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ORIGINAL ARTICLE

# Resistance Patterns of Urinary Tract Pathogens Isolated from Patients with Type 2 Diabetes Mellitus on Sodium Glucose Co-transporter 2 Inhibitors Admitted in a Tertiary Hospital in the Philippines: A Single-Center Retrospective Cohort Study

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**Abstract**

Background. Congruent with the increasing prevalence of diabetes, a growing armamentarium of anti-diabetes medications has been introduced. Among these are sodium glucose co-transporter-2 inhibitors (SGLT2i).

Objectives. SGLT2i use has been linked to an increased incidence of urogenital infections. The study aims to compare resistance patterns of urinary tract isolates among patients with diabetes who are on SGLT2i and not on SGLT2i.

Methodology. Single-center retrospective cohort study. A total of 464 patients (75 on SGLT2i, 389 not on SGLT2i) with DM type 2 and urinary tract infection were included. Urine culture results were compared.

Results. A similar pattern of urinary tract isolates was found between groups except for *C. albicans* being more common in the SGLT2i group. There was no significant association between the presence of resistant urinary tract pathogens and the use of SGLT2i. There was no statistically significant difference in resistance rates between groups, except for imipenem ($p = 0.015$).

Conclusion. SGLT2i use per se does not play a pivotal role in mediating bacterial resistance in urinary tract pathogens among patients with DM type 2. We do not recommend for or against the use of specific antimicrobials based on SGLT2 inhibitor alone. Patient's clinical profile along with urine culture test results remain key factors in patient management.

*Key words: diabetes, SGLT2 inhibitors, urinary tract infection, urine culture, resistance*

## INTRODUCTION

Diabetes mellitus (DM) type 2 is a progressive and debilitating disease associated with various macrovascular and microvascular complications. Patients with DM type 2 are at high risk for a multitude of infections including asymptomatic bacteriuria (ASB), urinary tract infections (UTI) and non-sexually transmitted genital infections (vulvo-vaginal infections and balanitis).[1,2] There are "pathogen"-related mechanisms such as an increased bacterial adherence to uroepithelial cells (particularly *E. coli*-expressing type-1 fimbriae) which would explain the increased prevalence of bacteriuria in patients with diabetes, and the "host"-related mechanisms such as an alteration in polymorphonuclear function and adhesion, chemotaxis and phagocytosis.[3] These factors, plus glucosuria and/or diabetes-associated bladder dysfunction, would explain the increase in the prevalence of UTI in patients with type 2 diabetes.

### Sodium glucose co-transporter-2 inhibitors

Congruent with the increasing prevalence of DM type 2 globally, a growing armamentarium of anti-diabetes medications has been introduced to target different organ systems that play a role in the pathophysiology of DM type 2. Among these, sodium glucose co-transporter-2 inhibitors (SGLT2i) are relatively new treatment options for diabetes. These drugs promote the renal excretion of glucose by inhibiting glucose reabsorption in the proximal convoluted tubules. Moreover, SGLT2i have demonstrated beneficial outcomes in patients with cardiac and renal comorbidities.[4-6] Thus, in addition to glycemic control, its proven cardiorenal benefit makes this class of drugs very promising. However, SGLT2i have been linked to an increased incidence of urogenital infections, which may limit their utility in some patients.

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While most UTIs caused by SGLT2i were of mild to moderate severity, the US FDA had revised labels for all SGLT2i by adding a warning for severe UTI in 2015. This warning was prompted by post-marketing adverse event reports of urosepsis and pyelonephritis in patients using these agents. Literature on SGLT2i and UTI have been inconsistent, as older meta-analyses with fewer clinical trials showed a higher UTI risk,[7] while more recent meta-analyses did not demonstrate an increased risk of severe or non-severe UTI with SGLT2i use.[8-11] However, the generalizability of the above meta-analyses may be limited as these participants may be part of clinical trials and/or have insurance claims, in which glycemic control may be better. In our setting, in which the majority of patients have poor diabetes control, recurrent mild to moderate UTI secondary to SGLT2i use may be more common,[12] possibly underreported, and are more likely to have received a multitude of antibiotics as outpatient.

Despite the higher frequency of UTI among patients with diabetes on SGLT2i and the higher risk of antibiotic resistance due to repeated use of antibiotics as outpatient, there are currently no studies that specifically identify resistance patterns of urinary tract pathogens among diabetic patients on SGLT2i. The study therefore will provide relevant information regarding the characterization and antimicrobial susceptibility patterns of urinary tract pathogens among type 2 DM patients on SGLT2i. The study will also specifically compare the urine isolate resistance patterns among patients on SGLT2i and those not on SGLT2i.

## OBJECTIVES

The study compared the resistance patterns of urinary tract pathogens among patients with type 2 diabetes on SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) and those not on SGLT2 inhibitors. Specifically, this study:

1. Compared the incidence of resistant urinary tract pathogens among admitted DM type 2 patients on SGLT2i therapy and those not on SGLT2i therapy. Resistant urinary tract pathogens will be categorized as follows:
    a. ESBL + enterobacteriaceae
    b. Fluoroquinolone-resistant urinary tract pathogens
    c. Carbapenem-resistant enterobacteriaceae
    d. Vancomycin-resistant enterococcus
    e. Fluconazole-resistant fungal infection
    f. Methicillin-resistant Staphylococcus sp.
2. Determined and compared the antibiotic resistance patterns of the isolated urinary tract pathogens among admitted DM type 2 patients on SGLT2i therapy and those not on SGLT2i.
3. Determined the association of the following factors to resistant urinary tract pathogens among DM type 2 patients on SGLT2i therapy:
    a. Age, sex, body mass index (BMI), duration of diabetes, HbA1c and estimated glomerular filtration rate (eGFR) at time of treatment initiation, functional status (chairbound/bedridden), duration of SGLT2i therapy, the use of concomitant oral hypoglycemic agents and presence of concomitant comorbidities such as chronic kidney disease (CKD), congestive heart failure (CHF) and stroke.

## METHODOLOGY

This is a retrospective cohort study. Medical chart reviews of all patients with type 2 diabetes mellitus admitted from January 2021 to October 2023 in Chong Hua Hospital, a tertiary private hospital in Cebu City, were done. All patients with a diagnosis of type 2 diabetes mellitus and urinary tract infection were included in the study. Review and approval of the study protocol by the Chong Hua Hospital Institutional Ethics Review Board (CHH IERB) was obtained prior to initiation of the study.

### Study population and data collection

The study specifically included the following patients:

1. Admitted at Chong Hua Hospital under the Department of Internal Medicine from January 2021 to October 2023
2. Patients greater than 18 years old, diagnosed with type 2 diabetes mellitus based on ADA criteria
3. Diagnosed with urinary tract infection *(presence of one or more of the following: dysuria, frequency, urgency, hematuria, lower abdominal pain, flank pain, nocturia, fever with or without chills, costovertebral angle tenderness)* with urine culture and sensitivity test result

The study excluded the following patients:

1. Newly diagnosed with Type 2 DM during admission
2. Incomplete and inaccessible medical charts
3. Unavailable urine culture and sensitivity test results

The study was limited to a review of medical charts. The following data were collected:

1. SGLT2 inhibitor used: canagliflozin, dapagliflozin, empagliflozin
2. Urine culture and sensitivity test results (to include the number of isolated pathogens, identification of the isolated pathogen and its antibiotic susceptibility pattern)
3. Patient demographics: age, sex, height, weight, diabetes duration, HBA1c, eGFR, functional status, SGLT2i therapy, use of other DM medications, concomitant comorbidities and diagnosis of sepsis

### Statistical analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables (nominal/ordinal), mean and standard deviation for normally distributed interval/ratio variables, and median and interquartile range for non-normally distributed interval/ratio variables.

Mann-Whitney U test was used to compare the median values of continuous variables between groups (SGLT2i vs. no SGLT2i) and absence vs. presence of resistant urinary tract pathogens). Chi-square test was used to compare the frequency of categorical variables between groups. Fisher's exact test was used in place of the Chi-square test for comparisons with small samples that were not fit for Chi-square.

Odds ratios and the corresponding 95% confidence intervals from binary logistic regression were computed to determine the association between patient characteristics and the presence of resistant urinary tract pathogens.

Missing observations were not inputted and were excluded from the analysis. Implausible values, including extreme outliers, were identified during data cleaning and corrected as necessary. All statistical analyses were performed using a 5% level of significance. Data analysis was conducted using Stata version 15.0 (StataCorp, 2017).

## RESULTS

A total of 464 patients (Figure 1) with diabetes mellitus type 2 and a diagnosis of urinary tract infection were included. Of these, 75 patients were in the SGLT2i therapy group and 389 patients in the non-SGLT2i therapy group.

### Patient characteristics

The demographic and clinical characteristics of patients on SGLT2i therapy versus those not receiving the treatment were compared (Table 1). The median age of the included patients was 70 years (IQR: 61-80 years). Significant differences were noted between the two groups in terms of gender distribution and biguanide use. The SGLT2i group had a notably higher proportion of males (40%) compared to the non-SGLT2i group (17.5%). Furthermore, the use of biguanides was lower among patients receiving SGLT2i (38.7%) compared to those not on this therapy (52.7%). Beyond these differences, the two patient groups exhibited comparable demographics and clinical variables across several parameters, including age distribution, duration of diabetes and baseline HbA1c levels, with all *p*-values >0.05.

### Isolated urinary tract pathogens

*E. coli* was the most prevalent pathogen across both cohorts (Table 2.1). Further comparison of both groups showed that *C. albicans* was found more frequently in the SGLT2i therapy group than in the non-SGLT2i therapy group (19.61% vs. 7.22%). and is the second most common isolated pathogen in this group. Other pathogens, including *K. pneumoniae*, *P. mirabilis*, *E. faecalis* and *C. koseri*, demonstrated variability in prevalence between the groups, with *P. aeruginosa* only detected in the non-SGLT2i therapy group.

### Resistant urinary tract pathogens

The incidence of resistant urinary tract pathogens, identified as the growth of the following in culture: ESBL + *Enterobacteriaceae*, Fluoroquinolone-esistant uropathogens, Carbapenem-resistant *Enterobacteriaceae*, Vancomycin-resistant *enterococcus*, Fluconazole-resistant fungal infection and Methicillin-resistant *Staphylococcus* sp., was also compared between the 2 groups (Table 2.2).

In the SGLT2i group, ESBL-producing *Enterobacteriaceae* was observed to be more prevalent (17.6%) compared to the non-SGLT2i group (13.1%). This finding may indicate that although SGLT2i doesn't increase the overall risk for antibiotic resistance in urinary pathogens, it may have the potential to foster the growth of the more resistant strains, probably due to a higher risk of recurrent UTI.

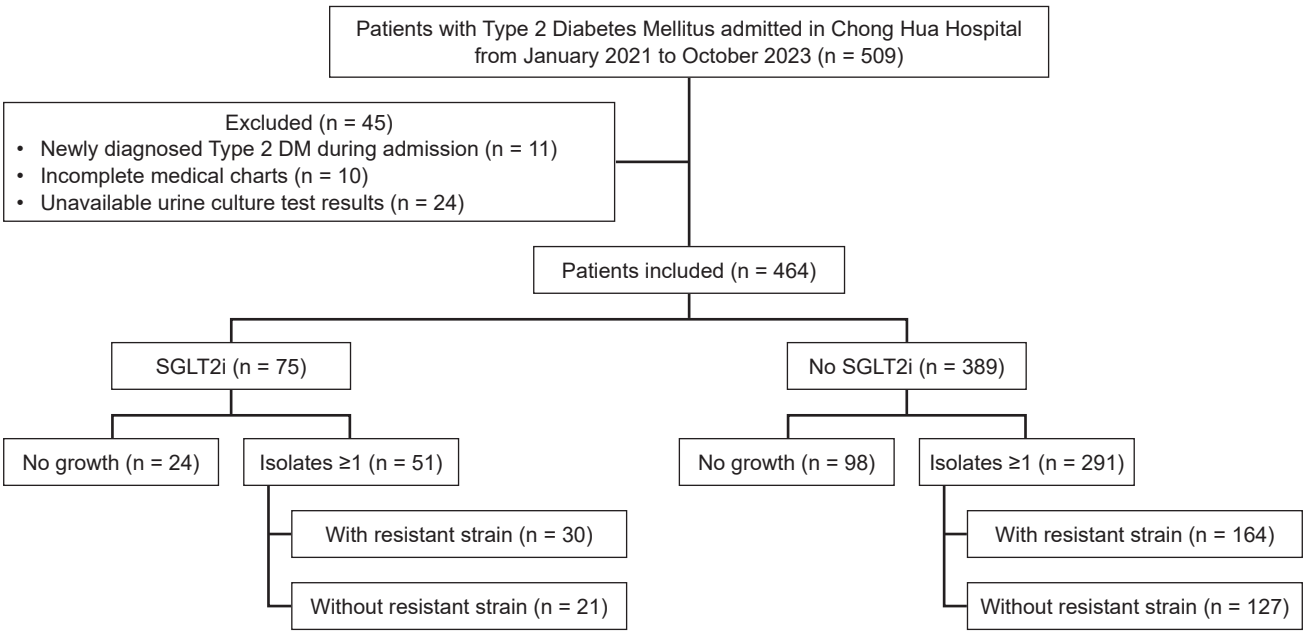


**Figure 1.** Diagram of the study population as further categorized to those on SGLT2i therapy and not on SGLT2i therapy.

**Table 1.** Clinical demographic data of patients on SGLT2 inhibitor and not on SGLT2 inhibitor therapy

| Variables | Total (n = 464) | SGLT2i (n = 75) | Non-SGLT2i (n = 389) | p-value |
|---|---|---|---|---|
| | Median (IQR) Frequency (%) | | | |
| ***Age (years)*** | 70 (61-80) | 70 (63-81) | 70 (60-79) | 0.466*; 0.415† |
| <40 | 10 (2.16) | 0 | 10 (2.57) | |
| 40-54 | 49 (10.56) | 6 (8) | 43 (11.05) | |
| 55-69 | 168 (36.21) | 30 (40) | 138 (35.48) | |
| ≥70 | 237 (51.08) | 39 (52) | 198 (50.9) | |
| ***Sex*** | | | | <0.001† |
| Male | 98 (21.12) | 30 (40) | 68 (17.48) | |
| Female | 366 (78.88) | 45 (60) | 321 (82.52) | |
| ***BMI (kg/m²)*** | | | | 0.587† |
| <18.5 | 20 (4.4) | 2 (2.7) | 18 (4.72) | |
| 18.5-22.9 | 123 (27.03) | 18 (24.32) | 105 (27.56) | |
| ≥23 | 312 (68.57) | 54 (72.97) | 258 (67.72) | |
| ***Duration of diabetes (years)*** | | | | 0.697† |
| 1-5 | 151 (37.94) | 22 (33.33) | 129 (38.86) | |
| 6-10 | 66 (16.58) | 12 (18.18) | 54 (16.27) | |
| >10 | 181 (45.48) | 32 (48.48) | 149 (44.88) | |
| ***Baseline HbA1c (%)*** | | | | 0.157† |
| <7.0 | 228 (51.94) | 37 (52.86) | 191 (51.76) | |
| ≥7.0 - <8.0 | 68 (15.49) | 13 (18.57) | 55 (14.91) | |
| ≥8.0 - <9.0 | 42 (9.57) | 10 (14.29) | 32 (8.67) | |
| >9.0 | 101 (23.01) | 10 (14.29) | 91 (24.66) | |
| ***eGFR (ml/min)*** | | | | 0.929† |
| >60 | 187 (40.39) | 30 (40) | 157 (40.46) | |
| 30-60 | 196 (42.33) | 33 (44) | 163 (42.01) | |
| <30 | 80 (17.28) | 12 (16) | 68 (17.53) | |
| ***Concomitant oral hypoglycemics*** | | | | |
| DPPIV Inhibitor | 269 (57.97) | 37 (49.33) | 232 (59.64) | 0.098† |
| Biguanide | 234 (50.43) | 29 (38.67) | 205 (52.7) | 0.026† |
| SUR | 115 (24.78) | 18 (24) | 97 (24.94) | 0.864† |
| TZD | 11 (2.37) | 1 (1.33) | 10 (2.57) | 0.519† |
| Insulin | 144 (31.03) | 18 (24) | 126 (32.39) | 0.150† |
| GLP1 agonist | 7 (1.51) | 3 (4) | 4 (1.03) | 0.053† |
| ***Menopausal status (n = 123)*** | | | | 0.768† |
| Pre-menopause | 10 (8.13) | 1 (6.25) | 9 (8.41) | |
| Post-menopause | 113 (91.87) | 15 (93.75) | 98 (91.59) | |
| ***Concomitant comorbidities*** | | | | |
| CAD/CHF | 363 (78.23) | 61 (81.33) | 302 (77.63) | 0.477† |
| CKD | 67 (14.44) | 11 (14.67) | 56 (14.4) | 0.951† |
| Stroke | 65 (14.01) | 8 (10.67) | 57 (14.65) | 0.362† |
| BPH | 16 (3.45) | 3 (4) | 13 (3.34) | 0.775† |
| Nephrolithiasis, urolithiasis, obstructive uropathy | 21 (4.53) | 4 (5.33) | 17 (4.37) | 0.713† |
| Chairbound/ bedridden functional status | 94 (20.26) | 9 (12) | 85 (21.85) | 0.052† |
| Sepsis | 78 (16.81) | 14 (18.67) | 64 (16.45) | 0.639† |

Statistical tests used: *Mann-Whitney U test; †Chi-square test

**Table 2.1.** Isolated urinary tract pathogens among patients on SGLT2i therapy and not on SGLT2i therapy

| Isolated pathogens | SGLT2 (n = 51) | Non-SGLT (n = 291) | *p*-value |
|---|---|---|---|
| | Frequency (%) | | |
| ***Escherichia coli*** | 17 (33.33) | 133 (45.7) | 0.101† |
| ***Candida albicans*** | 10 (19.61) | 21 (7.22) | 0.014§ |
| ***Klebsiella pneumoniae*** | 6 (11.76) | 41 (14.09) | 0.657† |
| ***Proteus mirabilis*** | 1 (1.96) | 15 (5.15) | 0.483§ |
| ***Enterococcus faecalis*** | 4 (7.84) | 14 (4.81) | 0.323§ |
| ***Citrobacter koseri*** | 3 (5.88) | 8 (2.75) | 0.216§ |
| ***Staphylococcus haemolyticus*** | 0 | 2 (0.69) | >0.999§ |
| ***Pseudomonas aeruginosa*** | 0 | 7 (2.41) | 0.599§ |

Statistical tests used: *Mann-Whitney U test; †Chi-square test; §Fisher's exact test

**Table 2.2.** Incidence of resistant urinary tract pathogens among type 2 DM patients on SGLT2 inhibitor therapy and not on SGLT2 inhibitor therapy

| Variables | SGLT2i (n = 51) | Non-SGLT2i (n = 291) | *p*-value |
|---|---|---|---|
| | Frequency (%) | | |
| ***Overall Incidence of resistant strains**** | 40% | 42.5% | |
| ***ESBL + Enterobacteriaceae*** | 9 (17.6) | 38 (13.06) | 0.380† |
| ***Fluoroquinolone resistant uropathogens*** | 17 (33.3) | 101 (34.71) | 0.849† |
| ***Carbapenem resistant Enterobacteriaceae*** | 1 (1.96) | 4 (1.37) | 0.556§ |
| ***Vancomycin resistant Enterococcus*** | 1 (1.96) | 0 | 0.149§ |
| ***Fluconazole resistant Fungal infection*** | 0 | 0 | - |
| ***Methicillin-Resistant Staphylococcus sp.*** | 5 (9.8) | 23 (7.90) | 0.587§ |
| ***Extensively drug resistant Pseudomonas*** | 1 (1.96) | 0 | 0.149§ |

Statistical tests used: *Mann-Whitney U test; †Chi-square test; §Fisher's exact test

*Note: Incidence is calculated based on the number of patients with one or more resistant strains over the total number of patients on SGLT2i (and total number of patients not on SGLT2i in the second column)

### Antimicrobial susceptibility patterns

Antimicrobial resistance patterns were also compared between the two groups (Table 3). For gram-negative bacteria, no significant differences in resistance rates were observed between the two groups for most antibiotics, including amoxicillin/clavulanic acid, piperacillin/tazobactam, cefoxitin, cefuroxime, ceftazidime, ceftriaxone, cefepime, amikacin, gentamicin, ciprofloxacin and trimethoprim-sulfamethoxazole. The resistance rates for

**Table 3.** Antimicrobial susceptibility patterns among Type 2 DM patients on SGLT2i and not on SGLT2i therapy

| | SGLT2i | | | Non-SGLT2i | | | *p*-value |
|---|---|---|---|---|---|---|---|
| ***Culture*** | | | | | | | 0.220 |
| No growth | 24 (32) | | | 98 (25.19) | | | |
| One or more isolate | 51 (68) | | | 291 (74.81) | | | |
| | **S** | **I** | **R** | **S** | **I** | **R** | |
| ***Gram negative*** | | | | | | | |
| Penicillin | | | | | | | |
| Amoxicillin/ clavulanic | 31 (79.5) | 4 (10.3) | 4 (10.3) | 170 (70.8) | 23 (9.6) | 47 (19.6) | 0.187 |
| Piperacillin/ tazobactam | 32 (84.2) | 0 | 6 (15.8) | 221 (89.5) | 5 (2) | 21 (8.5) | 0.227 |
| Ampicillin | 0 | 0 | 5 (100) | 9 (16.7) | 2 (3.7) | 43 (79.6) | 0.582 |
| Cephalosporins | | | | | | | |
| Cefoxitin | 31 (83.8) | 2 (5.4) | 4 (10.8) | 205 (82.3) | 9 (3.6) | 35 (14.1) | 0.798 |
| Cefuroxime | 19 (50) | 3 (7.9) | 16 (42.1) | 149 (60.6) | 17 (6.9) | 80 (32.5) | 0.271 |
| Ceftazidime | 27 (65.9) | 1 (2.4) | 13 (31.7) | 195 (76.5) | 1 (0.4) | 59 (23.1) | 0.243 |
| Ceftriaxone | 21 (67.7) | 0 | 10 (32.3) | 156 (76.8) | 0 | 47 (23.2) | 0.269 |
| Cefepime | 31 (79.5) | 0 | 8 (20.5) | 215 (85.3) | 1 (0.4) | 36 (14.3) | 0.337 |
| Aminoglycosides | | | | | | | |
| Amikacin | 37 (97.4) | 1 (2.6) | 0 | 245 (99.2) | 0 | 2 (0.8) | >0.999 |
| Gentamicin | 36 (92.3) | 1 (2.6) | 2 (5.1) | 224 (87.8) | 2 (0.8) | 29 (11.4) | 0.398 |
| Fluoroquinolones | | | | | | | |
| Ciprofloxacin | 22 (57.9) | 1 (2.6) | 15 (39.5) | 159 (62.6) | 1 (0.4) | 94 (37) | 0.858 |
| Others | | | | | | | |
| Imipenem | 32 (84.2) | 1 (2.6) | 5 (13.2) | 226 (95.4) | 4 (1.7) | 7 (2.9) | 0.015 |
| Trimethoprim- Sulfamethoxazole | 25 (67.6) | 0 | 12 (32.4) | 153 (64) | 0 | 86 (36) | 0.716 |
| Nitrofurantoin | 2 (40) | 1 (20) | 2 (40) | 0 | 0 | 0 | - |
| Tobramycin | 1 (100) | 0 | 0 | 0 | 0 | 0 | - |
| Colistin | 0 | 0 | 0 | 1 (33.3) | 1 (33.3) | 1 (33.3) | - |
| Polymxin b | 0 | 0 | 0 | 0 | 1 (100) | 0 | - |
| ***Gram positive*** | | | | | | | |
| Penicillin | 3 (60) | 0 | 2 (40) | 16 (80) | 0 | 4 (20) | 0.562 |
| Tetracycline | 2 (22.2) | 0 | 7 (77.8) | 23 (60.5) | 0 | 15 (39.5) | 0.063 |
| Vancomycin | 8 (88.9) | 0 | 1 (11.1) | 43 (100) | 0 | 0 | 0.173 |
| Linezolid | 7 (100) | 0 | 0 | 32 (100) | 0 | 0 | - |
| Ampicillin | 3 (60) | 0 | 2 (40) | 16 (100) | 0 | 0 | 0.048 |
| Amoxicillin | 2 (50) | 0 | 2 (50) | 11 (100) | 0 | 0 | 0.057 |
| Piperacillin/ Tazobactam | 2 (50) | 0 | 2 (50) | 10 (100) | 0 | 0 | 0.066 |
| Oxacillin | 1 (20) | 0 | 4 (80) | 1 (3.8) | 0 | 25 (96.2) | 0.301 |
| Ciprofloxacin | 4 (57.1) | 0 | 3 (42.9) | 28 (77.8) | 0 | 8 (22.2) | 0.347 |
| Levofloxacin | 0 | 0 | 0 | 2 (100) | 0 | 0 | - |
| Tigecycline | 4 (100) | 0 | 0 | 15 (100) | 0 | 0 | - |
| Cefoxitin | 1 (25) | 0 | 3 (75) | 1 (3.8) | 0 | 25 (96.2) | 0.253 |
| Erythromycin | 4 (80) | 0 | 1 (20) | 13 (46.4) | 1 (3.6) | 14 (50) | 0.346 |
| Clindamycin | | | | | | | |
| Streptomycin | 1 (100) | 0 | 0 | 2 (100) | 0 | 0 | - |
| Gentamicin | | | | | | | |
| TMS | 5 (100) | 0 | 0 | 17 (63) | 0 | 10 (37) | 0.155 |
| Chloramphenicol | 0 | 0 | 0 | 1 (100) | 0 | 0 | - |
| Rifampicin | 0 | 0 | 0 | 1 (25) | 0 | 3 (75) | - |
| Ertapenem | 0 | 0 | 0 | 2 (100) | 0 | 0 | - |
| Nitrofurantoin | 2 (40) | 1 (20) | 2 (40) | 0 | 0 | 0 | - |
| Fungal | | | | | | | |
| Fluconazole | 10 (100) | 0 | 0 | 19 (95) | 0 | 1 (5) | >0.999 |
| Flucytosine | 11 (100) | 0 | 0 | 17 (89.5) | 0 | 2 (10.5) | >0.999 |
| Caspofungin | 11 (100) | 0 | 0 | 20 (95.2) | 0 | 1 (4.8) | >0.999 |
| Micafungin | 11 (100) | 0 | 0 | 20 (95.2) | 0 | 1 (4.8) | >0.999 |
| Amphotericin B | 2 (66.7) | 0 | 1 (33.3) | 5 (100) | 0 | 0 | 0.375 |
| Voriconazole | 9 (100) | 0 | 0 | 19 (95) | 0 | 1 (5) | >0.999 |

S – susceptible; I – Intermediate; R – Resistant

*p*-value for the sensitivity testing was based on "resistance"

Critical region with multiple comparison adjustment is 0.0125

these antibiotics were broadly similar across both groups ($p$ >0.05). However, there was a significant difference in imipenem resistance, with a resistance rate of 13.2% in the SGLT2i group compared to 2.9% in the non-SGLT2i group ($p$ = 0.015). This suggests that patients on SGLT2i therapy might have a higher risk of harboring imipenem-resistant bacteria. For gram-positive bacteria, the resistance patterns for penicillin, tetracycline, vancomycin and linezolid showed no significant differences between the two groups ($p$ >0.05). Similarly, no significant difference was observed in the resistance to fluconazole for fungal isolates ($p$ >0.05).

It is also worth noting that in both groups, resistance rates were highest with ampicillin (79%-100%), cefuroxime (32%-42%), ciprofloxacin (37%-39.5%), nitrofurantoin, trimethoprim-sulfamethoxazole, ceftriaxone and ceftazidime.

Table 4 presents the clinical and demographic profile between patients with and without growth of resistant strains on urine culture. Age appeared to be a statistically significant factor, with older patients having resistant strains compared to those without resistant strains (71.5 vs. 68

**Table 4.** Patient factors associated with and without growth of resistant strains on urine culture (n = 464)

| Variables | With resistant strain (n = 194) | Without resistant strain (n = 270) | *p*-value |
|---|---|---|---|
| | Median (IQR) frequency (%) | | |
| ***Age (years)*** | 71.5 (62-82) | 68 (60-79) | 0.046*; 0.045† |
| <40 | 2 (1.03) | 8 (2.96) | |
| 40-54 | 13 (6.7) | 36 (13.33) | |
| 55-69 | 71 (36.6) | 97 (35.93) | |
| ≥70 | 108 (55.67) | 129 (47.78) | |
| ***Sex*** | | | 0.108† |
| Male | 34 (17.53) | 64 (23.7) | |
| Female | 160 (82.47) | 206 (76.3) | |
| ***BMI (kg/m²)*** | | | 0.141† |
| <18.5 | 5 (2.63) | 15 (5.66) | |
| 18.5-22.9 | 58 (30.53) | 65 (24.53) | |
| ≥23 | 127 (66.84) | 185 (69.81) | |
| ***Duration of diabetes (years)*** | | | 0.322† |
| 1-5 | 59 (36.88) | 92 (38.66) | |
| 6-10 | 22 (13.75) | 44 (18.49) | |
| >10 | 79 (49.38) | 102 (42.86) | |
| ***Baseline HbA1c (%)*** | | | 0.522† |
| <7.0 | 95 (51.35) | 133 (52.36) | |
| ≥7.0 - <8.0 | 31 (16.76) | 37 (14.57) | |
| ≥8.0 - <9.0 | 21 (11.35) | 21 (8.27) | |
| >9.0 | 38 (20.54) | 63 (24.8) | |
| ***eGFR (ml/min)*** | | | 0.242† |
| >60 | 83 (43.01) | 104 (38.52) | |
| 30 – 60 | 73 (37.82) | 123 (45.56) | |
| <30 | 37 (19.17) | 43 (15.93) | |
| ***Concomitant oral hypoglycemic*** | | | |
| DPPIV Inhibitor | 110 (56.7) | 159 (58.89) | 0.638† |
| Biguanide | 93 (47.94) | 141 (52.22) | 0.363† |
| SUR | 50 (25.77) | 65 (24.07) | 0.676† |
| TZD | 6 (3.09) | 5 (1.85) | 0.386† |
| Insulin | 56 (28.87) | 88 (32.59) | 0.392† |
| GLP1 agonist | 4 (2.06) | 3 (1.11) | 0.407† |
| ***Menopausal status (n = 123)*** | | | 0.879† |
| Pre-menopause | 4 (7.69) | 6 (8.45) | |
| Post-menopause | 48 (92.31) | 65 (91.55) | |
| ***Concomitant comorbidities*** | | | |
| CAD/CHF | 154 (79.38) | 209 (77.41) | 0.611† |
| CKD | 29 (14.95) | 38 (14.07) | 0.792† |
| Stroke | 26 (13.4) | 39 (14.44) | 0.750† |
| BPH | 6 (3.09) | 10 (3.7) | 0.722† |
| Nephrolithiasis, urolithiasis, obstructive uropathy | 8 (4.12) | 13 (4.81) | 0.724† |
| Chairbound/ bedridden functional status | 41 (21.13) | 53 (19.63) | 0.691† |
| Sepsis | 34 (17.53) | 44 (16.3) | 0.727† |
| ***SGLT2 use*** | | | 0.728† |
| Without SGLT2 | 164 (84.54) | 225 (83.33) | |
| With SGLT2 | 30 (15.46) | 45 (16.67) | |
| ***Drug class (n = 75)*** | | | 0.919† |
| Empagliflozin | 21 (70) | 31 (68.89) | |
| Dapagliflozin | 9 (30) | 14 (31.11) | |

Statistical tests used: *Mann-Whitney U test; †Chi-square test

years, $p = 0.046$). Other demographic and clinical variables were comparable between the two groups ($p > 0.05$).

Table 5 presents an analysis of the association between SGLT2i use and specific patient characteristics with the presence of resistant urinary tract pathogens. Among the variables included, age was found to be significantly associated with the presence of resistant urinary tract pathogens among DM type 2 patients. Specifically, each additional year of age slightly increased the likelihood of having a resistant urinary tract pathogen (OR = 1.02, 95% CI [1.00, 1.03], $p = 0.027$). Other variables also did not show a significant association with the presence of resistant pathogens in this patient population.

**Table 5.** Association of SGLT2i use, patient characteristics with presence of resistant urinary tract pathogens

| Variables | OR (95% CI) | *p*-value |
|---|---|---|
| ***Age (years)*** | 1.02 (1.00 – 1.03) | 0.027 |
| Sex | | |
| Male | Reference | - |
| Female | 1.46 (0.92 – 2.33) | 0.109 |
| ***BMI (kg/m²)*** | | |
| 18.5-22.9 | Reference | - |
| <18.5 | 0.37 (0.13 – 1.09) | 0.072 |
| ≥23 | 0.77 (0.51 – 1.17) | 0.221 |
| ***Duration of diabetes (years)*** | | |
| 1-5 | Reference | - |
| 6-10 | 0.78 (0.42 – 1.43) | 0.422 |
| >10 | 1.21 (0.78 – 1.87) | 0.400 |
| ***Baseline HbA1c (%)*** | | |
| <7.0 | Reference | - |
| ≥7.0 - <8.0 | 1.17 (0.68 – 2.02) | 0.566 |
| ≥8.0 - <9.0 | 1.40 (0.72 – 2.71) | 0.317 |
| >9.0 | 0.84 (0.52 – 1.37) | 0.491 |
| ***eGFR (ml/min)*** | | |
| >60 | Reference | - |
| 30 – 60 | 0.74 (0.49 – 1.12) | 0.156 |
| <30 | 1.08 (0.64 – 1.82) | 0.779 |
| ***Concomitant oral hypoglycemic*** | | |
| DPPIV Inhibitor | 0.91 (0.63 – 1.33) | 0.638 |
| Biguanide | 0.84 (0.58 – 1.22) | 0.363 |
| SUR | 1.10 (0.72 – 1.68) | 0.676 |
| TZD | 1.69 (0.51 – 5.62) | 0.391 |
| Insulin | 0.84 (0.56 – 1.25) | 0.392 |
| GLP1 agonist | 1.87 (0.41 – 8.47) | 0.415 |
| ***Menopausal status (n = 123)*** | | |
| Pre-menopause | Reference | - |
| Post-menopause | 1.25 (0.35 – 4.53) | 0.730 |
| ***Concomitant comorbidities*** | | |
| CAD/CHF | 1.12 (0.72 – 1.76) | 0.611 |
| CKD | 1.07 (0.64 – 1.81) | 0.792 |
| Stroke | 0.92 (0.54 – 1.56) | 0.750 |
| BPH | 0.83 (0.30 – 2.32) | 0.722 |
| Nephrolithiasis, urolithiasis, obstructive uropathy | 0.85 (0.35 – 2.09) | 0.724 |
| Chairbound/ bedridden functional status | 1.10 (0.69 – 1.73) | 0.691 |
| Sepsis | 1.09 (0.67 – 1.78) | 0.727 |
| ***SGLT2 use*** | | |
| Without SGLT2 | Reference | - |
| With SGLT2 | 0.91 (0.55 – 1.51) | 0.729 |
| ***Drug class (n = 75)*** | | |
| Empagliflozin | 1.05 (0.39 – 2.88) | 0.919 |
| Dapagliflozin | 0.95 (0.35 – 2.59) | 0.919 |

## DISCUSSION

Urinary tract infection is highly prevalent among patients with diabetes.[13-15] A recent descriptive cross-sectional study in a tertiary hospital in India has shown the prevalence of UTI at 75.4%. Additionally, the overall multidrug resistance (defined as an isolate resistant to two or more antimicrobial agents) was observed in 87.4% of the bacterial isolates.[16] This can be explained by several mechanisms, including an increase in urinary glucose concentration, promoting growth of microorganisms, incomplete bladder emptying and subsequent urologic manipulation, immunologic alterations and the history of multiple antibiotic use common in patients with diabetes.[17-23] The pharmacologically-induced increased urinary glucose concentrations with SGLT2i might then provide a favorable growth environment for genitourinary microorganisms.[3] However, literature regarding the association of SGLT2i and UTI is conflicting.[24-29] Yet since its debut in 2013, with the increasing use of SGLT2i, we are currently seeing an increase in the reported prevalence of urinary tract infections with these agents. A recent study by Tanriverdi et al., has shown a 54.9% urine culture positivity rate among patients on SGLT2i therapy compared to 16% in the non-SGLT2 inhibitor therapy group. Among those with positive urine cultures, *Escherichia coli* was isolated in 83.3%, and both *E. coli* and *K. pneumoniae* were isolated in 16.7%.[30]

In the present study, across both cohorts, *E. coli* was the most frequently isolated pathogen. A similar pattern of common urinary pathogen isolates was also noted in existing literature, with the most common being: *E. coli*, *Enterococcus* spp., *Klebsiella* spp.[16,31] Upon further comparison of both groups, *C. albicans* was found to be more common in the SGLT2i group (19.61% vs. 7.22%) and is the second most common pathogen isolated in the group. This observation could be explained by a study by Hiyama et al., wherein the effect of glucosuria on the growth of *Candida* spp. was investigated, showing that viable cell numbers of *Candida* spp. was more than tenfold higher in the urine added with 3000 mg/dL glucose as compared to that in plain urine.[32]

In terms of the presence of resistant urinary tract pathogens, there seems to be no significant difference in the incidence between those on SGLT2i (40%) and those not on SGLT2i (42%). This implies that SGLT2i use by itself does not play a pivotal role in mediating bacterial resistance in urinary tract pathogens. SGLT2i group however had a slightly increased prevalence of ESBL-producing *Enterobacteriaceae* (17.6% vs 13.1%) and Methicillin-resistant *Staphylococcus* species (9.8% vs 7.9%). Due to its association with higher risk of recurrent urinary tract infections, its potential influence on fostering the more prevalent resistant strains cannot be undermined. The mechanism of these observed differences is beyond the scope of the study.

Antimicrobial susceptibility patterns were also analyzed, with most antibiotics demonstrating no significant difference in resistance rates between groups. In general, the increased resistance rates to commonly used antibiotics reflect its possible frequent usage in outpatient settings. Alarmingly, the resistance rate to imipenem was significantly higher in the SGLT2i group (1.9% vs. 1.37%, $p$ <0.015), demonstrating a pronounced risk of imipenem-resistant bacterial infections among these patients. Whether this could be due to frequent use of carbapenems from recurrent admissions for UTI is beyond the scope of this study and perhaps may be an avenue for future research.

The association between SGLT2i use and patient-specific characteristics with the presence of resistant strains was also examined. Among the various factors included, age was the only significant factor, with each additional year increasing the likelihood of harboring resistant strains (OR = 1.02, 95% CI [1.00,1.03], $p$ = 0.027), pointing to the heightened susceptibility of older individuals to harboring UTI with resistant strains. The association of increasing age and harboring of resistant strains could be influenced by multiple factors, including incomplete bladder emptying (e.g., autonomic neuropathy), prior history of multiple antibiotic use and hospital admissions in the elderly group. Data did not show a statistically significant overall impact of SGLT2i on the propensity for developing resistant pathogens as mentioned above.

## CONCLUSION

In the study, we examined the resistance patterns of urinary tract pathogens among DM type 2 patients, categorizing them into those receiving SGLT2i and those who were not receiving SGLT2i. A similar pattern of urinary tract isolates was found between the two groups except for *C. albicans*, which was more common in the SGLT2i group. No significant association was established between the presence of resistant urinary tract pathogens and the use of SGLT2i. There was also no difference in antimicrobial resistance rates between groups except for imipenem.

In conclusion, it has been shown that among DM type 2 patients, SGLT2i use is not associated with a higher risk of antimicrobial resistance as compared to those not on SGL2i therapy. Thus, the study would not recommend for or against the use of specific antimicrobials based on SGLT2i use alone. Rather, the patient's history and clinical condition, along with urine culture and sensitivity test results, should remain the main factors in determining patient management.

The strength of this research lies in its thorough investigation of antimicrobial resistance within a targeted DM type 2 patient cohort, providing real world evidence on SGLT2i treatment and resistance patterns against urinary tract pathogens in a local setting. Nevertheless, its observational design constrains the ability to establish causative links between observed associations. Future research, adopting long-term, prospective methodologies and larger populations, is warranted to confirm these observations and explore the underlying mechanisms of resistance development.

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**Statement of Authorship**
All authors certified fulfillment of ICMJE authorship criteria.

**CRediT Author Statement**
**CRCC:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - original draft preparation, Writing - review and editing, Visualization, Supervision, Project administration, Funding acquisition; **CCYT:** Conceptualization, Methodology, Validation, Resources, Writing - original draft preparation, Writing - review and editing, Supervision, Project administration

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Datasets generated and analyzed are included in the published article.

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