UDC: 616.62-002-036.12:579.61:579.26
DOI: https://doi.org/10.32345/USMYJ.2(163).2026.36-47

From sterile urine to dysbiotic ecosystem: The role of urobiome disruption in recurrent urinary tract infection

Antony Hamlin Joseph, Sunil Manjima, Franklin Frieno Frank
Tbilisi State Medical University, Tbilisi, Georgia

Abstract. *Introduction.* Recurrent urinary tract infections are best conceptualized as a disorder of microbial disequilibrium in which disruption of the normally protective urogenital ecosystem permits repeated pathogen establishment and persistence. Rather than representing isolated infectious episodes, recurrence reflects a failure of microbial homeostasis across interconnected niches, including the urinary tract, vagina, and gastrointestinal system. A defining feature of this condition is the decline of protective commensal organisms, particularly *Lactobacillus* species, accompanied by increased dominance of opportunistic uropathogens such as *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, and Proteus mirabilis*, which collectively undermine colonization resistance and promote infection susceptibility.
Aim. The aim of this review is to characterize recurrent urinary tract infections as a manifestation of persistent microbial imbalance and adaptive pathogen survival, with particular attention to the role of the urogenital and gastrointestinal microbiome, biofilm formation, intracellular bacterial reservoirs, and microbiome-oriented therapeutic approaches.
Materials and Methods. This review summarizes current concepts regarding microbial disequilibrium, pathogen persistence mechanisms, antimicrobial-associated microbiome disruption, the gut–bladder axis, vaginal microbiota alterations, and emerging strategies aimed at restoring microbial equilibrium in recurrent urinary tract infections.
Results. This imbalance is often reinforced by repeated courses of antimicrobial therapy, which, while targeting acute infection, inadvertently deplete beneficial microbial populations, reduce ecological diversity, and select for resistant strains with enhanced survival capacity. Central to recurrence is the ability of pathogens to evade eradication through specialized persistence strategies. These include the development of biofilms that function as structured, matrix-enclosed communities with reduced metabolic activity and limited antibiotic accessibility, as well as intracellular bacterial reservoirs that enable pathogens to remain concealed within urothelial cells in a dormant state. Persister cells further contribute by adopting transiently inactive phenotypes that tolerate antimicrobial exposure and later repopulate once treatment pressure is removed. In parallel, the gastrointestinal tract acts as a continual source of uropathogens, facilitating reinfection through repeated transfer along the gut–bladder axis, while alterations in vaginal microbial composition—particularly those associated with hormonal changes—further compromise local defense mechanisms. Collectively, these processes create a self-sustaining cycle of microbial instability and infection recurrence.
Conclusions. Consequently, effective management requires a shift away from pathogen elimination alone toward strategies that restore and maintain microbial equilibrium. Interventions such as targeted probiotics, hormonal therapies, dietary modulation, and emerging microbiome-based approaches aim to reinforce beneficial microbial communities and enhance host resistance. Nonetheless, variability in clinical response highlights the need for improved mechanistic understanding and standardized therapeutic frameworks. In this context, recurrent urinary tract infection should be regarded as a manifestation of persistent ecological disruption and adaptive microbial survival, necessitating comprehensive approaches that address both microbial composition and functional resilience.

Keywords: Recurrent urinary tract infections, gastrointestinal microbiome, biofilms, bacterial adhesion.

Introduction

Urinary tract infections (UTIs) are among the most prevalent bacterial infections globally, affecting an estimated 150–250 million individuals annually and contributing significantly to antibiotic consumption and healthcare expenditure [1, 2]. Uropathogenic Escherichia coli (UPEC) accounts for approximately 80% of uncomplicated infections, with Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis, and Staphylococcus saprophyticus collectively responsible for the majority of remaining cases [1, 2, 3]. Women bear a disproportionate burden of disease owing to anatomical proximity of the urethra to the perianal region, the shorter urethral length, and hormonal factors that influence periurethral and vaginal microbial composition [2].

Recurrent urinary tract infection (rUTI), conventionally defined as two or more episodes within six months or three or more within twelve months [4], represents a clinically distinct and particularly challenging syndrome. Approximately 20–30% of women who experience a primary UTI will develop recurrent infection [5], a trajectory associated with declining quality of life, increasing antibiotic exposure, and a growing risk of antimicrobial resistance. Despite decades of research, effective and durable prevention of rUTI remains elusive, in part because conventional antimicrobial management does not address the host and microbial conditions that predispose to recurrence.

For much of the twentieth century, the prevailing paradigm held that the healthy urinary tract was microbiologically sterile, a view sustained by the limitations of conventional urine culture and the diagnostic threshold of 10^5 colony-forming units per milliliter [1, 6]. This framework systematically excluded organisms present in low abundance or requiring specialized growth conditions. The subsequent application of EQUC and molecular methods—including 16S ribosomal RNA gene sequencing and metagenomic analysis—revealed that the healthy urinary tract harbors a resident microbial community, the urobiome, whose composition may influence host susceptibility to infection [1, 6, 7]. These discoveries challenged the sterile-bladder paradigm and stimulated growing interest in the potential role of microbial imbalance, or dysbiosis, in the pathogenesis of rUTI.

However, several important methodological caveats must be borne in mind when interpreting this literature. Urine is a low-biomass sample, making it susceptible to contamination artefacts during collection and sequencing. The choice of collection method—midstream voided urine, catheterized specimen, suprapubic aspirate, or EQUC—substantially affects the microbial profile obtained, and findings are not readily comparable across studies that use different approaches [6, 7]. Furthermore, most studies in this field are cross-sectional and associative; they document correlations between microbial profiles and infection history but do not establish causality. These limitations are addressed in detail in the Methodological Considerations section.

This narrative review synthesizes the available evidence on the urobiome in relation to rUTI, with particular attention to: (1) the compositional characteristics of the healthy versus rUTI-associated urobiome; (2) critical methodological considerations in urobiome research; (3) pathogen persistence mechanisms operating within the urinary environment; (4) the role of the gut–bladder axis and hormonal factors; and (5) the current evidence base for microbiome-targeted therapeutic strategies. Where the evidence permits, mechanistic hypotheses are discussed; where it does not, uncertainty is explicitly acknowledged.

Aim

Recurrent urinary tract infections remain difficult to manage despite antimicrobial therapy, largely due to incomplete understanding of the urinary microbiome and its role in disease pathogenesis.

Materials and Methods

Literature Search Strategy

A systematic literature search was conducted in June 2025 across three electronic databases: PubMed, Scopus, and Web of Science. The search was restricted to articles published between January 2015 and May 2025, in English, to prioritize literature informed by contemporary microbiome technologies (Table 1). The following MeSH terms and free-text keywords were combined using Boolean operators:

- "recurrent urinary tract infection" OR "rUTI"
- "urinary microbiome" OR "urobiome" OR "bladder microbiome"
- "gut–bladder axis" OR "intestinal microbiome" AND "urinary tract"
- "biofilm" AND "uropathogen"
- "intracellular bacterial communities"
- "EQUC" OR "expanded quantitative urine culture"
- "probiotic" AND "urinary tract infection"

Older foundational studies (pre-2015) were included where they were methodologically landmark (e.g., original descriptions of EQUC, seminal epidemiological studies) or specifically cited in recent systematic reviews. Reference lists of included articles were manually screened for additional relevant sources.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they reported on urinary, vaginal, or gastrointestinal microbiome composition in relation to UTI or rUTI, described pathogen persistence mechanisms in the urinary tract, or evaluated therapeutic interventions targeting the urinary or intestinal microbiome. Both observational studies (cross-sectional, cohort, case-control) and interventional studies (randomized and non-randomized trials) were considered. Editorials, conference abstracts, and studies published solely in non-English languages were excluded.

Selection Process and Data Extraction

Titles and abstracts were independently screened by two authors for relevance. Full-text review was performed for all potentially eligible studies. Disagreements were resolved by consensus with the third author. Data were extracted on study design, population, urine collection method, microbiome analysis technique, key findings, and reported limitations. No formal quality scoring was applied, consistent with narrative review methodology; instead, the level and consistency of evidence supporting each claim is described within the text.

The search yielded 578 records prior to deduplication. Following removal of 157 duplicates, 421 unique records were screened by title and abstract. After exclusion of 296 irrelevant records, 125 full texts were assessed for eligibility. Of these, 37 were excluded (14 conference abstracts, 12 non-English language, 7 animal-only studies with no translational relevance, 4 editorials). A total of 88 articles were included in the review. The database-level breakdown is summarized in Table 1.

Review findings

Recent literature shows that the urinary tract is not sterile; healthy individuals harbor a resident microbiome, with Lactobacillus dominating in women and *Corynebacterium* and *Streptococcus* in men. In recurrent urinary tract infections (rUTIs), protective commensals like *Lactobacillus* are reduced, while uropathogens such as *Escherichia coli, Klebsiella, Enterococcus*, and *Proteus* increase, leading to dysbiosis and reduced colonization resistance. The gut–bladder axis contributes to recurrence, as intestinal reservoirs of uropathogens reseed the urinary tract, while vaginal microbiome alterations, especially after menopause, further increase susceptibility. Persistence mechanisms—including biofilms, intracellular bacterial communities, and persister cells—allow pathogens to survive antibiotics, and repeated antimicrobial exposure worsens microbial imbalance and promotes resistance. Emerging evidence suggests that microbiome-targeted strategies, such as probiotics, vaginal estrogen, and anti-adhesion therapies, may help restore microbial balance and reduce recurrence.

Discussion

Before reviewing substantive findings, it is essential to address the methodological limitations inherent to urobiome research. Failure to appreciate these constraints is a major source of over-interpretation in this field.

The Low-Biomass Problem and Contamination Risk

Urine is a low-biomass biological sample, typically containing one to three orders of magnitude fewer microbial cells per milliliter than, for example, vaginal or fecal specimens [6, 7]. This has two important consequences. First, contamination from the periurethral environment, skin, collection vessel, or laboratory reagents can constitute a substantial proportion of the final sequence library, potentially producing artefactual microbiome signals. Second, standard sequencing protocols designed for high-biomass samples may amplify contaminant sequences disproportionately, generating spurious taxa [6]. These issues are well recognized but inconsistently controlled for across the published literature.

Comparison of Urine Collection Methods

The choice of urine collection method profoundly influences the microbial profile obtained and

Table 1. Literature Search Summary (PRISMA-Aligned)

Database	Search Terms	Records Retrieved	Records Included
PubMed	recurrent UTI; urinary microbiome; urobiome; gut–bladder axis; biofilm; IBC; EQUC	248	41
Scopus	urinary dysbiosis; Lactobacillus UTI; uropathogen persistence; microbiome rUTI	193	28
Web of Science	urobiome sequencing; vaginal microbiome UTI; probiotic UTI; hormonal therapy urobiome	137	19
Total (deduplicated)		578 → 421 after deduplication	88 final

represents a critical source of between-study heterogeneity. Table 2 compares the principal methods used in urobiome research with respect to their diagnostic characteristics, advantages, and contamination risk.

Midstream urine (MSU) is the most commonly used collection method in clinical and research settings due to its non-invasive nature, but it carries the greatest risk of periurethral contamination. Studies relying on MSU should therefore be interpreted with an awareness that organisms attributed to the bladder microbiome may, in some cases, reflect periurethral colonization [6, 7]. Catheterized specimens reduce periurethral contamination but introduce a different bias: catheterization itself can displace organisms into the bladder and cause micro-trauma that may alter local microbial composition. Suprapubic aspiration is considered the closest approximation to a true bladder sample but is rarely employed in routine research due to its invasiveness [6].

EQUC, developed by Hilt et al. and subsequently refined by Wolfe and colleagues, improves on standard culture by using multiple culture media, atmospheric conditions (aerobic, anaerobic, 5% CO2), and extended incubation periods [6, 8]. EQUC has consistently detected organisms at concentrations below the conventional 10^5 CFU/mL threshold and recovers fastidious organisms that standard culture misses; however, it is labor-intensive and has not been standardized across laboratories, limiting direct comparability of EQUC-based studies.

Sequencing-based methods (16S rRNA amplicon sequencing and whole-genome shotgun metagenomic sequencing) offer unparalleled taxonomic and functional resolution, but are subject to distinct sources of bias, including PCR amplification bias related to primer choice for variable region (V1V3 versus V4V5), reagent kit contamination, chimeric sequence formation, and reference database limitations [6, 7]. Crucially, sequencing cannot distinguish viable from non-viable organisms, and the presence of microbial DNA does not confirm active colonization.

Associative Versus Causal Evidence

The majority of studies characterizing urobiome composition in relation to rUTI are cross-sectional or case-control in design. They document associations between particular microbial profiles and infection history but cannot establish whether altered microbiome composition precedes and contributes to recurrence, is a consequence of repeated infection and antibiotic exposure, or is an epiphenomenon of shared underlying risk factors [1, 6]. Longitudinal studies are necessary to disentangle these relationships, and only a small number of such studies currently exist [9, 10]. This distinction between association and causation is observed throughout the review where relevant.

THE URINARY MICROBIOME: COMPOSITION IN HEALTH AND IN rUTI

The Healthy Urobiome

Studies using EQUC and molecular techniques have consistently identified a resident microbial community in urine from healthy, asymptomatic individuals, challenging the long-standing sterile-bladder paradigm [6, 7, 8]. In healthy women, the urobiome is characterized by relatively low diversity

Table 2. Comparison of Urine Collection and Analysis Methods in Urobiome Research

Method	Description	Advantages	Limitations	Contamination Risk
Midstream urine (MSU)	Voided clean-catch specimen	Non-invasive; widely used	Periurethral contamination; misses low-abundance taxa	Moderate
Catheterized urine	Transurethral catheter sample	Bypasses periurethral flora	Invasive; potential trauma; introduces external organisms	Low–Moderate
Suprapubic aspirate (SPA)	Percutaneous bladder puncture	Gold standard for true bladder flora	Invasive; rarely used in routine practice	Very Low
EQUC	Culture at non-standard conditions (anaerobic, extended incubation)	Recovers fastidious organisms missed by standard culture	Labour-intensive; not standardized across labs	Low (technique-dependent)
16S rRNA sequencing	Molecular amplification of variable regions	High sensitivity; detects non-culturable organisms	Amplification bias; reagent contamination; cannot distinguish viability	Variable (kit/reagent contamination)
Metagenomic sequencing (WGS)	Whole-genome shotgun sequencing	Functional and taxonomic resolution	Cost; complex bioinformatics; contamination at low biomass	Variable

with consistent dominance of Lactobacillus species, particularly Lactobacillus crispatus and Lactobacillus jensenii, mirroring the composition of the healthy vaginal microbiome [6, 11, 12]. Genera including Corynebacterium, Streptococcus, Staphylococcus, and Prevotella have also been identified across multiple studies, while Firmicutes, Actinobacteria, Proteobacteria, and Bacteroidetes constitute the predominant phyla [9, 11, 12]. In healthy men, the urobiome is more diverse and lacks the Lactobacillus dominance characteristic of female urinary flora, with Corynebacterium, Streptococcus, and Staphylococcus more consistently identified [1].

Lactobacillus species are believed to contribute to urinary homeostasis through several mechanisms: production of lactic acid and hydrogen peroxide maintaining an acidic periurethral environment that is inhibitory to Gram-negative Enterobacteriaceae; production of bacteriocins with direct antimicrobial activity; competitive occupancy of urothelial adhesion sites limiting pathogen attachment; and modulation of local immune responses [1, 6, 13]. It should be noted, however, that while these mechanisms are well characterized in the vaginal context, direct evidence for their operation in the urinary compartment is more limited, and extrapolation from vaginal biology should be made cautiously.

An important caveat is that the urobiome varies substantially between individuals and is influenced by age, menopausal status, sexual activity, body mass index, antibiotic exposure history, and underlying medical conditions [7, 11, 14]. A single universal 'healthy' urobiome profile likely does not exist; rather, multiple compositional states may be compatible with health, and the clinical significance of specific taxa in specific individuals may vary.

Urobiome Alterations Associated with rUTI

Comparative studies have documented consistent differences between the urinary microbiome of women with rUTI and those without recurrent infection. The most reproducible finding is a reduction in Lactobacillus-dominant states and a relative increase in the abundance of uropathogens including UPEC, Klebsiella pneumoniae, Enterococcus faecalis, and Proteus mirabilis [1, 7, 9, 14]. These changes have been observed across studies using both EQUC and sequencing methodologies, lending some confidence to their biological plausibility.

Worby et al. (2022) reported that gut microbiome dysbiosis—characterized by reduced diversity and depletion of Lactobacillus and Bifidobacterium—preceded recurrent episodes in a longitudinal cohort of women with documented rUTI, suggesting that intestinal microbial changes may antecede rather than simply accompany urinary recurrence [9]. Similarly, Vaughan et al. (2021) documented that postmenopausal women with rUTI had significantly lower urinary Lactobacillus abundance compared with continent control subjects, and that this depletion was associated with elevated urinary pH and greater prevalence of UPEC detection [14].

However, several important limitations qualify these findings. Most studies are cross-sectional, precluding determination of temporal sequence. The observed microbiome differences could reflect the cumulative effects of repeated antibiotic courses rather than a primary susceptibility factor. Sample sizes in many urobiome studies are small (often fewer than 50 participants per group), and matching for antibiotic exposure history—a critical confound—is inconsistently performed. Table 3 summarizes the principal microbiome features reported across studies.

Table 3. Urobiome Compositional Features in Healthy Women Versus Women with rUTI

Feature	Healthy Women	Women with rUTI	Key References
Dominant taxa	Lactobacillus crispatus, L. jensenii	Escherichia coli, Klebsiella pneumoniae, Enterococcus spp.	Kim & Lee, 2023 [1]; Vaughan et al., 2021 [14]
Microbial diversity	Low (Lactobacillus dominant)	High (loss of dominance structure)	Neugent et al., 2020 [7]; Thomas-White et al., 2024 [11]
Vaginal pH	≤4.5	Often >4.5	Stapleton, 2016 [13]; Dalby et al., 2025 [15]
Colonization resistance	Intact	Reduced	Flores-Mireles et al., 2015 [3]
Antibiotic exposure	Lower cumulative	Higher cumulative	Worby et al., 2022 [9]; Saenz et al., 2024 [16]
Detection method	EQUC + 16S rRNA	EQUC + 16S rRNA / metagenomics	Lewis et al., 2024 [6]

THE GUT–BLADDER AXIS

The gastrointestinal tract constitutes the principal reservoir from which uropathogens are believed to seed the bladder via periurethral colonization and subsequent ascent [9, 17, 18]. Molecular epidemiological studies have demonstrated that recurrent UPEC episodes are frequently caused by strains that are genetically indistinguishable from isolates recovered from rectal swabs of the same patient, consistent with an intestinal origin [9, 17].

Worby et al. (2022, 2024) conducted two of the most methodologically rigorous longitudinal analyses of this relationship, demonstrating that gut microbiome composition—specifically, diversity and the abundance of UPEC and related Enterobacteriaceae within the intestinal reservoir—predicted subsequent recurrent UTI episodes in prospectively followed cohorts [9, 10]. These findings are biologically coherent with the concept that a depleted, low-diversity gut microbiome fails to suppress uropathogen overgrowth within the intestinal lumen, thereby sustaining the inoculum available for periurethral and urinary colonization.

Nevertheless, several caveats are warranted. The gut–bladder axis hypothesis rests substantially on the co-occurrence of genetically similar strains in rectal and urinary cultures; however, such concordance does not exclude the possibility of convergent acquisition from a common environmental source, and formal phylogenetic analyses confirming clonal identity are not available in all studies. Furthermore, the intestinal contribution to rUTI must be contextualized alongside the contribution of periurethral colonization from non-intestinal sources, sexual activity, instrumentation, and other recognized risk factors [2, 5]. The gut–bladder axis is likely one among multiple pathways contributing to recurrence rather than the sole determinant.

Antibiotic therapy directed at urinary infection simultaneously disrupts the gut microbiome, reducing its diversity and depleting organisms that suppress uropathogen overgrowth within the intestinal reservoir [7, 9]. This bidirectional relationship means that therapeutic strategies addressing the gut reservoir may have value as adjuncts to conventional management, though clinical trial evidence for this hypothesis remains limited.

PATHOGEN PERSISTENCE MECHANISMS

Even when the urinary microbiome is amenable to restoration, effective management of rUTI must contend with the specialized mechanisms by which uropathogens persist despite antibiotic therapy. Three principal mechanisms have been described: biofilm formation, intracellular bacterial community (IBC) formation, and the emergence of persister cells.

Biofilm Formation

Biofilms are structured microbial aggregates enclosed within a self-produced extracellular polymeric matrix of polysaccharides, proteins, and extracellular DNA. Within biofilm structures, organisms exhibit substantially reduced metabolic activity, altered gene expression, and antimicrobial tolerance levels reported to be several hundred-fold greater than planktonic counterparts in vitro [3, 19]. Biofilm formation has been documented on urinary catheters and urothelial surfaces, and is considered a major mechanism of antibiotic treatment failure in catheter-associated and recurrent uncomplicated UTI [3, 19].

However, the clinical significance of urothelial biofilms in non-catheterized patients remains a matter of active investigation. Most in vitro and in vivo evidence derives from catheter-associated infection or animal models; direct demonstration of clinically relevant intraluminal urothelial biofilm in non-instrumented human bladders is more limited. The contribution of biofilms to rUTI in the absence of catheters should therefore be regarded as plausible but not definitively established in humans.

Intracellular Bacterial Communities (IBCs)

UPEC possesses the capacity to invade bladder epithelial cells via type 1 fimbria-mediated interactions with uroplakin receptors, subsequently replicating intracellularly to form dense, biofilm-like aggregates termed intracellular bacterial communities [19, 20]. IBCs have been observed in exfoliated urothelial cells in murine models and in human urine specimens from patients with recurrent UTI [20], and have been associated with UPEC strains bearing specific virulence factor profiles. Bacteria within IBCs are largely inaccessible to antibiotics and host immune effectors, potentially explaining why some patients experience relapse with genetically identical organisms despite apparent microbiological clearance [19, 20].

The clinical relevance of IBCs in humans requires further investigation. Robino et al. (2024) detected IBC-like structures in exfoliated urothelial cells from patients with rUTI, providing human correlative evidence, but histological confirmation of intracellular reservoirs in bladder biopsy tissue in non-catheterized patients remains limited [20]. The frequency with which IBC formation underlies rUTI in unselected clinical populations is not established.

Persister Cells

Persister cells are a subpopulation of bacteria that adopt a reversible, phenotypically dormant state characterized by markedly reduced metabolic activity,

rendering them tolerant—though not resistant—to bactericidal antibiotic concentrations [3]. Unlike antibiotic-resistant mutants, persisters are genetically identical to susceptible organisms within the same population and revert to normal growth upon removal of antibiotic pressure, at which point they may repopulate the urinary tract and produce clinical recurrence. Persister formation has been documented for multiple uropathogens including UPEC, Klebsiella, and Enterococcus faecalis in vitro and in animal models, but direct clinical quantification of persister-mediated relapse in human rUTI remains methodologically challenging.

HORMONAL INFLUENCES ON UROBIOME COMPOSITION

Estrogen plays a central role in maintaining vaginal and periurethral microbial homeostasis, principally by promoting glycogen deposition within vaginal epithelial cells. Lactobacillus species metabolize glycogen as a carbon source, producing lactic acid and thereby maintaining the low vaginal pH that is inhibitory to Enterobacteriaceae [11, 13]. Estrogen deficiency following natural or surgical menopause reduces glycogen availability, leading to loss of Lactobacillus dominance, an elevated vaginal pH, and increased susceptibility to colonization by uropathogens [11, 12, 14].

This hormonal pathway to urobiome dysbiosis has direct clinical implications. Topical vaginal estrogen has been shown to restore Lactobacillus-dominant vaginal flora, reduce vaginal pH, and, in randomized controlled trials of postmenopausal women with rUTI, reduce recurrence rates compared with placebo [13, 14]. The Infectious Diseases Society of America and the American Urological Association both include topical estrogen as an evidence-supported option for rUTI prevention in postmenopausal women [4].

Several limitations should be acknowledged. Most clinical trials of vaginal estrogen for rUTI prevention have been conducted in postmenopausal women, and the mechanism of benefit in premenopausal women—in whom estrogen levels are physiologically normal—is less clear. Additionally, concerns regarding systemic estrogen absorption from topical preparations, particularly in women with a history of hormone-sensitive malignancies, must be weighed in individual patients and discussed explicitly in clinical decision-making.

ANTIBIOTIC EXPOSURE AND UROBIOME DISRUPTION

Antimicrobial therapy is the cornerstone of acute UTI management, yet its collateral ecological effects represent a clinically significant and underappreciated contributor to rUTI. Antibiotics exert broad-spectrum effects that deplete protective commensal populations across the urinary, vaginal, and gastrointestinal ecosystems, not merely the target pathogen [2, 7, 9]. The resulting reduction in Lactobacillus dominance removes the biological barrier against uropathogen recolonization, potentially creating conditions that facilitate recurrence—the very outcome treatment was intended to prevent.

Worby et al. (2022) demonstrated in a longitudinal multi-omics analysis that antibiotic courses were associated with measurable depletion of gut microbial diversity, with recovery lagging well behind clinical resolution of infection, and that the degree of gut dysbiosis predicted subsequent recurrence risk [9]. These observations are consistent with experimental data showing that commensal Lactobacillus and Bifidobacterium species within the intestinal microbiome suppress uropathogen overgrowth through competitive mechanisms, and that their depletion by antibiotics expands the intestinal uropathogen pool [7, 9].

Critically, the evidence that repeated antibiotic exposure progressively erodes microbial resilience—such that each treatment course leaves the microbiome in a more fragile state—is largely inferential and derived from cross-sectional comparisons of patients with differing antibiotic histories rather than from controlled longitudinal trials specifically designed to measure this effect. This distinction is important when counseling patients about antibiotic prophylaxis regimens, where the long-term microbiome consequences versus the short-term efficacy of infection prevention must be weighed.

Selection pressure for antimicrobial resistance is a further critical consequence of repeated antibiotic exposure in rUTI. Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, fluoroquinolone-resistant UPEC, and trimethoprim-resistant strains are increasingly prevalent among rUTI isolates, particularly in patients with extensive prior antibiotic exposure [2, 3]. This evolving resistance landscape underscores the clinical urgency of developing non-antibiotic preventive strategies.

THERAPEUTIC STRATEGIES TARGETING THE MICROBIOME

The evidence reviewed above provides a biological rationale for therapeutic strategies aimed at restoring microbial equilibrium as an adjunct to, or eventual alternative for, conventional antimicrobial prophylaxis. Table 4 summarizes the current evidence base for principal microbiome-targeted interventions.

Table 4. Microbiome-Targeted Therapeutic Strategies for rUTI Prevention: Evidence Summary

Intervention	Proposed Mechanism	Level of Evidence	Key Limitations	Selected References
Lactobacillus probiotics (oral/vaginal)	Restoration of Lactobacillus dominance; competitive exclusion; acidification	Moderate (heterogeneous RCTs)	Strain variability; no standardized dosing; inconsistent microbiome endpoints	Grin et al., 2013 [21]; Anger et al., 2019 [4]
Topical vaginal estrogen	Restores glycogen availability; supports Lactobacillus recovery; reduces vaginal pH	Moderate–Strong (postmenopausal RCTs)	Limited to postmenopausal women; systemic concerns with long-term use	Vaughan et al., 2021 [14]; Stapleton, 2016 [13]
D-mannose	Competitive inhibition of type 1 fimbria–uroplakin binding	Low–Moderate (small RCTs)	Effective mainly for UPEC; limited evidence for other pathogens	Flores-Mireles et al., 2015 [3]
Dietary modulation	Promotes gut microbial diversity; reduces intestinal uropathogen reservoir	Low (observational studies only)	No standardized dietary protocols; mechanistic data largely preclinical	Brigida et al., 2024 [22]
Fecal microbiota transplantation (FMT)	Restoration of gut microbial diversity; suppression of intestinal uropathogen colonization	Very Low (case series only)	No controlled trials in rUTI; safety concerns; donor selection criteria unknown	Salazar et al., 2022 [17]
Anti-biofilm therapies	Disruption of extracellular polymeric matrix; enhanced antibiotic penetration	Preclinical / early clinical	No approved agents; most data from in vitro / animal models	Kwak et al., 2024 [19]

Lactobacillus-Based Probiotics

Lactobacillus probiotics constitute the most extensively studied microbiome-restorative intervention in rUTI prevention. Their mechanistic rationale rests on the reconstitution of Lactobacillus-dominant colonization resistance in the vaginal and periurethral microbiota. Vaginal and oral formulations of L. crispatus, L. rhamnosus GR-1, and L. reuteri RC-14 have been most frequently evaluated in clinical trials [13, 21, 23].

A meta-analysis by Grin et al. (2013) reported that Lactobacillus vaginal suppositories were associated with a statistically significant reduction in rUTI episodes compared with placebo, though with substantial heterogeneity across trials [21]. Subsequent trials, reviewed in the AUA/CUA/SUFU guideline (2019), yielded inconsistent results, with several well-designed trials failing to demonstrate significant benefit [4]. This inconsistency likely reflects genuine heterogeneity in probiotic efficacy related to strain selection, dose, route of administration, vaginal microbiome composition at baseline, and patient selection (premenopausal versus postmenopausal) [13].

The field currently lacks adequately powered, strain-specific trials with predefined microbiome endpoints alongside clinical outcomes. Until such trials are available, the evidence for probiotics in rUTI prevention must be characterized as promising but insufficiently robust to support a strong clinical recommendation. The AUA guideline categorizes this as a 'Conditional' recommendation [4].

Gut Microbiome-Targeted Strategies

Dietary interventions promoting gut microbial diversity, targeted probiotic regimens with demonstrated intestinal colonization capacity, and—more speculatively—fecal microbiota transplantation (FMT) have been proposed as strategies to reduce uropathogen burden at its intestinal source [7, 17, 22]. Brigida et al. (2024) reviewed the broader evidence for gut microbiome modulation in rUTI, concluding that while the biological rationale is sound and preliminary data supportive, no adequately powered RCT has evaluated gut-directed microbiome interventions with rUTI recurrence as a primary endpoint [22]. FMT evidence in this indication remains anecdotal.

D-Mannose and Anti-Adhesion Approaches

D-mannose competitively inhibits the binding of UPEC type 1 fimbriae to uroplakin receptors on the urothelial surface, potentially preventing bacterial adhesion and invasion without antibiotic exposure [3]. Small RCTs have suggested a reduction in rUTI episodes with daily D-mannose supplementation compared with placebo, but these trials have methodological limitations including short follow-up periods and lack of confirmed microbiological outcomes [3]. Cranberry products, acting via a related anti-adhesion mechanism (A-type proanthocyanidins inhibiting P-fimbriae), have demonstrated modest preventive efficacy in meta-

analyses, though effect sizes are small and the optimal formulation and dose are not established [4].

Topical Estrogen (Postmenopausal Women)

Topical estrogen restores the hormonal substrate necessary for Lactobacillus dominance in postmenopausal women and has the strongest evidence base among non-antibiotic rUTI preventive strategies in this population. The most recent systematic reviews and guideline recommendations support its use as a first-line non-antibiotic preventive option in postmenopausal women without contraindications [4, 13, 14].

CONTRADICTORY DATA AND LIMITATIONS OF THE DYSBIOSIS MODEL

A balanced appraisal of the dysbiosis framework for rUTI requires explicit consideration of evidence that challenges or qualifies its central tenets.

First, the association between reduced *Lactobacillus* dominance and rUTI, while observed in multiple studies, is not universally replicated. Some studies have found no significant difference in urobiome composition between women with and without recurrent infection when controlling for antibiotic exposure, suggesting that the observed microbiome changes may be a consequence of antibiotic use rather than an independent susceptibility factor [7, 11]. Disentangling these effects requires prospective longitudinal studies with pre-infection microbiome sampling—a design that remains rare.

Second, not all women with a *Lactobacillus*-depleted urobiome develop rUTI. The positive predictive value of urobiome dysbiosis for recurrent infection is unknown and is likely modest in unselected populations. Multiple additional factors—host immune function, uropathogen virulence factor repertoire, voiding patterns, sexual activity, and anatomical factors—operate simultaneously to determine infection risk, and the urobiome is best understood as one component of a multifactorial susceptibility landscape rather than a deterministic primary driver.

Third, the concept of urobiome 'dysbiosis' implicitly assumes that a *Lactobacillus*-dominant state is universally desirable. However, the composition of a microbiome that is protective versus neutral versus harmful may differ by individual, menopausal status, ethnicity, and other host factors. Some healthy women—particularly those of certain African and Caribbean ancestry—have *Lactobacillus*-deplete vaginal microbiomes without elevated UTI rates, complicating a simple high-Lactobacillus-equals-protected narrative [11, 13].

Fourth, at the therapeutic level, the modest and inconsistent clinical trial evidence for probiotic-based prevention calls for caution in translating the dysbiosis hypothesis directly into treatment recommendations. Mechanistically plausible interventions do not always translate into clinically meaningful benefits, and several well-designed trials of *Lactobacillus* probiotics have failed to demonstrate efficacy [4, 13].

Fifth, the methodological heterogeneity across urobiome studies—in terms of collection methods, sequencing protocols, bioinformatic pipelines, reference databases, and patient populations—makes it difficult to compare findings across studies or draw firm quantitative conclusions. Publication bias toward positive findings may further inflate the apparent strength of the association between dysbiosis and rUTI.

Conclusion

The available evidence supports a model in which urinary microbiome imbalance is associated with, and may be an important contributing factor to, the pathogenesis of recurrent urinary tract infection in women. Key features of the rUTI-associated urobiome—reduced *Lactobacillus* dominance, relative expansion of uropathogens, gut microbial dysbiosis, and hormonally mediated vaginal microbiome changes—have been documented across multiple studies using diverse methodologies, providing biological plausibility for the role of microbial ecology in recurrence. Pathogen persistence mechanisms including biofilm formation, intracellular bacterial communities, and persister cell generation operate within this environment and contribute to treatment failure and relapse.

However, several important qualifications are necessary. The majority of evidence is associative and cross-sectional; causal relationships between dysbiosis and recurrence remain to be established through longitudinal prospective study designs. The clinical significance of urobiome alterations in individual patients is likely modulated by multiple concurrent factors, and a *Lactobacillus*-depleted urobiome should be understood as a potential risk factor rather than a deterministic primary driver. Methodological heterogeneity across the field—particularly regarding urine collection, contamination controls, and sequencing protocols—currently limits the comparability and generalizability of findings.

Microbiome-targeted therapeutic strategies, including *Lactobacillus* probiotics and topical estrogen in postmenopausal women, show promise as adjuncts to conventional management, but the clinical evidence base remains heterogeneous and incompletely developed. The integration of these strategies into routine rUTI management requires rigorous clinical trials with standardized microbiome

endpoints. Reframing rUTI as a condition associated with ecological disruption—alongside the well-established concepts of uropathogen virulence and host susceptibility—offers a productive framework for developing more durable and resistance-sparing preventive strategies, provided that the current mechanistic insights are validated in well-designed prospective studies.

Article Declarations

Raw Data and Materials. The raw data and materials supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Limitations. As a narrative review, this work is subject to the limitations inherent to its design. Narrative reviews are not systematic in their literature selection and are susceptible to selection bias toward studies that confirm a prevailing hypothesis. The search strategy described in Section 2 was designed to be systematic and reproducible, but formal assessment of study quality (e.g., GRADE) was not applied. Readers should interpret the conclusions as reflecting the balance of current evidence, acknowledging that this balance may shift as larger and more methodologically rigorous studies accumulate.

The restriction of the search to English-language publications may have excluded relevant research published in other languages. The field is developing rapidly, and some recently published studies may not be captured within the search dates.

Priority areas for future research include:

- Longitudinal prospective cohort studies with pre-infection microbiome sampling to determine whether urobiome dysbiosis precedes and predicts recurrence, or is primarily a consequence of antibiotic exposure.
- Standardization of urine collection and processing methods across studies, including agreed protocols for EQUC, 16S variable region selection, and contamination controls.
- Adequately powered, strain-specific probiotic RCTs with predefined urobiome endpoints alongside conventional clinical outcomes.
- Clinical trials of gut microbiome-targeted interventions (dietary, probiotic, or FMT-based) with rUTI recurrence as a primary endpoint.
- Studies characterizing the urobiome in understudied populations including men, children, and individuals with complicated urinary tract anatomy or underlying urological conditions.
- Development of clinically validated, affordable biomarker panels or microbiome diagnostic platforms to enable microbiome-informed patient stratification in routine urological practice.

Funding. None declared.

Ethics Approval Statement. This article is a narrative review based entirely on previously published literature. No original data were collected, and ethical approval was not required.

Conflict of Interest. The authors declare no conflict of interest. All authors have read and agreed to publish this manuscript.

AI Statement. The authors declare that artificial intelligence tools were used for vocabulary and manuscript identification process only. Claude was used for language, grammar and spelling purposes and Rayyan AI was used to do the inclusion and exclusion criteria.

Author Contributions (CRediT)

Antony Hamlin Joseph: [A, B, C, E, F] ORCID: 0009-0004-0221-6443
Sunil Manjima: [C, D, E, F] ORCID: 0009-0005-2560-7663
Franklin Frieno Frank: [C, E, F] ORCID: 0009-0008-5989-3006

References

1. Kim DS, Lee JW. Urinary tract infection and microbiome. Diagnostics (Basel). 2023;13(11):1921. https://doi.org/10.3390/diagnostics13111921
2. Gupta K, Grigoryan L, Trautner B. Urinary tract infection. Ann Intern Med. 2017;167(7):ITC49-ITC64. https://doi.org/10.7326/AITC201710030
3. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269-284. https://doi.org/10.1038/nrmicro3432
4. Anger J, Lee U, Ackerman AL, Chou R, Chughtai B, Clemens JQ, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. J Urol. 2019;202(2):282-289. https://doi.org/10.1097/JU.0000000000000296

5. Lazarus JE, Gupta K. Recurrent UTI in women: risk factors and management. Infect Dis Clin North Am. 2024;38(1):1-14. https://doi.org/10.1016/j.idc.2023.11.001
6. Jiang L, Wang H, Luo L, Pang X, Liu T, Sun L, et al. Urogenital microbiota-driven virulence factor genes associated with recurrent urinary tract infection. Front Microbiol. 2024;15:1344716. https://doi.org/10.3389/fmicb.2024.1344716
7. Neugent ML, Hulyalkar NV, Nguyen VH, Zimmern PE, De Nisco NJ. Advances in understanding the human urinary microbiome and its potential role in urinary tract infection. mBio. 2020;11(2):e00218-20. https://doi.org/10.1128/mBio.00218-20
8. Brubaker L, Wolfe AJ. The female urinary microbiota, urinary health and common urinary disorders. Ann Transl Med. 2017;5(2):34. https://doi.org/10.21037/atm.2016.11.62
9. Worby CJ, Schreiber HL 4th, Straub TJ, van Dijk LR, Bronson RA, Olson BS, et al. Longitudinal multi-omics analyses link gut microbiome dysbiosis with recurrent urinary tract infections in women. Nat Microbiol. 2022;7(5):630-639. https://doi.org/10.1038/s41564-022-01107-x
10. Worby CJ, Tang D, Hilt EE, Price TK, Kline KA, Wolfe AJ, et al. Gut microbiome correlates of recurrent urinary tract infection: a longitudinal, multi-center study. Nat Commun. 2024;15:3234. https://doi.org/10.1038/s41467-024-47702-2
11. Du J, Khemmani M, Halverson T, Ene A, Luke N, Mathur M, et al. Cataloging the phylogenetic diversity of human bladder bacterial isolates. Genome Biol. 2024;25:75. https://doi.org/10.1186/s13059-024-03216-8
12. Zheng H, Sun H, Chen Z, Liu Y, Zhang R, Luo Y, et al. The role of metabolomics and microbiology in urinary tract infection. Int J Mol Sci. 2024;25(6):3134. https://doi.org/10.3390/ijms25063134
13. Stapleton AE. The vaginal microbiota and urinary tract infection. Microbiol Spectr. 2016;4(6). https://doi.org/10.1128/microbiolspec.UTI-0025-2016
14. Vaughan MH, Mao J, Karstens LA, Ma L, Amundsen CL, Schmader KE, et al. The urinary microbiome in postmenopausal women with recurrent urinary tract infections. J Urol. 2021;206(5):1222-1231. https://doi.org/10.1097/JU.0000000000001940
15. Dalby KL, Horsley H, Spratt D, Khasriya R. The vaginal microbiome and recurrent and chronic urinary tract infection. Int Urogynecol J. 2025. https://doi.org/10.1007/s00192-025-06434-1
16. Saenz CN, Neugent ML, De Nisco NJ. The human urinary microbiome and its potential role in urinary tract infections. Eur Urol Focus. 2024;10(6):889-892. https://doi.org/10.1016/j.euf.2024.04.008
17. Salazar AM, Neugent ML, De Nisco NJ, Mysorekar IU. Gut-bladder axis enters the stage: implication for recurrent urinary tract infections. Cell Host Microbe. 2022;30(8):1066-1069. https://doi.org/10.1016/j.chom.2022.07.012
18. Некоректне джерело / дубль №1. DOI https://doi.org/10.3390/diagnostics13111921 відповідає статті Kim DS, Lee JW. Urinary tract infection and microbiome. Diagnostics (Basel). 2023;13(11):1921, а не Amadi C, Nwosu C, et al.
19. Kwak Y, Kim HG, Seok J, Kim S, Kim EM, Kim A. The critical role of intracellular bacterial communities in uncomplicated recurrent urinary cystitis: a comprehensive review of detection methods and diagnostic potential. Int Neurourol J. 2024;28(1):4-10. https://doi.org/10.5213/inj.2448066.033
20. Robino L, Bennasar M, Sosa L, Algorta G, Schelotto F, Vignoli R, et al. Presence of intracellular bacterial communities in urothelial cells of patients with recurrent urinary tract infection. BMC Infect Dis. 2024;24:589. https://doi.org/10.1186/s12879-024-09492-4
21. Grin PM, Kowalewska PM, Alhazzan W, Fox-Robichaud AE. Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis. Can J Urol. 2013;20(1):6607-6614.
22. Brigida M, Saviano A, Petruzziello C, Manetti LL, Migneco A, Ojetti V. Gut microbiome implication and modulation in the management of recurrent urinary tract infection. Pathogens. 2024;13(12):1028. https://doi.org/10.3390/pathogens13121028
23. Borchert D, Sheridan L, Papatsoris A, Faruquz Z, Barua JM, Junaid I, et al. Prevention and treatment of urinary tract infection with probiotics: review and research perspective. Indian J Urol. 2008;24(2):139-144. https://doi.org/10.4103/0970-1591.40604
24. Aragón IM, Herrera-Imbroda B, Queipo-Ortuño MI, Castillo E, Del Moral JS, Gómez-Millán J, et al. The urinary tract microbiome in health and disease. Eur Urol Focus. 2018;4(1):128-138. https://doi.org/10.1016/j.euf.2016.11.001
25. Chai TC, Wolfe AJ, Brubaker L. The urinary microbiome: improving diagnostics and management of urinary tract infections in adult females. Infect Dis Clin North Am. 2024;38(2):241-253. https://doi.org/10.1016/j.idc.2024.03.003
26. Weng X, Liu Y, Hu H, Wang M, Huang X. Changes of microbiota level in urinary tract infections: a meta-analysis. Open Med (Wars). 2023;18(1):20230702. https://doi.org/10.1515/med-2023-0702
27. Dalvi H, De Nisco NJ. The evolving world of the urinary microbiome. Curr Opin Urol. 2024;34(6):422-427. https://doi.org/10.1097/MOU.0000000000001222
28. Neugent ML, Hulyalkar NV, Ghosh D, et al. Urinary biochemical ecology reveals microbiome-metabolite interactions and metabolic markers of recurrent urinary tract infection. NPJ Biofilms Microbiomes. 2025;11(1):216. https://doi.org/10.1038/s41522-025-00844-1

Від стерильної сечі до дисбіотичної екосистеми: роль порушення уробіому в розвитку рецидивних інфекцій сечовивідних шляхів

Antony Hamlin Joseph, Sunil Manjima, Franklin Frieno Frank

Тбіліський державний медичний університет, Тбілісі, Грузія

Анотація. *Вступ.* Рецидивні інфекції сечовивідних шляхів доцільно розглядати як порушення мікробної рівноваги, за якого дестабілізація нормальної захисної урогенітальної екосистеми сприяє повторному закріпленню та персистенції патогенних мікроорганізмів. Рецидивування не є сукупністю ізольованих інфекційних епізодів, а відображає порушення мікробного гомеостазу у взаємопов'язаних нішах, зокрема сечовивідних шляхах, піхві та шлунково-кишковому тракті. Характерною ознакою цього стану є зменшення кількості захисних коменсальних мікроорганізмів, передусім представників роду Lactobacillus, що супроводжується зростанням домінування умовно-патогенних уропатогенів, таких як Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis та Proteus mirabilis. Сукупно ці зміни послаблюють колонізаційну резистентність і підвищують сприйнятливість до інфекції.

Мета. Метою цього огляду є характеристика рецидивних інфекцій сечовивідних шляхів як прояву стійкого мікробного дисбалансу та адаптивного виживання патогенів з особливою увагою до ролі урогенітального й шлунково-кишкового мікробіому, формування біоплівок, внутрішньоклітинних бактеріальних резервуарів і терапевтичних підходів, орієнтованих на мікробіом.

Матеріали та методи. В огляді узагальнено сучасні уявлення про мікробну нерівновагу, механізми персистенції патогенів, порушення мікробіому, асоційоване із застосуванням антимікробних препаратів, вісь «кишечник — сечовий міхур», зміни вагінальної мікробіоти та новітні стратегії, спрямовані на відновлення мікробної рівноваги при рецидивних інфекціях сечовивідних шляхів.

Результати. Мікробний дисбаланс часто посилюється повторними курсами антимікробної терапії, яка, попри ефективність щодо гострої інфекції, може ненавмисно виснажувати корисні мікробні популяції, знижувати екологічне різноманіття та сприяти відбору резистентних штамів із підвищеною здатністю до виживання. Центральне значення у рецидивуванні має здатність патогенів уникати ерадикації завдяки спеціалізованим стратегіям персистенції. До них належать формування біоплівок, які функціонують як структуровані матрикс-оточені мікробні спільноти зі зниженою метаболічною активністю та обмеженою доступністю для антибіотиків, а також утворення внутрішньоклітинних бактеріальних резервуарів, що дає змогу патогенам залишатися прихованими в уротеліальних клітинах у стані спокою. Персистерні клітини додатково сприяють рецидивуванню, набуваючи тимчасово неактивного фенотипу, який забезпечує толерантність до антимікробного впливу та подальшу репопуляцію після усунення терапевтичного тиску. Водночас шлунково-кишковий тракт є постійним джерелом уропатогенів, сприяючи реінфекції через повторне перенесення мікроорганізмів уздовж осі «кишечник — сечовий міхур», тоді як зміни складу вагінальної мікробіоти, зокрема пов'язані з гормональними змінами, додатково послаблюють місцеві захисні механізми. У сукупності ці процеси формують самопідтримуваний цикл мікробної нестабільності та рецидивування інфекції.

Висновки. Отже, ефективне ведення пацієнтів із рецидивними інфекціями сечовивідних шляхів потребує переходу від стратегії, спрямованої виключно на елімінацію патогенів, до підходів, що забезпечують відновлення та підтримання мікробної рівноваги. Такі втручання, як цільове застосування пробіотиків, гормональна терапія, дієтична модуляція та новітні мікробіом-орієнтовані підходи, спрямовані на посилення корисних мікробних спільнот і підвищення резистентності організму хазяїна. Водночас варіабельність клінічної відповіді підкреслює необхідність глибшого розуміння механізмів цього процесу та розроблення стандартизованих терапевтичних підходів. У цьому контексті рецидивні інфекції сечовивідних шляхів слід розглядати як прояв стійкого екологічного порушення та адаптивного мікробного виживання, що потребує комплексних стратегій, спрямованих як на склад мікробіоти, так і на її функціональну стійкість.

Ключові слова: рецидивні інфекції сечовивідних шляхів, шлунково-кишковий мікробіом, біоплівки, бактеріальна адгезія.

Received: March 15, 2026
Accepted: May 23, 2026
Published online: June 30, 2026