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Metabolic and microbial crossroads: Sodium-glucose cotransporter-2 inhibitors and urinary tract infections in (Asian) diabetes care

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ABSTRACT

The global rise of type 2 diabetes, particularly in Asian populations, has led to widespread adoption of sodium-glucose cotransporter-2 (SGLT2) inhibitors for glycemic control. While effective, these agents elevate the risk of urinary tract infections (UTIs) by inducing glycosuria, which creates a nutrient-rich environment that favors uropathogen growth. Asian individuals may be disproportionately vulnerable to SGLT2 inhibitor–associated UTIs due to a confluence of factors, including lower body mass index, increased visceral adiposity, congenital urinary tract anomalies, and genetic polymorphisms that impair uroepithelial integrity and immunity. This review integrates emerging evidence on the molecular, anatomical, and immunometabolic mechanisms that underlie infection susceptibility in this population. Special attention is given to the role of *Escherichia coli* virulence pathways—including adhesin expression, siderophore production, and biofilm formation—along with host immune impairments in diabetes that facilitate infection persistence. The review also explores how recurrent antibiotic use in these settings accelerates antimicrobial resistance, particularly among extended-spectrum β-lactamase -producing strains. Targeted public health strategies—encompassing glycemic control, antimicrobial stewardship, and non-antibiotic therapies—are needed. This synthesis provides a framework for developing personalized, regionally informed approaches to UTI prevention and management in high-risk diabetic Asian populations.

Introduction

As the prevalence of diabetes continues to rise globally, particularly in Asia, the need for public health services to address downstream complications, such as urinary tract infections (UTIs) [1,2], has become more urgent. The International Diabetes Federation (IDF) reports that Southeast Asia alone accounted for 90 million adults with diabetes in 2019, with this number projected to increase to 153 million by 2045 [3]. Similarly, the World Health Organization (WHO) highlights that countries like China and India are experiencing some of the highest diabetes rates globally, with millions more cases anticipated by 2030 [4]. This escalating prevalence of diabetes presents a significant public health challenge, one that necessitates a comprehensive response to diabetes-related complications, particularly those affecting the genitourinary system.

Individuals with diabetes are inherently more vulnerable to UTIs due to a combination of impaired immune function, poor glycemic control, and increased glucose levels in the urine, which create a conducive environment for bacterial growth. This vulnerability is further compounded for women, particularly in South and Southeast Asia, who are already at a higher risk for recurrent UTIs due to anatomical and hormonal factors [5]. Given the significant burden that diabetes places on health systems across Asia, the potential rise in UTI-related complications demands immediate attention from public health services. Addressing this growing concern is particularly pressing in regions where healthcare infrastructure may already be strained by the demands of managing the diabetes epidemic.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, a class of antihyperglycemic medications, have become a cornerstone in the management of type 2 diabetes due to their proven cardiovascular and renal benefits. These medications work by inhibiting glucose reabsorption in the kidneys, resulting in increased glucose excretion via the urine (glucosuria). However, while this mechanism effectively lowers blood glucose levels, it also increases the risk of genitourinary infections, including UTIs, as glucosuria provides an ideal nutrient medium for bacterial growth in the urinary tract [6,7]. The high adoption rates of

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SGLT2 inhibitors in Asia are driven, in part, by the region's unique metabolic characteristics. Diabetes tends to manifest at lower body mass index (BMI) levels in Asian populations compared to other ethnic groups—a phenomenon known as the "Asian paradox." Asians typically exhibit higher levels of visceral fat and lower muscle mass, even at lower BMI levels, which increases their risk of insulin resistance and related metabolic disorders [8]. These factors heighten the need for glycemic control agents such as SGLT2 inhibitors, but they also raise concerns about the UTI risk. Public health strategies must therefore consider how to balance the metabolic benefits of SGLT2 inhibitors with the need to prevent and manage UTIs effectively.

In addition to the metabolic features that predispose Asian individuals to type 2 diabetes mellitus—such as lower BMI, higher visceral adiposity, and reduced insulin sensitivity—there is mounting evidence that anatomical and genetic factors contribute to the elevated risk of UTIs in this population, particularly in the context of SGLT2 inhibitor use. For example, a large population-based study in Taiwan found that vesicoureteral reflux (VUR) was diagnosed in approximately 10.2 % of hospitalized children with a first UTI, with a particularly high incidence in those aged ≤1 year and in those with coexisting congenital anomalies of the kidney and urinary tract (CAKUT), such as hydronephrosis, duplex collecting systems, and neuropathic bladder [9]. Importantly, VUR in these patients was associated with greater progression to renal scarring and end-stage renal disease, suggesting that anatomical vulnerabilities play a critical role in infection severity and recurrence [9].

Adding to this anatomical predisposition, genetic polymorphisms appear to amplify susceptibility to VUR. A prospective cohort study of Indian children with CAKUT demonstrated that the A allele of the angiotensin II receptor type 2 (AGTR2) gene, located at single nucleotide polymorphism (SNP) rs3736556, was meaningfully associated with VUR [10]. The AGTR2 gene is critical for urinary tract development during embryogenesis, particularly in regulating ureteric bud growth, branching morphogenesis, and insertion into the bladder wall. Individuals carrying the A allele may exhibit altered AGTR2 signaling, potentially disrupting ureteric development or ureterovesical junction competence. In this study, children with the TT genotype—homozygous for the T allele and lacking the A allele—had a significantly lower incidence of VUR, suggesting that the presence of the A allele may impair normal urinary tract development and increase susceptibility to reflux.

Further supporting this genetic contribution, a meta-analysis of 14 case–control studies comprising over 1100 children with VUR examined the role of the angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism. This polymorphism involves either the insertion (I) or deletion (D) of a 287 base pair sequence in intron 16 of the ACE gene, resulting in three genotypes: II (homozygous insertion), DI (heterozygous), and DD (homozygous deletion). The meta-analysis found that both the DI and DD genotypes were significantly associated with increased VUR risk across multiple populations. In Asian children specifically, the DI genotype was associated with a 59 % increased risk of VUR compared to the II genotype, highlighting a possible ethnic vulnerability mediated by renin-angiotensin pathway gene variants [11].

Beyond host genetics and anatomical predisposition, maternal risk factors—particularly those relevant to Asian populations—may further amplify the risk of congenital urinary tract anomalies and subsequent UTI susceptibility. A case-control study conducted in Taiwan demonstrated that maternal obesity, when defined using Asian-specific BMI thresholds (≥24 kg/m^2), was an independent risk factor for the development of CAKUT in offspring, including VUR [12]. These findings are consistent with growing literature implicating maternal metabolic dysregulation, particularly in the context of obese pregnancies, as a contributor to abnormal fetal nephrogenesis and urinary tract morphogenesis—likely mediated through epigenetic modifications, oxidative stress, and low-grade inflammation in the intrauterine environment [12].

In individuals with pre-existing structural vulnerabilities such as VUR or CAKUT, the glucosuria induced by SGLT2 inhibitors compounds the risk of infection by creating a nutrient-rich urinary milieu. Elevated urinary glucose concentrations support the proliferation and enhanced virulence of uropathogens, particularly *Escherichia coli*, by stimulating the expression of type 1 fimbriae (adhesins) and siderophores (iron-scavenging molecules). These virulence factors facilitate uroepithelial adherence, biofilm formation, and evasion of host immune defenses and antibiotic therapy, leading to increased colonization and persistence of infection [13].

Taken together, these converging lines of evidence span maternal-fetal exposures, host genetics, congenital anomalies, and microbial adaptation and underscore the disproportionate vulnerability of Asian populations to UTIs under SGLT2 inhibitor therapy. Fig. 1 illustrates how this susceptibility emerges from the synergistic interplay of genetic predisposition, developmental programming, and pharmacologically induced glycosuria, all converging within an anatomically and immunologically compromised urinary tract.

Mechanisms of UTI risk in SGLT2 inhibitors

Building on the host and population-level vulnerabilities discussed above, this section explores how SGLT2 inhibitors exacerbate infection risk through glycosuric and immunological pathways. SGLT2 inhibitors have transformed the management of type 2 diabetes by improving glycemic control through the inhibition of glucose reabsorption in the proximal renal tubules. Agents such as dapagliflozin, canagliflozin, and empagliflozin lower blood glucose by inducing glycosuria, which effectively increases urinary glucose excretion by blocking the SGLT2 transporters responsible for glucose reabsorption [14]. However, the pharmacological effects of SGLT2 inhibitors have been associated with an increased incidence of UTIs, particularly in susceptible populations such as women and those with a history of recurrent infections [15]. These findings warrant careful consideration in the risk-benefit assessment of SGLT2 inhibitors in clinical practice, particularly for populations prone to recurrent or complicated UTIs.

Glycosuria

The induction of glycosuria is the principal mechanism by which SGLT2 inhibitors create an environment conducive to bacterial proliferation within the urinary tract. Elevated glucose concentrations in the urine act as a nutrient source for uropathogens, including the most prolific UTI culprit *E. coli*, [16] which utilize glucose for growth and virulence expression [17]. This metabolic environment, characterized by alterations in urinary osmolarity, enhances the ability of pathogenic bacteria to colonize the urinary epithelium, contributing to the development of both asymptomatic bacteriuria and symptomatic UTIs [18]. The interaction between *E. coli* and glucose is crucial for bacterial growth and virulence expression. As a facultative anaerobe, *E. coli* thrives in both oxygen-rich and oxygen-poor environments, like the urinary tract. The increased glucose in the urine of diabetic patients or those on SGLT2 inhibitors offers *E. coli* an easily accessible carbon source, promoting its proliferation and enhancing its pathogenicity.

At the molecular level, glucose serves as a primary energy substrate for *E. coli* through glycolysis, where it is metabolized into pyruvate, generating adenosine triphosphate (ATP) and precursors for other biosynthetic pathways. This metabolic process not only supports bacterial growth but also influences the expression of virulence-associated genes through several regulatory mechanisms [19]. One critical regulatory pathway modulated by glucose availability is the cyclic adenosine monophosphate (cAMP)-catabolite repression system. In environments with high glucose concentrations, such as the diabetic urinary tract, *E. coli* undergoes catabolite repression, which reduces intracellular cAMP levels. As a result, the cAMP receptor protein (CRP), a global transcriptional regulator, is inactivated, leading to the downregulation of genes required for the utilization of secondary carbon sources and

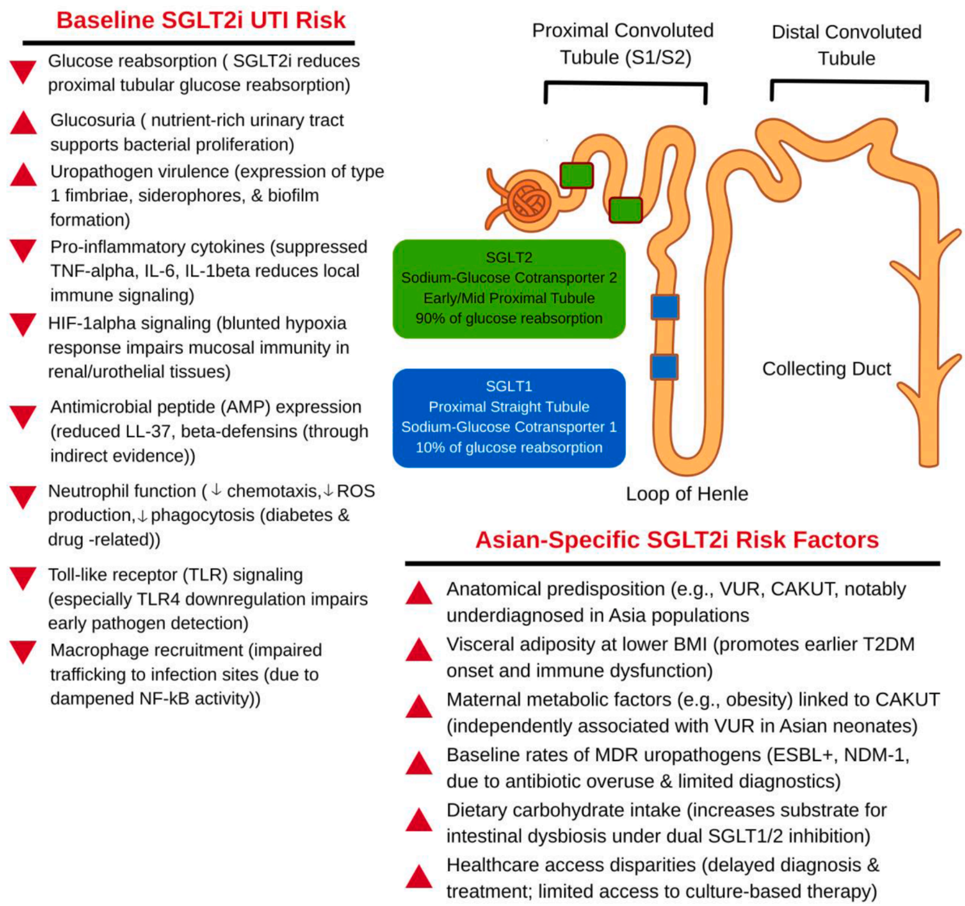

Fig. 1. Immunometabolic and anatomical drivers of UTI risk in SGLT2i-treated individuals: Emphasis on Asian populations.

several virulence genes [20]. This repression can influence *E. coli*'s expression of key virulence factors, like adhesins and siderophores, which are essential for infection establishment and persistence. Glucose availability particularly affects the expression of adhesins, such as type 1 fimbriae. These fimbriae, encoded by the *fim* gene cluster, are essential for *E. coli's* ability to adhere to uroepithelial cells in the bladder. Adhesion is a critical initial step in the pathogenesis of UTIs, as it allows the bacteria to resist urinary flow and avoid being flushed out of the urinary tract [21]. Studies have shown that elevated glucose concentrations enhance the expression of type 1 fimbriae, promoting stronger bacterial adherence to host cells. This adherence is mediated through the binding of fimbrial proteins to mannose residues on the surface of uroepithelial cells, a process that is crucial for the establishment and persistence of infection [19]. In the glycosuric environment of diabetic patients or those treated with SGLT2 inhibitors, this upregulation of adhesin expression provides *E. coli* with a significant survival advantage. By increasing its ability to adhere to the bladder epithelium, *E. coli* can evade both the mechanical clearance of bacteria by urine flow and the host's immune defenses. This is particularly concerning in patients with recurrent UTIs, where enhanced bacterial adhesion can lead to chronic or relapsing infections that are difficult to treat with conventional antibiotics [22,23].

In addition to modulating adhesin expression, glucose-induced osmotic stress activates a variety of bacterial stress response pathways that contribute to *E. coli's* persistence in the urinary tract. One of the key stress response regulators is the RNA polymerase sigma factor S (RpoS) sigma factor, which controls the general stress response in *E. coli* [24]. The RpoS regulon includes genes involved in resistance to osmotic, oxidative, and acid stress, all of which are relevant to the hostile environment of the urinary tract. Under conditions of glycosuria, *E. coli* experiences osmotic stress due to the high concentration of solutes in the urine. This stress activates the RpoS pathway, enhancing the bacteria's ability to withstand osmolarity fluctuations and immune system attacks [25]. The activation of RpoS is particularly important in chronic infections, as it enhances bacterial survival under conditions that would otherwise be lethal. For example, RpoS upregulates the expression of genes involved in biofilm formation, which provides *E. coli* with protection against both the host immune response and antibiotic treatments. Biofilms are structured communities of bacteria encased in an extracellular matrix that shields them from environmental stress and enhances their resistance to antimicrobial agents [26]. In the context of SGLT2 inhibitor-induced glycosuria, biofilm formation allows *E. coli* to persist in the urinary tract, complicating treatment and increasing the likelihood of recurrent infections [27].

Glucose availability plays a pivotal role in regulating *E. coli*'s ability to acquire essential nutrients, such as iron, which is crucial for bacterial growth and virulence. Iron is a limiting factor during infection, as the host employs nutritional immunity to sequester iron and inhibit bacterial proliferation. To counter this defense, *E. coli* produces siderophores—iron-chelating molecules that extract iron from host proteins such as transferrin and lactoferrin [28]. This process is vital for the pathogen's survival, particularly in iron-limited environments like the urinary tract. One of the key mechanisms regulating siderophore production in *E. coli* is the cyclic AMP-catabolite repression protein (cAMP-CRP) system, which is modulated by glucose availability. In high-glucose conditions, such as those induced by SGLT2 inhibitors, the cAMP-CRP system represses genes associated with the utilization of secondary carbon sources while simultaneously upregulating genes involved in siderophore biosynthesis [29]. This upregulation enhances the production of siderophores, particularly enterobactin, enabling

E. coli to effectively compete for iron in the iron-scarce environment of the urinary tract.

Iron is indispensable for multiple bacterial processes, including DNA synthesis, electron transport, and oxidative phosphorylation, which are essential for survival and pathogenicity. However, during UTIs, *E. coli* encounters a formidable challenge: the host's tightly regulated iron sequestration mechanisms, designed to limit microbial access to iron. This is a central feature of nutritional immunity, where host proteins bind and restrict free iron to thwart bacterial growth [30]. To overcome this, uropathogenic *E. coli* (UPEC) strains, which are responsible for the majority of UTIs, deploy a diverse array of siderophores to scavenge iron from the host. These include enterobactin, salmochelin, yersiniabactin, and aerobactin—each with high iron-binding affinity and specialized roles in facilitating iron acquisition in iron-limited environments [31]. The production of these siderophores represents a critical virulence strategy, allowing *E. coli* to bypass host defenses and sustain growth during infection, particularly in glucose-rich and iron-limited conditions associated with SGLT2 inhibitor therapy. By modulating both virulence factor expression and nutrient acquisition strategies, glucose availability indirectly enhances *E. coli*'s ability to establish and maintain infection, underscoring the interconnectedness of metabolic regulation and pathogenicity in the context of UTIs. This relationship between glucose, iron, siderophore production, and virulence factor regulation underscores the complexity of *E. coli* pathogenesis in the context of SGLT2 inhibitor-induced UTIs. Futhremore, in diabetic patients treated with SGLT2 inhibitors, recurrent UTIs often require frequent courses of antibiotics. This creates selective pressure that encourages the survival and proliferation of resistant bacterial strains. Over time, these conditions can lead to chronic infections, necessitating repeated antibiotic treatments, which accelerate the development of resistance, particularly in extended-spectrum beta-lactamases (ESBL)-producing *E. coli* [32].

Host-Pathogen

Host-pathogen interactions play a critical role in the pathogenesis of SGLT2 inhibitor-associated UTIs. In diabetic patients, the combination of hyperglycemia and insulin resistance leads to immunological dysregulation, impairing both innate and adaptive immune responses [33]. This includes a range of immune impairments, notably reduced neutrophil function, diminished toll-like receptor (TLR) expression, and impaired phagocytosis, all of which significantly compromise the host's ability to mount an effective immune response against uropathogens. Neutrophils, as the first line of defense in the innate immune system, play a crucial role in identifying and eliminating invading pathogens through mechanisms such as chemotaxis, degranulation, and the generation of reactive oxygen species (ROS). In individuals with type 2 diabetes, hyperglycemia and insulin resistance have been shown to reduce neutrophil chemotaxis and impair their ability to generate ROS, which in turn diminishes their bactericidal activity [34,35]. This reduction in neutrophil function allows *E. coli* and other uropathogens to persist in the urinary tract, evading early immune clearance.

Beyond diabetes-related immune dysfunction, SGLT2 inhibitors may further increase infection risk by altering the urinary environment through glycosuria and impairing innate immune responses. Although beneficial for glycemic and cardiovascular outcomes, these drugs may weaken host defenses against uropathogens. Specifically, SGLT2 inhibitors have been linked to neutrophil dysfunction [36] and suppression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β [37]. While direct evidence is limited that SGLT2 inhibitors suppress antimicrobial peptides like LL-37 or defensins, their glycosuria and modulation of inflammatory pathways [38] may indirectly affect mucosal immunity and antimicrobial peptide expression. This potential relationship warrants further investigation. Additionally, inhibition of NF-κB signaling and impaired macrophage recruitment may delay pathogen clearance in the urinary tract [39]. Emerging evidence indicates that SGLT2 inhibitors suppress HIF-1α signaling, a transcription factor involved in modulating inflammatory responses and oxidative stress in inflamed tissues. This suppression may contribute to their observed anti-inflammatory effects in the diabetic kidney [40]. These immunomodulatory effects, when coupled with glycosuria and colonization by multidrug-resistant uropathogens, highlight the complex and multifactorial relationship between SGLT2 inhibitor therapy and UTI risk.

Additionally, diminished toll-like receptor (TLR) expression further exacerbates this vulnerability. TLRs are pattern recognition receptors critical for the detection of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides (LPS) on Gram-negative bacteria like *E. coli*. When TLRs are downregulated or dysfunctional, the innate immune system's ability to recognize and initiate a pro-inflammatory response against invading pathogens is severely compromised. In particular, reduced TLR4 expression in diabetic patients has been associated with a blunted immune response, leading to delayed cytokine production and impaired recruitment of immune cells to the site of infection [41].

Impaired phagocytosis represents another key immune deficit in diabetic individuals. Phagocytosis is essential for engulfing and destroying uropathogens, and hyperglycemia has been shown to interfere with this process by altering the actin cytoskeleton dynamics in macrophages and neutrophils, leading to reduced engulfment and clearance of bacteria [42]. Furthermore, advanced glycation end-products, which accumulate in diabetic patients, have been implicated in disrupting receptor-mediated phagocytosis, further diminishing the immune system's capacity to eliminate pathogens.

Collectively, the impairments in neutrophil function, TLR signaling, and phagocytosis create a synergistic effect that significantly weakens the host's innate immune defenses, leading to increased susceptibility to uropathogenic *E. coli*. These immune deficiencies are particularly pronounced in patients with type 2 diabetes, who are already vulnerable due to hyperglycemia and insulin resistance. The compromised immune response facilitates the development of recurrent and complicated UTIs, as the body struggles to effectively eliminate pathogens from the urinary tract. In addition to these immune impairments, the hyperglycemic environment in diabetic patients further exacerbates the risk of infection by promoting bacterial adhesion to the urothelium. Elevated glucose levels increase the expression of mannose-binding receptors on bladder epithelial cells, which enhances *E. coli*'s ability to attach via type 1 fimbriae [19]. This adhesion is a critical factor in the pathogenesis of UTIs, as it enables the bacteria to evade host defenses and establish persistent infections.

Sex-Specific risk and susceptibility

The risk of SGLT2 inhibitor-associated UTIs is notably higher in female patients, who are already anatomically predisposed to UTIs due to their shorter urethra and proximity to the vaginal and anal regions, which facilitate bacterial colonization and ascent into the urinary tract. The introduction of glycosuria induced by SGLT2 inhibitors further heightens this risk [18]. In addition to anatomical susceptibility, several immunological and hormonal factors in women may exacerbate the risk of UTIs. Estrogen deficiency, particularly in postmenopausal women, has been associated with reduced epithelial barrier function and altered vaginal microbiota, both of which contribute to an increased risk of uropathogen colonization [43]. Moreover, glycosuria alters the normal microbial ecology of the urinary tract, potentially fostering an environment that favors pathogen growth over protective commensal organisms. This disruption of the urinary microbiome can make it easier for pathogens to establish infections, particularly when host immune defenses are already compromised due to hyperglycemia or immune-modulating conditions like diabetes [44].

The risk is heightened in women with recurrent UTIs, particularly in diabetic patients with compromised immune function. The use of SGLT2 inhibitors complicates infection management, and repeated exposure to uropathogens, along with frequent or inappropriate antibiotic use, can promote the selection of MDR organisms [45]. These resistant strains, such as ESBL-producing *E. coli*, pose clinical challenges due to limited treatment options and increased rates of treatment failure, especially in diabetic patients, leading to longer hospital stays and higher healthcare costs [46].

In light of these factors, management strategies for UTIs in women treated with SGLT2 inhibitors must consider both the increased bacterial growth driven by glycosuria and the rising threat of antimicrobial resistance. Preventative measures, such as strict glycemic control, the judicious use of antimicrobials, and the development of alternative therapeutic strategies (such as non-antibiotic treatments like d-mannose or probiotics) may offer benefits in reducing UTI risk and preventing the selection of MDR organisms [47]. Additionally, further research into targeted interventions—such as immunomodulatory therapies or vaccines—could provide a future avenue for preventing UTIs, particularly in high-risk populations like diabetic women treated with SGLT2 inhibitors.

Antimicrobial resistance and UTI recurrence

A major concern associated with the increased incidence of UTIs in patients treated with SGLT2 inhibitors is the potential contribution to the development and spread of antimicrobial resistance. By inducing persistent glycosuria, these agents create a nutrient-rich urinary environment that favors uropathogen proliferation. Beyond promoting infection, this metabolic state may also drive the genotypic and phenotypic evolution of microbial resistance traits [48].

At the genotypic level, recurrent antibiotic exposure in such infections selects for *E. coli* strains harboring resistance genes—such as those encoding beta-lactamases—located on mobile genetic elements like plasmids, transposons, and integrons, which facilitate horizontal gene transfer [49]. Moreover, glucose-rich conditions increase bacterial metabolic activity, which may raise mutation rates and enhance recombination, further accelerating resistance development. This includes upregulation of the bacterial SOS response, a stress-induced pathway known to promote mutagenesis under selective pressure [50]. Thus, SGLT2 inhibitors may not only increase UTI incidence but also serve as a catalyst for the molecular evolution of multidrug-resistant organisms in the urinary tract [51]. As summarized in Table 1, these resistance mechanisms span beta-lactamase production, efflux pump activation, and target-site alterations—underscoring the complex genetic and phenotypic adaptations that emerge in glycosuric environments.

Phenotypically, the glycosuric environment created by SGLT2 inhibitor therapy induces notable alterations in *E. coli* virulence factor expression. One of the most consequential adaptations is biofilm formation, which enhances bacterial persistence by shielding pathogens from both the host immune system and antimicrobial agents. Within these structured communities, bacteria exhibit reduced metabolic activity and limited drug penetration—two hallmarks of heightened antibiotic tolerance [62].

Elevated urinary glucose concentrations promote biofilm development. Biofilm formation enables uropathogens to persist in the urinary tract by shielding them from immune clearance and antimicrobial therapy. This tolerance is largely mediated by persister cells within the biofilm matrix, which remain viable during treatment and repopulate the biofilm after therapy cessation, leading to infection chronicity and relapse [63]. Moreover, the biofilm matrix facilitates horizontal gene transfer between bacterial cells, accelerating the spread of resistance determinants and compounding the challenge of antimicrobial resistance (AMR). Table 2 shows biofilm-associated antibiotic tolerance is multifactorial, involving metabolic dormancy, extracellular matrix protection, persister cell populations, altered gene expression, and efflux pump activation. These mechanisms contribute to the persistence of infection despite appropriate antibiotic therapy, particularly in the

Table 1
Antibiotic resistance genes and their mechanisms in uropathogenic bacteria.

Antibiotic Resistance Gene (ARG)	Associated Antibiotic Class	Mechanism of Resistance	Reference
bla_TEM, bla_SHV, bla_CTX-M	Beta-lactams (Penicillins, Cephalosporins)	Production of ESBLs that hydrolyze beta-lactam antibiotics.	[52]
bla_OXA-48	Carbapenems	Production of OXA-48-like carbapenemase, leading to carbapenem resistance.	[53]
mcr-1	Polymyxins (Colistin)	Modifies lipid A in the bacterial membrane, reducing colistin binding and causing resistance.	[54]
aac(6′)-Ib-cr	Aminoglycosides, Fluoroquinolones	Acetylation of aminoglycosides and modification of fluoroquinolones, reducing antibiotic efficacy.	[55]
qnrA, qnrB, qnrS	Fluoroquinolones	Protection of DNA gyrase and topoisomerase IV from fluoroquinolone inhibition.	[56]
sul1, sul2, sul3	Sulfonamides	Mutations in dihydropteroate synthase, conferring resistance to sulfonamide antibiotics.	[57]
tetA, tetB	Tetracyclines	Efflux pump that actively exports tetracyclines out of the bacterial cell, reducing intracellular concentration.	[58]
ermB	Macrolides	Methylation of 23S rRNA, preventing macrolide binding to the bacterial ribosome.	[59]
vanA, vanB	Glycopeptides (Vancomycin)	Alteration of peptidoglycan precursors, preventing vancomycin from binding and inhibiting cell wall synthesis.	[60]
dfrA	Trimethoprim	Mutation in dihydrofolate reductase, rendering trimethoprim ineffective in inhibiting folate synthesis.	[61]

Table 2
Factors influencing antibiotic tolerance in biofilm-associated bacteria.

Factor	Description	Effect on Antibiotic Tolerance	Reference
Decreased Metabolic Activity	Biofilm-associated bacteria enter a slow-growth or dormant state within the biofilm matrix.	Reduced antibiotic efficacy as most antibiotics target actively dividing cells.	[63]
Biofilm Matrix	The extracellular polymeric substance (EPS) matrix produced by biofilm bacteria.	Physically limits antibiotic penetration, shielding bacteria from high antibiotic concentrations.	[64]
Persister Cells	Subpopulations of dormant cells within the biofilm that are highly tolerant of antibiotics.	Persister cells can survive antibiotic treatment and repopulate the biofilm after the antibiotic is removed.	[63]
Altered Gene Expression	Bacteria in biofilms exhibit differential gene expression compared to planktonic cells.	Genes involved in stress responses and antibiotic resistance are upregulated in biofilms.	[65]
Efflux Pumps	Biofilm bacteria upregulate efflux pump systems that actively expel antibiotics from the cell.	Increased resistance to antibiotics by reducing intracellular drug concentrations.	[66]

context of recurrent UTIs.

In patients with SGLT2 inhibitor-associated UTIs, the development of antimicrobial resistance is complicated by the frequent involvement of ESBL-producing *E. coli*. ESBLs confer resistance to a wide range of beta-lactam antibiotics, including penicillins, cephalosporins, and aztreonam, which are commonly prescribed for UTI treatment [67]. This is particularly concerning as ESBL-producing strains are often multidrug-resistant, exhibiting resistance to other antibiotic classes such as fluoroquinolones and aminoglycosides, further limiting treatment options. Additionally, these strains frequently harbor genes encoding resistance to carbapenems (Table 3), a class of antibiotics reserved as a last resort for multidrug-resistant infections [53]. The glycosuric environment induced by SGLT2 inhibitors, combined with frequent UTI recurrence and the selection pressure exerted by repeated antibiotic use, fosters the emergence and persistence of these resistant strains.

The rising incidence of multidrug-resistant UTIs underscores the need for a more judicious approach to SGLT2 inhibitor use, especially in populations at high risk of recurrent infections, such as those with diabetes or urinary tract abnormalities. Preventative strategies should prioritize optimizing glycemic control, minimizing unnecessary antibiotic use, and exploring alternative therapies (e.g., d-mannose, probiotics, or immunomodulatory treatments) that do not exacerbate antimicrobial resistance. Further research into genetic mechanisms of resistance and phenotypic adaptations, including biofilm formation, is critical for developing novel therapeutic strategies to combat these resistant pathogens effectively.

Broader implications in (Asian) diabetic patients and UTI management

The rising incidence of MDR UTIs among patients with type 2 diabetes mellitus—particularly those treated with SGLT2 inhibitors—presents a growing challenge for both clinical care and public health. The convergence of hyperglycemia, glycosuria, and immune dysregulation establishes a urinary tract environment that is especially conducive to colonization and persistence of uropathogens such as *E. coli*.

SGLT2 inhibition induces persistent glycosuria, which creates a nutrient-rich milieu that supports microbial proliferation and enhances bacterial virulence via upregulation of adhesins (type 1 fimbriae), siderophores, and biofilm formation. While renal SGLT1 provides some distal compensation by reabsorbing glucose in the S3 segment, this is insufficient to prevent glucosuria. In dual SGLT1/SGLT2 inhibition (e.g., sotagliflozin), increased glucose delivery to the distal gut can induce microbial dysbiosis and potential fecal–urinary transmission of uropathogens, a concern especially relevant in Asian populations consuming high-carbohydrate diets [13]. Simultaneously, immune impairments intrinsic to type 2 diabetes mellitus—such as reduced neutrophil function, impaired ROS generation, and decreased antimicrobial peptide expression—compound infection risk [13]. These vulnerabilities may be further exacerbated by the immunomodulatory effects of SGLT2 inhibitors, including suppression of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and HIF-1α, which together may delay pathogen clearance in the urinary tract.

These risks are especially pronounced in Asian populations, where type 2 diabetes mellitus manifests at lower BMI thresholds, with greater visceral adiposity and a higher baseline burden of immune dysfunction [12]. Additionally, structural anomalies such as VUR are more common and frequently underdiagnosed in Asian children, predisposing them to recurrent UTIs and upper tract complications [9]. Compounding these host-related factors is the regional prevalence of MDR uropathogens, including ESBL- and carbapenemase-producing *E. coli*, particularly in South and Southeast Asia—regions also characterized by high SGLT2 inhibitor use, widespread antibiotic access, and limited microbiological surveillance [73]. An overview of these interacting pathways (Table 4) is important for designing personalized and region-specific UTI management strategies. These strategies must incorporate individualized risk stratification, integrated glycemic and infection control, and antimicrobial stewardship policies, particularly in high-risk diabetic populations in Asia.

Table 3
Key carbapenem resistance genes and their mechanisms in enterobacteriaceae.

Carbapenem Resistance Gene	Gene Family	Mechanism of Resistance	Reference
bla_KPC	KPC (Klebsiella pneumoniae carbapenemase)	Hydrolyzes carbapenems and other beta-lactams.	[68]
bla_NDM-1	NDM (New Delhi metallo-beta-lactamase)	Metallo-beta-lactamase that requires zinc ions for activity and hydrolyzes carbapenems.	[69]
bla_OXA-48	OXA-48-like beta-lactamase	Hydrolyzes carbapenems but with weak activity against broad-spectrum cephalosporins.	[70]
bla_VIM	VIM (Verona integron-encoded metallo-beta-lactamase)	Metallo-beta-lactamase that hydrolyzes carbapenems and other beta-lactams.	[71]
bla_IMP	IMP (Imipenemase metallo-beta-lactamase)	Metallo-beta-lactamase that hydrolyzes carbapenems and other beta-lactams.	[72]

Note: Each of these genes encodes a beta-lactamase enzyme that hydrolyzes carbapenem antibiotics, contributing to multidrug resistance in bacterial strains.

Global spread of resistance in high antibiotic-use regions

The problem of AMR is particularly severe in Southeast Asia, where antibiotics are often overused, misused, or available without prescription. This contributes to the rapid emergence and spread of resistant organisms. In Southeast Asia, studies show that up to 70 % of UTI-causing *E. coli* strains are resistant to first-line antibiotics like beta-lactams and fluoroquinolones [9]. The prevalence of ESBL-producing *E. coli* and carbapenem-resistant Enterobacteriaceae in this region severely limits treatment options, complicating the management of recurrent UTIs. Moreover, the frequent movement of people across borders increases the likelihood of transnational AMR spread, further straining healthcare systems [74].

Public health implications of AMR in diabetic populations

The confluence of diabetes, SGLT2 inhibitor use, and the spread of AMR presents a complex public health issue. Individuals with diabetes are already predisposed to infections due to compromised immune function, and the use of SGLT2 inhibitors increases the likelihood of recurrent UTIs. Women, especially in South and Southeast Asia, face disproportionately higher risks due to anatomical and hormonal factors. The spread of MDR uropathogens in these regions further complicates UTI management, leading to more severe infections and increased healthcare costs. In high-risk regions, including Southeast Asia, where AMR rates are rising rapidly, healthcare systems must balance the benefits of SGLT2 inhibitors with the risks of recurrent infections and AMR. The growing prevalence of carbapenem-resistant *E. coli* and other MDR pathogens poses a significant threat to effective infection management, limiting the efficacy of last-resort antibiotics such as carbapenems and colistin.

A multi-pronged approach is needed to mitigate the impact of AMR in diabetic populations on SGLT2 inhibitors, with a focus on prevention, early detection, and appropriate management of UTIs. Table 5 summarizes key recommendations.

To effectively address the growing threat of MDR infections in diabetic populations using SGLT2 inhibitors, public health systems must

Table 4
Mechanistic cascade of SGLT1, SGLT2, and SGLT2i-associated UTI risk with emphasis on Asian population vulnerabilities.

Step	Component	Mechanism / Function	Physiological Impact	UTI Risk Implication	Asian-Specific Considerations
1	SGLT2 (Proximal tubule S1/S2)	Reabsorbs ~90 % of filtered glucose via sodium-glucose cotransport	Prevents glycosuria and preserves energy balance	No urinary glucose → unfavorable environment for pathogens	No specific ethnic polymorphisms, but high SGLT2i use in Asia due to cardiometabolic benefits
2	SGLT1 (Proximal tubule S3)	High-affinity, low-capacity transporter reabsorbing ~10 % of glucose	Minor compensation for glucose spillover in normoglycemia	Not associated with UTI in isolation	Functionally normal; becomes relevant under SGLT2 inhibition
3	SGLT2 Inhibitors (e.g., dapagliflozin)	Inhibit SGLT2 → induce glycosuria (~40–80 g/day)	Reduces plasma glucose; causes persistent urinary glucose excretion	Creates nutrient-rich medium for *E. coli, Klebsiella*	High uptake in Asia due to efficacy at lower BMI and cardio-renal indications
4	Compensatory SGLT1 Reabsorption	Reabsorbs a fraction of escaped glucose downstream	Partially blunts glycosuria but does not reverse it	Glycosuria persists → promotes pathogen proliferation	Not sufficient to mitigate glycosuria-induced risk
5	Intestinal SGLT1 (Dual inhibition with sotagliflozin)	Reduces glucose absorption in gut → delays postprandial peaks	↑ unabsorbed glucose in distal gut → alters microbiota	Dysbiosis may increase *E. coli* burden; potential for fecal–urinary transmission	Asian diets are high in carbohydrates → greater fermentable glucose load
6	Glycosuria-Induced Uropathogen Expansion	Glucose enhances *E. coli* adhesion (fimbriae), iron uptake (siderophores), and biofilm	Increases pathogen fitness and immune evasion	Promotes asymptomatic bacteriuria, recurrent UTI, and antibiotic resistance	*E. coli* strains in Asia show higher MDR rates (ESBL, NDM-1) due to antibiotic overuse
7	Immune Dysfunction in T2DM	↓ Neutrophil function, ROS production, AMP expression (LL-37, defensins)	Compromised innate immunity → poor microbial clearance	Facilitates colonization and ascending infection	Asian T2DM phenotype: earlier onset, higher visceral fat, chronic inflammation
8	SGLT2i-Induced Immunomodulation	↓ TNF-α, IL-6, IL-1β; ↓ HIF-1α; possible ↓ AMP expression	Anti-inflammatory in kidney; may impair UTI defenses	Delays pathogen clearance; promotes persistence	Limited Asian data, but likely synergizes with diabetes-related immune dysfunction
9	Anatomical Predisposition (e.g., VUR)	Urine reflux → stasis and retrograde microbial ascent	Facilitates recurrent upper UTI and renal scarring	Strong independent risk factor for pyelonephritis	Higher prevalence of VUR in Asian children, especially girls; often underdiagnosed
10	Clinical Outcome	Recurrent UTI with MDR pathogens; antibiotic failure	↑ healthcare utilization, CKD risk, hospitalization	Difficult to treat; may lead to urosepsis or nephropathy	Rising diabetes and AMR rates + healthcare access inequities compound burden in Asia

Table 5
Recommendations for managing SGLT2 inhibitor-associated UTIs and antimicrobial resistance.

Recommendation	Description
Provider and Patient Education	Increase awareness about the risks of SGLT2 inhibitor-associated UTIs, emphasizing AMR and appropriate antibiotic use in diabetic populations.
Routine UTI Screening	Implement routine screening for UTIs, particularly in high-risk diabetic women and older adults, to detect and treat infections early.
Glycemic Control Programs	Promote better glycemic control to reduce hyperglycemia and glycosuria, both of which increase UTI susceptibility in diabetic populations.
Antibiotic Stewardship	Introduce antibiotic stewardship programs to manage AMR, emphasizing the responsible use of antibiotics in treating recurrent UTIs.
Surveillance and Rapid Diagnostics	Strengthen surveillance systems and employ rapid diagnostics to monitor MDR pathogens and guide effective treatment decisions.
Non-Antibiotic Therapies	Explore non-antibiotic treatments, such as D-mannose, probiotics, and vaccines targeting uropathogens, to reduce reliance on antibiotics.
Public Health Campaigns	Launch campaigns aimed at educating patients and healthcare providers on AMR risks, the importance of appropriate antibiotic use, and hygiene.
Alternative or Adjunct Therapies	Investigate the use of adjunct therapies to SGLT2 inhibitors for high-risk populations to prevent recurrent infections and reduce AMR risk.
Multidisciplinary Collaboration	Foster collaboration among endocrinologists, infectious disease specialists, and public health officials to manage UTI risks in diabetics.
Monitor SGLT2 Inhibitor Use	Track and monitor the use of SGLT2 inhibitors in diabetic populations to ensure awareness of increased UTI risks and AMR trends.
Research and Surveillance on MDR Uropathogens	Invest in research and surveillance to monitor MDR uropathogens and assess the impact of SGLT2 inhibitors on UTI management in diabetic patients.

adopt a strategic and multifaceted approach to managing UTIs. Central to this strategy is the careful evaluation of the risk-benefit ratio of SGLT2 inhibitors, particularly in patients who are at high risk for recurrent UTIs. Individuals with anatomical abnormalities of the urinary tract or poor glycemic control are especially vulnerable, and for these populations, alternative therapies or additional preventive measures should be prioritized. By evaluating the potential risks and benefits on a patient-by-patient basis, healthcare providers can make more informed decisions about treatment options, ensuring that the use of SGLT2 inhibitors does not unnecessarily increase the risk of severe infections.

Equally important is the optimization of glycemic control. Proper management of blood glucose levels is critical in reducing hyperglycemia and glycosuria, both of which create an environment conducive to bacterial growth in the urinary tract. Improved glycemic control can limit the availability of nutrients for uropathogens, thereby reducing the incidence of recurrent infections. In this context, public health interventions that promote better diabetes management—through lifestyle changes, patient education, and access to appropriate medications—are crucial to mitigating the risk of UTIs.

Another cornerstone of this multifaceted approach is the implementation of judicious antibiotic use. Antibiotic stewardship programs must be prioritized to curb the overuse and misuse of antibiotics, which accelerates the development of resistant strains. These programs should be reinforced by the use of rapid diagnostic tools that can quickly and accurately identify pathogens and their susceptibility to antibiotics. This approach enables more targeted therapies, reducing unnecessary broad-spectrum antibiotic use, which is a key driver of AMR. Additionally, non-antibiotic interventions must be explored as a complementary strategy to prevent recurrent UTIs without contributing to AMR. Emerging therapies such as d-mannose, probiotics, and immunomodulatory treatments have shown promise in reducing bacterial adhesion to the urinary tract and modulating the microbiome, offering alternative avenues for infection prevention. Furthermore, vaccines targeting uropathogens or their virulence factors could provide long-term protection for at-risk populations, significantly reducing reliance on antibiotics.

By integrating these key elements—risk-benefit assessment, optimized glycemic control, judicious antibiotic use, and the development of non-antibiotic interventions—public health systems can adopt a comprehensive approach to managing the intersection of diabetes, SGLT2 inhibitors, and MDR infections. This proactive and holistic strategy will not only mitigate the risks associated with the use of SGLT2 inhibitors and recurrent UTIs but also play a critical role in the global fight against antimicrobial resistance.

Conclusion and future directions

The implications of SGLT2 inhibitor-associated UTIs extend far beyond individual patient care, highlighting significant public health concerns regarding the evolution of MDR bacteria, particularly in the context of diabetes management. The interplay between hyperglycemia, immunosuppression, glycosuria, and frequent antibiotic use in diabetic populations creates an environment that fosters both infections and the development of antibiotic resistance. This is especially concerning in regions like Asia, where rising diabetes rates coincide with increased antibiotic usage and escalating MDR pathogen prevalence. The growing threat of MDR organisms, particularly in high-risk diabetic populations, necessitates more sophisticated and integrated management strategies that address both metabolic and infectious complications.

While our review underscores the biological plausibility and clinical observations suggesting that SGLT2 inhibitors increase UTI risk through glycosuria-driven microbial proliferation, the broader literature presents conflicting evidence. A large meta-analysis of 77 randomized controlled trials [75] found no statistically significant increase in UTIs with SGLT2 inhibitor use overall, though agent-specific differences were observed—most notably, dapagliflozin was associated with a higher UTI risk. These discrepancies likely stem from heterogeneity in study designs, diagnostic criteria, population characteristics, and the use of microbiologically confirmed infections versus self-reported symptoms. Additional factors such as urine flow dynamics, host immune responses, and regional antimicrobial resistance patterns may further modulate infection risk. To address these inconsistencies, future studies should adopt standardized UTI definitions, stratify patients by sex, age, glycemic control, and UTI history, and incorporate long-term real-world data to assess recurrence and severity. Furthermore, mechanistic investigations into SGLT2 inhibitor-induced changes in the urinary microbiome and host immunity will be essential to identifying high-risk subgroups—particularly elderly diabetic women in Asia—and to refining evidence-based guidelines that balance metabolic benefits with infection risk mitigation.

Given the immunomodulatory effects of SGLT2 inhibitors, future studies should investigate their impact on host-pathogen interactions, particularly in diabetic populations at high risk for recurrent infections. Further research is needed to determine whether the observed increase in UTI risk is driven by blunted inflammatory responses, impaired neutrophil function, or dysregulated cytokine signaling. A deeper understanding of these mechanisms will inform the development of targeted therapeutic strategies to balance the metabolic benefits of SGLT2 inhibitors with the need to mitigate infection risk

Public health initiatives should prioritize multifaceted approaches, including improved glycemic control, antibiotic stewardship, and the exploration of non-antibiotic therapies, to mitigate the compounded risks associated with SGLT2 inhibitors. Additionally, future research should focus on exposing the molecular mechanisms of host-pathogen interactions within the glycosuric urinary tract, as this will provide critical insights into how MDR pathogens evolve in this environment. Understanding these interactions at a deeper level could lead to the development of novel therapeutic interventions that address both metabolic dysregulation and infection prevention. This research will be crucial in preserving the effectiveness of current antibiotic regimens, particularly in Asia, where diabetes and antibiotic resistance intersect to form a growing public health challenge.

Safeguarding the future of antibiotic efficacy and improving patient outcomes in diabetic populations will require a comprehensive and proactive public health approach. This includes fostering innovative research, improving clinical management strategies, and promoting global collaboration to combat the rising tide of MDR infections associated with diabetes and SGLT2 inhibitor use. The path forward lies in an integrated understanding of metabolic and infectious diseases and the development of therapeutic interventions that can simultaneously address these dual threats.

CRediT authorship contribution statement

Rob E. Carpenter: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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