staphylococcus aureus* were grown. We lack data on SGLT-2i usage in UTI-responsible organisms. We think that the retrospective design and ignoring the effects of antidiabetic drugs are the main limitations of our study.

## Conclusion

Each center should regularly monitor the suspected organism profile and antibiotic resistance status.

**Ethics Committee Approval:** This study was approved by Ethics Committee of Gaziantep University Faculty of Medicine, (Date: 22/06/2022, Approval No: 226).

**Informed Consent:** Since this is a retrospective study, written informed consent was not obtained from the patients.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – E.G.A.C., E.A.; Design – E.G.A.C., E.A.; Supervision – E.G.A.C., E.A., Z.A.S.; Resources – E.G.A.C., E.A., Z.A.S.; Materials – E.G.A.C., E.G., E.A., Z.A.S.; Data Collection and/or Processing – E.G., E.G.A.C., E.A., Z.A.S.; Analysis and/or Interpretation – E.G.A.C., E.G., E.A., Z.A.S.; Literature Search – E.G.A.C.; Writing Manuscript – E.G.A.C., Z.A.S.; Critical Review – E.G.A.C., E.A., Z.A.S.

**Declaration of Interests:** The authors have no conflicts of interest to declare.

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