REVIEW PAPER

Impact of the urinary microbiome on urinary tract infection progression

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Introduction Urinary tract infections (UTIs) remain a significant challenge in modern urology, increasingly complicated by the shift away from the "sterile bladder dogma." This narrative review summarizes current knowledge (2020–2026) on the urinary microbiome in women, men, and children, emphasizing the transition toward personalized urological care.

Material and methods We conducted a comprehensive synthesis of 48 peer-reviewed articles from PubMed, Scopus, and Google Scholar. This narrative review evaluates the interplay between the urinary microbiome, host immune response, and pathogen virulence, while critically comparing traditional urine cultures with advanced diagnostic tools, such as next-generation sequencing (NGS) and expanded quantitative urine cultures (EQUC).

Results Our analysis highlights the role of dysbiosis in UTI progression and the increasing threat of multidrug-resistant pathogens within the ESKAPEE group. Findings reveal that while modern diagnostics offer a more detailed microbial profile, clinical implementation remains constrained by technical and standardization challenges.

Conclusions Standard urine culture is insufficient for managing recurrent or atypical UTIs. We advocate for a personalized diagnostic and therapeutic approach that integrates molecular insights, aiming to curb antibiotic overuse and improve patient outcomes in the era of rising drug resistance.

Key Words: urinary microbiome ‹› urobiota ‹› UTI ‹› NGS ‹› EQUC ‹› virulence factors

INTRODUCTION

Urinary tract infections (UTIs) represent one of the most serious problems in modern urology and general medicine, generating significant burdens for healthcare systems and negatively affecting patients' quality of life. For the better part of the last century, the diagnosis and treatment of these infections were based on the paradigm of bladder sterility in healthy individuals. This concept was established in the 1950s based on the studies of Edward Kass and the technical limitations of standard urine cultures [1, 2]. Seminal research by Hilt et al. [3] played a key role in shifting this paradigm, proving that the female bladder contains diverse communities of living bacteria detectable through enhanced culture techniques. Modern technological advancements, particularly culture-independent molecular methods such as 16S rRNA gene sequencing, have further revised this view by revealing a complex ecosystem of microorganisms inhabiting the urinary tract, hereafter referred to as the urinary microbiome [4, 5].

Recent literature reports indicate that methods based on 16S rRNA sequencing are characterized by significantly higher sensitivity in detecting bacteria than conventional polymerase chain reaction (PCR) methods or standard cultures [5]. However, the clinical interpretation of these molecular findings remains challenging due to the low microbial biomass of the urinary tract, potential sample contamination during collection, and a lack of standardized analytical pipelines.

In the context of human-microbe interactions, maintaining a healthy microbial ecosystem is often described as a state of eubiosis. This state is characterized by a balanced and diverse microbial community that actively promotes host health, mucosal integrity, and immunological homeostasis [6]. Disruption in this balance – whether through a loss of beneficial taxa, overgrowth of potential pathogens, or reduced overall diversity – is termed dysbiosis, a state frequently associated with local inflammation, altered host immune responses, and increased susceptibility to infections [6, 7].
Understanding the dynamics of the urinary microbiome is becoming crucial in the face of increasing antimicrobial resistance and clinical difficulties in differentiating symptomatic infections from asymptomatic bacteriuria (ASB), which poses a particular challenge in the geriatric population [8]. Although a clear causal link between specific dysbiotic profiles and clinical outcomes remains to be fully elucidated, exploring these microbial shifts offers promising diagnostic avenues. This paper aims to review current literature regarding the role of the urinary microbiome in the pathophysiology of UTIs, considering sex and age specificity, detailed analysis of uropathogen virulence mechanisms, and a critical evaluation of the utility and limitations of new diagnostic and therapeutic methods.

MATERIAL AND METHODS

Study design

This manuscript is a narrative review, structured to provide a comprehensive synthesis of current clinical and molecular evidence concerning the urinary microbiome and its role in uropathogenesis.

Search strategy

A comprehensive literature review was conducted across PubMed, Scopus, and Google Scholar databases, covering publications released up to April 2026. The search utilized key words including "urinary microbiome," "urobiota," "recurrent urinary tract infection," "NGS," "EQUC," and "uropathogen virulence factors." This strategy aimed to capture the broad evolution of diagnostic and therapeutic approaches in urology, distinguishing between foundational knowledge and contemporary advancements.

Eligibility criteria

Peer-reviewed articles (original research, systematic reviews, meta-analyses) published in English were selected for synthesis. A tiered approach was employed: foundational literature (predominantly pre-2020) was retained to establish the necessary theoretical framework for uropathogen classification and pathophysiology, while contemporary research (2020–2026) was prioritized for evaluating clinical diagnostic innovations (next-generation sequencing [NGS] and expanded quantitative urine cultures [EQUC]) and recent preventive strategies. Studies of low clinical relevance, older reports inconsistent with current standards, and animal model studies were excluded.

Data synthesis

A total of 48 bibliographic items were synthesized, deemed most representative of the discussed issues. This literature synthesis integrates historical milestones with current evidence to characterize sex- and age-specific shifts in microbial composition, detail contemporary drug resistance mechanisms, and critically evaluate the clinical efficacy of innovative UTI prevention methods.

FEMALE URINARY MICROBIOME

A significant aspect of the female genitourinary physiology is the strong link between the vaginal and bladder microenvironments, suggesting the existence of a functionally interconnected urogenital ecosystem. Analyses of paired catheterized urine samples and vaginal swabs from the same individual have shown significant taxonomic overlap. The genus *Lactobacillus* frequently dominates both niches, constituting an average of over 50% of the urinary microbiome and over 60% of the vaginal microbiota composition [9]. Komesu et al. [9] demonstrated that this high correlation between environments extends to specific species, with *Lactobacillus crispatus* and *Lactobacillus iners* being the most frequently co-occurring taxa. However, it is worth noting that *L. iners*, despite its prevalence, is often characterized as less ecologically stable and may provide weaker protection against dysbiosis than *L. crispatus* [9].
While *Lactobacillus* dominance is generally recognized as a biomarker of a healthy urinary tract, patients with recurrent urinary tract infections (rUTI) often exhibit a dysbiotic shift characterized by a decrease in these protective taxa, alongside an increase in overall microbial diversity and pathogen abundance [10, 11]. Recent studies in a Polish population by Chorbińska et al. [12] confirmed that biological sex remains a primary determinant of the urinary microbiome composition; for instance,

the genus *Howardella* and the strain *Streptococcus anginosus* were found to be more common in women. Furthermore, it has been observed that patients with a history of Bacillus Calmette-Guérin (BCG) therapy show a significantly higher abundance of *Lactobacillus* in their urine samples [12].

Metagenomic analyses indicate that in women with a history of rUTI, even during asymptomatic periods, the urinary microbiome differs from healthy controls through the enrichment of species such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecalis*. Additionally, anaerobic bacteria, such as *Finegoldia magna*, occur more frequently in these patients, though their abundance has been shown to decrease following estrogen therapy [11, 13, 14]. In patients presenting with rUTI symptoms but negative standard urine cultures, 16S rRNA gene sequencing has revealed the presence of fastidious pathogens such as *Ralstonia*, *Prevotella*, and *Dialister* [10].

Attempting to link these microbial profiles to clinical manifestations, Burnett et al. suggested specific symptomatic phenotypes. For instance, women with predominant symptoms of frequency and back pain (group B) displayed an increased proportion of *Lactobacillus* [15]. Conversely, the highly symptomatic cohort reporting severe pain, urgency, and foul-smelling urine (group E) was characterized by *Klebsiella* enrichment [15]. A distinct subset (group D), presenting with pain and urgency, frequently yielded no bacterial growth ("No Growth") in standard cultures [15]. While this could hypothesize a "non-bacterial cystitis" etiology where viruses, fungi, or unculturable microorganisms play a role, these clinical-microbiome associations remain purely observational, and direct causality has yet to be established.

Hormonal status, particularly systemic estrogen levels, represents a major endogenous factor shaping the female urinary microbiome. The decline in estrogen levels post-menopause correlates with a reduction in the *Lactobacillus* population and a concomitant rise in microbial diversity, matching the period of increased susceptibility to UTIs [4, 11, 13]. While local estrogen therapy is associated with restoring *Lactobacillus* dominance and a reduction in urge incontinence symptoms [4, 16], the underlying protective mechanism appears multifactorial. Thomas-White et al. demonstrated that estrogen therapy stimulates the bladder epithelium to produce antimicrobial peptides (AMPs) and strengthens epithelial barrier integrity [16]. Neugent et al. observed that in women with a history of rUTI, the physiological correlation between urine estrogen metabolite concentrations and the abundance of *L. gasseri* and *L. crispatus* is disrupted [11]. This suggests that in chronic rUTI patients, estrogen administration alone may be insufficient to rebuild a protective microflora, indicating potentially permanent alterations in microbiome ecology [11].

From a diagnostic perspective, standard urine culture (SUC) is increasingly criticized for yielding false-negative results, as it fails to capture bacteria requiring specialized growth conditions [2, 17]. The Expanded Quantitative Urine Culture (EQUC) protocol – which involves plating larger volumes of urine (0.1 ml) and extending incubation to 48 hours under varied atmospheric conditions – demonstrates significantly higher sensitivity in identifying fastidious organisms like *Enterococcus faecalis* [3, 17]. However, the clinical translation of these advanced diagnostic methods faces significant controversies and methodological barriers that limit their current real-world applicability. A primary challenge stems from the fact that the bladder is a notoriously low-biomass environment, making sequencing-based methods like 16S rRNA and expanded cultures highly susceptible to environmental and kit-derived contamination, which frequently leads to false-positive results.

Furthermore, sampling methods introduce profound biases; while transurethral catheterization is considered the most reliable technique to assess true bladder residents, it remains inherently invasive and carries a minor risk of introducing infection. Clean-catch voided urine is heavily prone to contamination from vulvar and urethral flora, severely complicating the differentiation between genuine bladder dysbiosis and external sample artifact. This issue is compounded by a total lack of global standardization regarding EQUC protocols, sequencing pipelines, and bioinformatics thresholds. From a clinical decision-making standpoint, the identification of low-abundance organisms via next-generation sequencing or expanded culture does not automatically imply pathogenicity. Distinguishing true infection from benign commensalism remains a formidable task, and there is currently insufficient evidence to prove that altering antimicrobial therapies based on molecular microbiome data translates into improved long-term patient outcomes.

MALE URINARY MICROBIOME AND BIOFILM DYNAMICS

The male urinary microbiome constitutes a unique ecosystem, the characteristics of which differ significantly from the female profile due to anatomical differences and the more frequent need for transurethral catheterization in older populations. Comparative studies by Hrbacek et al. showed

fundamental variations in microbial profiles depending on the collection method, noting that "first-void" and "mid-stream" urine are characterized by significantly higher biological diversity than catheterized samples [18]. This indicates that non-invasive samples in men are highly susceptible to contamination from the distal urethral flora, making catheterization a critical consideration for a reliable assessment of the true bladder microenvironment [18]. In catheterized samples, the genus *Pseudomonas* typically dominates [18].

The epidemiological specificity of infections in men manifests as a clear shift in the pathogen profile towards Gram-positive bacteria. A multicenter analysis conducted by Salm et al. [19] on a cohort of nearly 100,000 men showed that *Enterococcus faecalis* is the second most frequently isolated uropathogen, accounting for 16.1% of suspected infection cases. Surprisingly, the highest percentage of *E. faecalis* isolation (16.8%) was recorded in the group of young men (18–29 years), challenging the common clinical assumption that it serves exclusively as a geriatric pathogen [19]. Infections associated with *E. faecalis* in men exhibit a higher recurrence rate (25.9%) compared to *Escherichia coli* infections (22.2%), a clinical challenge that is compounded by increasing resistance to ciprofloxacin in this age group [19].

The placement of a urinary catheter radically alters the ecological landscape of the male urinary tract, introducing an abiotic surface that serves as a substrate for microbial colonization. Longitudinal studies in older men with chronic catheters showed that the urinary microbiome under such conditions is highly stable over time within a given patient, despite substantial inter-individual variability [20]. Under conditions of chronic catheterization, a spatial homogenization of the microbial communities appears to occur within the entire system, rendering the species composition in the bladder, on the catheter tip, and within the urethra highly congruent [20].

A central element of the pathogenesis of catheter-associated urinary tract infections (CAUTI) is biofilm formation, which constitutes a complex, highly functional architecture. Advanced proteomic analysis conducted by Garcia-Marques et al. [21] revealed that bacteria within a biofilm exhibit distinct phenotypic and metabolic characteristics compared to their planktonic counterparts suspended in urine. While human inflammation-related proteins dominate the fluid phase, the majority (61%) of the proteome in the biofilm consists of bacterial proteins [21]. Bacteria in the biofilm, such as *E. coli*, alter their metabolic pathways, downregulating the synthesis of amino acids readily available in urine in favor of upregulating translation and energy production pathways necessary to maintain the structural integrity of the biofilm [21]. Species such as *Enterococcus*, *Candida*, and *Proteus mirabilis* show a strong affinity for this biofilm phase, which may partly explain their enhanced tolerance to standard antimicrobial treatment [21]. A particular clinical challenge is crystalline biofilms formed by *Proteus mirabilis*, which lead to catheter incrustation and blockage through urine alkalization [22]. Furthermore, polymicrobial interactions frequently complicate this dynamic, particularly through bacterial-fungal co-infections. Joshi et al. demonstrated that the presence of *Candida* species within a bacterial biofilm (e.g., with *E. coli* or *P. aeruginosa*) structurally reinforces the matrix, making it thicker and more strongly adherent to the catheter surface than single-species biofilms [23]. These colonization dynamics depend heavily on exposure time; studies on short-term catheters revealed the presence of bacteria on catheter surfaces in the majority of patients, but this microbial presence did not serve as a direct causal predictor for the subsequent development of symptomatic infection [24, 25]. From a clinical applicability perspective, these findings strongly question the validity of routine antibiotic prophylaxis based solely on the documentation of asymptomatic colonization, highlighting that urologists should prioritize patient-centered symptomatic evaluation over exploratory microbiological findings to avoid driving further antimicrobial resistance.

PEDIATRIC URINARY MICROBIOME

In the pediatric population, the presence of bacterial genetic material can be confirmed in almost every urine sample, even in newborns [26]. The characteristics of this urinary microbiome show dynamic changes related to age and sex; the urinary microbial ecosystem of girls is characterized by higher biological diversity compared to boys, in whom this diversity appears to increase with age [27]. A history of recurrent infections is observed to correlate with a distinct microbial shift often conceptualized as a "microbiological scar," where children with recurrent UTIs frequently exhibit significantly reduced microbiological diversity and a reduction in the abundance of certain bacteria, including the genus *Enterococcus* [27]. During active infection, a drastic decrease in alpha diversity and a change in beta diversity profile occur, distinguishing children with infection from the control group [26].

Urinary microbiome analysis seems particularly important in the context of conditions predisposing to infections, such as bladder and bowel dysfunc-

tion (BBD), a recognized risk factor for UTIs [28]. Studies have shown that despite clinical burdens, the core urinary microbiome in children with BBD is similar to that observed in healthy children [28]. A subtle difference exists in the presence of additional bacterial genera associated with opportunistic infections, such as *Campylobacter* or *Streptococcus*, suggesting that the etiology of BBD may rely more heavily on underlying functional and physiological mechanisms rather than profound dysbiosis [28].

An equally significant impact on the urinary tract ecosystem is associated with long-term pharmacological interventions used in structural defects, such as vesicoureteral reflux (VUR) [29]. Although continuous antibiotic prophylaxis (CAP) remains a clinical standard in preventing UTI recurrence and subsequent renal scarring, its long-term utility must be carefully balanced against its tendency to disrupt microbial homeostasis [29]. Clinical data indicate that CAP correlates with specific taxonomic shifts, consisting of an enrichment of bacteria from the *Enterobacteriaceae* family alongside a simultaneous reduction in protective populations, especially from the *Bifidobacteriaceae* family [29]. This phenomenon is associated not only with a change in the bacterial profile but also with the escalation of antimicrobial resistance [29]. From a pediatric urology standpoint, this classic therapeutic trade-off underscores the need for a highly personalized approach to CAP, where the immediate risk of irreversible renal scarring is carefully weighed against the long-term, multi-systemic consequences of driven antimicrobial resistance and microbiome disruption.

MOLECULAR BASIS OF PATHOGENESIS AND ADAPTATION OF UROPATHOGENS

Uropathogenic *Escherichia coli* (UPEC) remains the primary etiological factor in urinary tract infections, accounting for approximately 75% of uncomplicated cases. The pathogenesis of UPEC involves sequential stages of adhesion, colonization, and host immune evasion [30]. Cellular internalization is initiated by the chaperone-usher fimbriae family, where type 1 fimbriae utilizing the FimH adhesin bind to mannosylated uroplakins on the bladder epithelium [31]. P fimbriae, via the PapG adhesin, display specific affinity for renal glycolipids, participating in the development of pyelonephritis. Clinical profiling indicates that curli fimbriae (encoded by *csgA*) and type 1 fimbriae (*fimH*) are frequently identified together among clinical isolates [32]. Additionally, F1C fimbriae (*foc* genes) and P fimbriae alleles, particularly *papGII*, are distributed among invasive strains, whereas type 3 fimbriae (*mrkD* adhesin) contribute to bacterial adherence on both biotic and medical surfaces [33, 32]. For genotypic screening, multiplex PCR assays are used to identify these profiles, reducing the rate of false-positive results associated with monoplex protocols [33].

UPEC can survive within host tissues by forming intracellular bacterial communities (IBCs). Following urothelial invasion, bacteria replicate within the cytoplasm, establishing biofilm frameworks that limit the penetration of neutrophils and standard antimicrobials. Pathogens can also transition into metabolic dormancy, persisting as quiescent intracellular reservoirs (QIRs) within deeper epithelial layers and contributing to infection recurrence after antibiotic clearance [31]. Furthermore, the urinary microbiome plays a role in urolithiasis, where a distinct 'core stone microbiome' serves as a niche for bacterial persistence within the calculi [34]. This adaptability correlates with the structural variability of the UPEC pan-genome [35]. Virulence gene profiling shows that the cytotoxic necrotizing factor 1 (*cnf1*) gene occurs frequently in clinical isolates, often co-occurring with genes encoding the autotransporter adhesin *upaH*, alfa-hemolysin (*hlyA*), and the invasin *ibeA*, while the cytolethal distending toxin gene *cdtB* is typically absent in non-catheterized cohorts [35].

Survival in the low-iron environment of the urinary tract is mediated by iron-acquisition pathways. UPEC secretes multiple siderophores, including aerobactin, yersiniabactin, and salmochelin, to sequester ferric iron and bypass host nutritional immunity [30]. The pathogens also produce cytotoxins, such as hemolysin (HlyA) and cytotoxic necrotizing factor 1 (CNF1), which induce host cell lysis and tissue alterations to facilitate deeper invasion [30, 31]. Characterizing these virulence gene configurations provides baseline data for molecular diagnostics; these conserved sequences can serve as templates for designing DNA microarray probes to profile uropathogen virulomes in reference laboratories [35, 36].

THERAPEUTIC AND PREVENTIVE PERSPECTIVES

Due to increasing antimicrobial resistance among uropathogens and the variable efficacy of standard antibiotic therapies in preventing recurrence, alternative preventive strategies targeting immunomodulation and microbiome modification are under clinical evaluation. Vaccine formulations, including Uromune (MV140), Uro-Vaxom (OM-89), Solco-Urovac, and ExPEC4V, have been studied for their capacity to prevent recurrent UTIs. Short-term data (under 6 months) indicate a reduction

in recurrence risk (odds ratio, OR = 0.17; 95% CI: 0.06–0.50), which remained consistent in evaluations extending beyond 6 months (OR = 0.20; 95% CI: 0.07–0.59) [37]. The lysat-based preparation Uro-Vaxom (OM-89) is currently included in the European Association of Urology (EAU) guidelines based on randomized controlled trials that report a short-term risk reduction (OR = 0.29) and post-intervention bacterial clearance rates between 81.3% and 96.3% after 6 months [37]. However, the clinical interpretation of these data is limited by substantial clinical trial heterogeneity, variations in study designs, and mixed real-world reproducibility, while regulatory barriers continue to restrict widespread deployment.

Probiotic interventions have also been evaluated, with recent data highlighting the role of the administration route. A randomized clinical trial indicated that vaginal or combined (oral and vaginal) supplementation with *Lactobacillus* strains provides a greater reduction in recurrence compared to exclusive oral administration, suggesting that direct mechanical recolonization of the urogenital niche influences clinical outcomes [38]. Conversely, a meta-analysis reported limited clinical efficacy for D-mannose in postmenopausal cohorts [39]. This indicates that the competitive inhibition of FimH fimbriae by D-mannose may be insufficient in the presence of age-related epithelial atrophy and structural alterations in the resident microbiome [39].

Bacteriophage therapy represents another modality evaluated for disrupting bacterial biofilms on urinary catheters, where standard antibiotics often fail [40]. Although experimental models show biofilm degradation, clinical translation is constrained by a lack of standardized manufacturing protocols, unestablished dosing regimens, and complex regulatory hurdles regarding biological agents [40]. For catheter-associated urinary tract infections (CAUTI), alternative preventive methods involve surface modifications with metal ion coatings, such as silver or copper, or the deployment of biofilm-degrading enzymes. Additionally, bacterial interference strategies, such as the intentional colonization of the bladder with non-pathogenic strains like *E. coli* 83972, are being examined for their ability to competitively exclude uropathogens from the local ecological niche.

THE ASSOCIATION OF HOST-UROPATHOGENS, HOST-MICROBIOTA AND HOST-IMMUNE SYSTEM

The human urinary system maintains homeostasis through a coordinated network involving communication between the urinary, immune, and nervous systems [41]. Local tissue homeostasis is mediated by innate and adaptive immune cells, such as macrophages, which express an array of immune biomolecules including interleukins and pattern-recognition receptors like Toll-like receptors (TLRs) [41]. Mammalian TLRs consist of an extracellular leucine-rich repeat domain, a transmembrane domain, and an intracellular Toll/interleukin-1 receptor domain [42]. Upon binding to specific microbial or host-derived ligands, these receptors initiate intracellular signaling cascades via adapter molecules such as myeloid differentiation factor 88 (MyD88) or TRIF, subsequently activating downstream transcription factors including nuclear factor-kB and mitogen-activated protein kinases [42]. Host physiological variables, such as genetics, immune function, age, and stress, directly shape resident microbial populations [43]. A balanced microbial community represents a state of eubiosis that actively supports host health through the production of beneficial metabolites, whereas an unbalancing or dysbiosis can disrupt homeostasis, promote inflammation, and alter host immune responses [43]. Systemic inflammation acts as a key health-related communication tool between the host immune apparatus and the gut microbiota [43]. In the urogenital tract, the interaction between host immunity and invading uropathogens dictates the severity and clinical presentation of urinary tract infections [44]. Uropathogens possess specific genetic regulatory mechanisms that alter their pathobiology and survival within the host; for example, the KguS/KguR two-component signaling regulon regulates genes involved in capsule biosynthesis, iron uptake, and acid resistance, directly modifying uropathogenic *Escherichia coli* (UPEC) fitness and murine colonization [44]. Pathogens also utilize population heterogeneity to navigate selective pressures in the urinary tract, where UPEC can regulate flagellin abundance and downstream transcriptional hierarchies to evade Toll-like receptor recognition and circumvent host-mediated bacterial killing [44].

Following entry into the urinary tract, invasive pathogens like *Escherichia coli* and *Klebsiella pneumoniae* attach to, internalize, and proliferate within bladder urothelial cells [44]. Their ability to persist enables differentiation into intracellular bacterial communities during the early stages of infection, or the formation of quiescent intracellular reservoirs that contribute to high recurrence rates, particularly in female populations [44]. High-throughput next-generation sequencing of the 16S rRNA gene has identified distinct variations

in the urinary microbiome composition of female patients with recurrent infections, demonstrating that specific bacterial genera, including *Corynebacterium*, *Ralstonia*, *Prevotella*, and *Dialister*, correlate with recurrent clinical profiles [44]. Furthermore, the distribution of these etiological agents exhibits clear age-specific patterns, where *Enterococcus faecium* serves as the primary pathogen among infants, while *Escherichia coli* remains the dominant etiological agent across childhood, adult, and geriatric cohorts [44]. To address these persistent infections and mitigate the risks of driven antimicrobial resistance, multi-antigen vaccine formulations like StroVac are evaluated to activate both the innate and adaptive immune branches against recurrent uropathogens [41].

UROPATHOGENS, UROBIOTA AND ANTIBIOTIC RESISTANCE

The escalation of antibacterial resistance among uropathogens represents a critical threat to global public health, particularly within the urinary tract microbiome ecosystem [45]. To conceptualize the primary bacterial drivers of this resistance, uropathogenic taxa are frequently classified within the high-priority ESKAPEE group, which has recently been extended to include *Escherichia coli* alongside *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species [45, 46]. Within this group, uropathogenic *Escherichia coli* (UPEC) demonstrates substantial genomic plasticity, possessing an open pan-genome that facilitates the accumulation of variable acquired carbapenemase genes [45]. Recent molecular surveillance of UPEC isolates reveals a high prevalence of acquired metallo-beta-lactamase genes, with *blaSPM* identified in 82.86%, *blaGIM* in 20.00%, and *blaVIM* in 16.19% of clinical strains [45]. This extensive resistome drives severe multi-drug resistant (MDR), extensively drug-resistant (XDR), and pan-drug resistant (PDR) phenotypes among uropathogens, with MDR profiles documented in up to 75.24% of UPEC isolates [45].

Similarly, *Acinetobacter baumannii* serves as another highly critical Gram-negative ESKAPEE pathogen responsible for severe healthcare-associated urinary tract infections and sepsis [47]. The genomic pool of *A. baumannii* is highly fluid, frequently carrying mobile genetic integrase genes (*intI*, *intII*) alongside near-universal distributions of carbapenemase genes, including *blaOXA-23-like* (100%), *blaOXA-24-like* (99%), *blaOXA-51-like* (97%), *blaNDM* (98%), and *blaSIM* (98%) [47]. These complex genotypic configurations result in severe clinical challenges, with up to 40% of *A. baumannii* strains exhibiting XDR profiles and 23% advancing to complete PDR status [47].

Furthermore, *Pseudomonas aeruginosa* represents an armed opportunistic uropathogen capable of causing catheter-associated urinary tract infections (cAUTIs) and bacteremia [46]. The dynamic pan-genome of *P. aeruginosa*, which ranges from 5.5 to 7.76 Mbp, enables the rapid acquisition of resistance determinants through horizontal gene transfer [46]. This mobilization is mediated by a complex mobilome composed of transposable elements, integrons, transposons, and specific *Pseudomonas aeruginosa* genomic islands (PAGIs) that actively disseminate acquired carbapenemase genes [46]. The global spread of these carbapenemases is closely linked to international high-risk epidemic clones, such as ST235, ST111, ST233, and ST244, which express versatile β-lactamase arsenals across diverse healthcare settings [46].

Beyond these traditional ESKAPEE members, other opportunistic species within the Enterobacterales order, such as *Serratia marcescens*, are emerging as dangerous nosocomial uropathogens [48]. *S. marcescens* exhibits intrinsic resistance to β-lactams via a chromosomal AmpC β-lactamase, which can be further amplified during antimicrobial therapy [48]. The evolutionary adaptation and resistome expansion of *S. marcescens* are driven by mobile genetic elements, facilitating transition into multidrug-resistant "superbug" phenotypes and carbapenem-resistant *Serratia marcescens* (CRSM) lineages [48]. Mechanistically, the dissemination of these diverse antibacterial resistance genes within the urinary microbiome relies on horizontal gene transfer driven by conjugation, natural transformation, transduction, and vesiduction via extracellular vesicles [48, 45].

STRENGTHS AND LIMITATIONS

While this review provides a comprehensive synthesis of contemporary urological data up to 2026, its narrative design introduces inherent methodological boundaries, and the potential for selection bias cannot be entirely excluded. Additionally, a significant portion of the compiled clinical-microbiome profiles relies on observational cohorts, meaning that direct causal relationships between specific dysbiotic states and recurrent infections remain hypothesis-driven. The clinical translation of advanced molecular diagnostic tools and innovative non-antibiotic therapies remains constrained by the marked heterogeneity of recent clinical trials

and a current lack of global standardization across bioinformatics and regulatory frameworks.

CONCLUSIONS

The conducted literature analysis leads to the conclusion that standard urine culture should not be treated as the sole and sufficient diagnostic tool in cases of recurrent or atypical urological complaints, justifying the need for broader implementation of expanded culture methods and molecular methods as they become available. Effective therapy of urinary tract infections requires a personalized approach, taking into account the urinary microbiome specificity of a given patient group, which may include restoring the *Lactobacillus* population in postmenopausal women through estrogen therapy and combating biofilm in catheterized men. In the era of increasing drug resistance, a precise distinction between asymptomatic colonization and active infection, supported by modern diagnostics, is key to limiting antibiotic overuse. Further long-term studies are necessary to evaluate the effectiveness of interventions modifying the urinary microbiome in preventing urinary tract infection recurrence.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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