



ORIGINAL CONTRIBUTION

Urinary Tract Infections in Kidney Transplant Recipients: A Narrative Review

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ABSTRACT

Background. Urinary tract infections (UTIs) are the most frequent infectious complication after kidney transplantation and are associated with rehospitalizations, impaired allograft function, and reduced graft and recipient survival. Their clinical relevance is amplified by chronic kidney disease (CKD)—related immune dysfunction and the rising burden of antimicrobial resistance

Methods. We provide a focused narrative review of classification, pathophysiology, risk factors, and evidence-based management and prevention strategies for UTIs in kidney transplant recipients, with emphasis on antimicrobial stewardship and non-antibiotic adjuncts

Results. Post-transplant UTI risk is highest in the early months and is driven by intensive immunosuppression, perioperative urological devices (bladder catheter, ureteral stents), delayed graft function/ischemia—reperfusion injury, and urodynamic abnormalities (post-void residual, vesicoureteral reflux). Female sex and pregnancy further increase susceptibility. Urine cultures must be interpreted in the context of time from transplantation and symptoms. Systematic treatment of asymptomatic bacteriuria is not beneficial and may increase antibiotic exposure and selection of multidrug-resistant organisms. Conversely, symptomatic, complicated, and recurrent UTIs warrant prompt empiric therapy followed by rapid de-escalation based on culture and susceptibility results. Preventive strategies targeting adhesion and colonization include adequate hydration, standardized cranberry preparations with therapeutically effective proanthocyanidin dosing, methenamine hippurate in selected patients, and topical vaginal estrogen in peri-/postmenopausal women; evidence for D-mannose and probiotics remains inconsistent. Emerging mechanistic insights highlight uromodulin as a key anti-adhesive and neutrophil (NET)-modulating defense factor, while SGLT2 inhibitors may modify tubular biomarkers; a UTI episode should not automatically prompt treatment discontinuation

Conclusions. UTI management after kidney transplantation should adopt an integrated, multi-modal approach combining stewardship-driven antibiotic use with tailored non-antibiotic preventive interventions to reduce recurrences, curb resistance, and preserve long-term allograft longevity.

URINARY tract infections (UTIs) represent an increasingly important clinical challenge, with the risk of

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complications varying substantially according to patient comorbidities. In patients with chronic kidney disease (CKD), UTIs are particularly problematic due to the high prevalence of infections caused by antimicrobial-resistant (AMR) organisms and their generally less favorable prognosis compared with the general population. Notably, UTIs are the most common infectious complication in kidney transplant recipients, in whom infection may involve 3 anatomically distinct urinary tracts (native upper urinary tract, allograft upper urinary tract, and lower urinary tract). In this setting, UTIs may originate from the native kidneys—which can become a persistent bacterial reservoir over time, as in autosomal dominant polycystic kidney disease (ADPKD) with infection of one or more cysts—or from the urinary tract of the renal allograft, negatively affecting both graft and recipient outcomes [1]. According to the most recent evidence, the incidence of UTIs per 100 transplant-days has been reported as 4.5 in kidney transplant recipients, 2.2 in kidney–pancreas recipients, 0.7 in heart recipients, 0.6 in liver recipients, and 0.2 in lung recipients [2]. These data underscore the clinical burden of UTIs in solid-organ transplant recipients and, more specifically, in kidney transplant recipients, particularly within the first 3 to 6 months after transplantation [3].

GENERAL PRINCIPLES AND CLASSIFICATION OF URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are commonly classified as complicated or uncomplicated, depending on the presence of specific risk factors and/or conditions, including urinary tract abnormalities, systemic comorbidities (eg, diabetes mellitus, malignancy, immunosuppression, and pregnancy), and clinical signs of sepsis up to septic shock. In contrast, an anatomically normal and functionally intact urinary tract, supported by preserved host defense mechanisms, is only rarely associated with the development of complicated UTIs. In kidney transplantation, delayed graft function (DGF) and ischemia–reperfusion injury are well-recognized conditions associated with an increased risk of UTIs. Acute tubulointerstitial injury, impaired innate immune defenses of the allograft, urinary stasis, and a greater need for urological devices contribute to the heightened vulnerability of these patients, particularly during the first months after transplantation. In an observational study by Alshaiikh et al., including 1512 recipients of deceased-donor kidney transplantation, DGF was associated with a significantly increased risk of UTIs within the first post-transplant year. Specifically, DGF was associated with a 70% higher risk of UTIs compared with immediate graft function (hazard ratio [HR] 1.70; 95% confidence interval [CI] 1.31–2.19; $P < .001$) [4]. For appropriate clinical framing, an additional entity—asymptomatic bacteriuria (ASB)—should be considered. ASB differs from symptomatic UTI by the presence of pathogenic urinary tract colonization in the absence of acute urinary symptoms (eg, frequency, dysuria, urgency), pyuria, or suprapubic pain. In the general population, ASB is defined in women by 2 consecutive midstream urine cultures yielding $\geq 10^5$ colony-forming units (CFU)/mL, whereas in men 1 positive midstream urine culture with $\geq 10^5$ CFU/mL is sufficient [5]. In kidney transplant

recipients, ASB is similarly defined by at least 1 positive urine culture ($\geq 10^5$ CFU/mL) in the absence of symptoms. UTIs should also be categorized according to recurrence and response to antimicrobial therapy. Recurrent UTIs are defined as ≥ 2 episodes within 6 months or ≥ 3 episodes within 12 months [6]. Finally, multidrug-resistant (MDR) infections are defined as acquired non-susceptibility to at least 1 agent in 3 or more antimicrobial classes [7].

PATHOPHYSIOLOGY AND MECHANISMS OF COLONIZATION

All these clinical entities may occur in patients with CKD, who constitute the clinical substrate from which candidates for kidney transplantation derive. The same conditions that predispose patients with CKD to UTIs are further amplified in kidney transplant recipients, increasing diagnostic and therapeutic complexity. In general, UTIs arise from periurethral colonization by uropathogens, which may migrate from the anal or genital region or be introduced from external sources, as may occur in sexually active young women. After invading the distal urethra, microorganisms ascend to the bladder, where they use extracellular structures such as pili and flagella to adhere to and invade the superficial urothelial cell layer. Although host immune mechanisms can counter these processes, some bacteria evade immune clearance, proliferate, and form biofilms. By exploiting nutrients from invaded host cells, they can persist and damage the urothelium through the production of toxins and proteases [8,9]. A broad spectrum of pathogens can cause UTIs, and this heterogeneity is even more clinically relevant in kidney transplant recipients. Moreover, the immunosuppression required to maintain graft function facilitates microbial traversal of already attenuated defensive barriers and urinary tract colonization despite post-transplant antibiotic prophylaxis (Table 1). From the earliest contact with the genitourinary tract, microorganisms encounter multiple hostile environments and defense mechanisms that hinder survival and colonization, including the acidic urinary pH and, in young women, the acidic vaginal milieu, both of which reduce the likelihood of colonization and subsequent infection. Among the most important antagonists of uropathogens are Lactobacilli, which rapidly limit bacterial proliferation and prevent adhesion to mucosal cells through lactic acid production. UTIs are statistically more common in women. This reflects anatomical and physiological factors that

Table 1. Most Important Pathogen Causing UTIs in Kidney Transplant Recipient

Uropathogen	Incidence
<i>Escherichia coli</i>	39%
<i>Enterococcus spp.</i>	16%
<i>Klebsiella spp.</i>	14%
<i>Staphylococcus spp.</i>	12%
<i>Enterobacter spp.</i>	8%
<i>Other bacterias</i>	5%
<i>Candida spp.</i>	4.3%

Note. Adapted from Hosseinpour et al. [10]; Denis et al. [11]

facilitate ascending infection, including a shorter urethra compared with men, closer proximity of the urethral meatus to the vagina and rectum with increased exposure to enteric bacteria, and the influence of sex hormones, which can modulate the protective microbiota. In the postmenopausal period, declining estrogen levels reduce intracellular glycogen—an essential substrate for *Lactobacillus*-mediated lactic acid production—and promote progressive atrophy of the vaginal squamous epithelium. Accordingly, whereas higher estrogen levels in premenopausal women support *Lactobacillus*-dominant flora, the estrogen deficiency of postmenopause is associated with loss of *Lactobacilli* and a consequent increased predisposition to UTIs [9]. Several studies have corroborated this increased susceptibility. A recent meta-analysis including 72,600 kidney transplant recipients showed that female sex is an independent risk factor for post-transplant UTIs, with an incidence more than threefold higher than in males (odds ratio [OR] 3.13; 95% CI: 2.35–4.17) [10]. These findings indicate that the vulnerability inherent to the female sex persists and may be further accentuated after kidney transplantation [10].

RISK FACTORS IN KIDNEY TRANSPLANT PATIENTS

In kidney transplant recipients, several iatrogenic conditions typical of the early post-transplant period should be considered, including the effects of induction immunosuppression, initiated as early as entry into the operating room, and the use of perioperative urological devices such as the indwelling bladder catheter for urine output monitoring and the double-J ureteral stent placed at the time of transplantation. Both are associated with a significant increase in the risk of urinary tract colonization by opportunistic pathogens (Table 2).

Vesicoureteral Stent

A retrospective study from the Netherlands involving 697 kidney transplant recipients compared an external ureteral stent (ES) connected to a drainage bag with an internal double-J stent (DJ), assessing the incidence of urological complications and the frequency of UTIs. All patients received the same induction regimen. The ES was used in 403 patients (57.8%) and removed after 7–12 days, whereas the DJ was used in 294 patients

(42.2%) and removed 3 to 4 weeks after surgery. The incidence of urological complications such as urinary leakage and ureteral stenosis was similar between groups; however, ES use emerged as a significant risk factor for UTIs and was associated with a higher rate of rehospitalizations, despite earlier removal compared with DJ. Although acute rejection episodes were more frequent in the ES group than in the DJ group (16.4% vs 6.1%, $P < .001$), no meaningful differences in final outcomes were observed. Overall, the DJ stent appears to be the preferred technique for stenting the ureteroneocystostomy, given the lower incidence of both UTIs and urological complications [12]. The systematic review by Visser et al. clearly supports early stent removal compared with the approximately 6-week dwell time still used in many transplant centers. Specifically, removal within 3 weeks, compared with later removal beyond 3 weeks, reduces the incidence of UTIs (OR 0.49; 95% CI: 0.33–0.75; $P = .0009$). In the comparative analysis of early (<3 weeks) versus late (>3 weeks) removal, early removal was not associated with an increased risk of urinary leakage (OR: 0.60; 95% CI: 0.29–1.23; $P = .16$), suggesting preserved integrity of the ureterovesical anastomosis. Therefore, stent removal at approximately 3 weeks after transplantation may represent an optimal balance, reducing UTIs without increasing major urological complications [13]. Consistent with these findings, the meta-analysis by Wang et al. emphasizes the potential benefit of timely stent removal between postoperative days 14 and 21. However, robust evidence is still lacking to confirm that early removal reduces urological complications (OR at 2 and 3 weeks: 2.79 and 1.97; $P = .18$ and $P = .26$, respectively). Similarly, no significant differences were observed in the risk of urinary leakage (OR: at 2 weeks: 3.02, $P = .18$; relative risk at 3 weeks: 2.00, $P = .27$) [14]. The observed trends suggest that additional adequately powered studies are needed to better define the true impact of early stent removal on urinary complication risk.

Immunosuppression

Impaired renal function reduces the host's ability to mount an effective response to infectious insults, to the extent that even microorganisms with low intrinsic pathogenicity may precipitate clinically significant deterioration in predisposed patients. In a systematic review exploring the association between CKD and infections, McDonald et al. showed that end-stage kidney disease is a major risk factor for infection and that this risk increases as glomerular filtration rate declines [15]. In CKD, chronic exposure to uremic toxins promotes oxidative stress and a state of low-grade chronic inflammation; these factors contribute to functional impairment of both innate and adaptive immune cells, including monocytes, neutrophils, T lymphocytes, and natural killer (NK) cells. As reported by Cohen et al. and Espi et al., these alterations represent the main mechanism underlying the acquired immunodeficiency typical of patients with CKD and help explain their increased susceptibility to infections [16,17]. In kidney transplant recipients, this already compromised immunological milieu is further shaped by the introduction of immunosuppressive therapy, which substantially interferes with lymphocyte function and neutrophil

Table 2. Risk Factors

Preoperative	Intraoperative	Postoperative
Female gender	Deceased donor	Immunosuppression
Old age	Double-J ureteral stents	Graft dysfunction
Diabetes mellitus	Prolonged indwelling urinary catheterization	Graft rejection
Pre-transplant UTIs	Retransplantation	Invasive urological procedures
Urinary tract abnormalities		
Prolonged dialysis		

Abbreviations: UTI, urinary tract infection
Note. Adapted from Pinchera B et al. [6]

responses [18], thereby impairing both innate and adaptive immunity. In this context, not only the intensity of immunosuppression but also its pharmacodynamic and pharmacokinetic characteristics play a pivotal role in determining infectious risk, contributing to marked interindividual heterogeneity. This variability is further amplified by concomitant comorbidities, which may necessitate adjustments to immunosuppressive regimens, including alternative administration strategies, in an attempt to achieve the best possible balance between rejection prevention and infection risk [19]. Calcineurin inhibitors, antimetabolites, and corticosteroids disrupt host immune defenses, creating a permissive environment for community-acquired microorganisms and, particularly, for opportunistic and drug-resistant pathogens, which are often responsible for severe and therapeutically challenging clinical syndromes. Importantly, kidney transplant recipients are also more frequently exposed to multidrug-resistant (MDR) organisms, often as a consequence of the need for close hospital follow-up during the first months after transplantation. Recurrent healthcare exposure and repeated contact with healthcare personnel increase the likelihood of acquiring nosocomial infections. In the study by Sommerer et al., a substantial proportion of transplant recipients (54.6% of 804 patients) experienced at least 1 infection during the first post-transplant year, and approximately 47.8% of these infections occurred within the first 3 months—the period of highest healthcare contact—of which 9.5% were caused by MDR organisms [20]. Infections due to multidrug-resistant Gram-negative bacteria account for a relevant share of infectious complications in solid-organ transplant recipients. In kidney transplantation, in particular, the prevalence of UTIs caused by ESBL-producing organisms may exceed 30% in high-emergency centers, reflecting the impact of prolonged healthcare exposure, urinary device use, and broad-spectrum antibiotic pressure [21].

Vesicoureteral Reflux

Multiple studies have shown that vesicoureteral reflux (VUR) promotes recurrent UTIs and renal injury even in non-transplant populations, contributing to adverse outcomes such as renal scarring within the spectrum of so-called reflux nephropathy [22]. Similarly, although extensive studies quantifying the magnitude of risk in kidney transplant recipients are lacking, VUR is nonetheless considered a recognized predisposing factor for bacterial ascent toward the renal allograft and for persistent urinary tract colonization, thereby increasing the risk of recurrent allograft UTIs and potentially compromising graft survival [23]. For this reason, post-void residual volume and VUR are carefully assessed during the pre-transplant urological evaluation, as they are predictive of adequate lower urinary tract function and subsequent allograft outcomes in both pediatric [24] and adult candidates [25]. Episodes of acute graft pyelonephritis (AGP) are widely acknowledged to be associated with an increased risk of graft loss, as they contribute to nephron loss and progressive functional impairment through the development of interstitial scarring sequelae. Histologically, allograft pyelonephritis is typically characterized by prominent

neutrophilic infiltration within tubules and the interstitium. Numerous polymorphonuclear leukocytes (PMNs) traverse the tubular basement membrane and accumulate within tubular lumina, forming aggregates and casts, with possible extension to peritubular capillaries and the development of microfoci of suppurative abscesses. Importantly, the presence of PMNs is not pathognomonic for allograft pyelonephritis: neutrophilic infiltrates may also be observed in other allograft conditions, including acute rejection, acute glomerulonephritis, or acute tubular necrosis. However, in allograft pyelonephritis, inflammatory lesions tend to be focal, in contrast to predominantly T cell-mediated acute cellular rejection [26], which typically exhibits a more diffuse and relatively uniform interstitial inflammatory infiltrate [27]. Conversely, any infectious episode triggers a local inflammatory response, with increased urinary and serum levels of pro-inflammatory cytokines [28]. These cytokines are potent drivers of lymphocyte activation [29] and have repeatedly been implicated in the pathophysiology of acute kidney allograft rejection. Therefore, recurrent UTIs may act as an immunological trigger facilitating rejection episodes and have been reported as an independent predictor of reduced graft function at 3 years after transplantation [30].

Pregnancy

Pregnancy represents a specific risk factor for the development of urinary tract infections (UTIs) in women with a kidney transplant. Pregnancy-related anatomical and physiological changes—such as ureteral dilatation, progesterone-mediated reduction in ureteral smooth muscle tone, and the resulting urinary stasis—facilitate bacterial colonization of the urinary tract. While these mechanisms are well established in the general population, they are of particular relevance in kidney transplant recipients, in whom they add to post-transplant-specific risk factors, including chronic immunosuppression, allograft-related urodynamic alterations, and a higher prevalence of asymptomatic bacteriuria (ASB). Observational studies and literature reviews indicate that, in kidney transplant recipients who become pregnant—whether through natural conception or assisted reproductive technologies [31]—UTIs are among the most frequent infectious complications [32] and may progress to allograft pyelonephritis, with potential consequences for renal function and maternal–fetal outcomes [33,34]. Therefore, pregnancy should be regarded as a clinically relevant risk condition in this subgroup, warranting closer urinary surveillance and prompt treatment of infections, including asymptomatic forms.

EMERGING ROLE OF UROMODULIN

While UTIs in kidney transplant recipients may lead to clinically relevant complications, potentially impairing allograft function, interindividual susceptibility also depends on intrinsic host protective factors. Among these, uromodulin represents a key first-line, natural defense against urothelial bacterial adhesion. Uromodulin (UMOD), also known as Tamm–Horsfall protein (THP), is the most abundant urinary glycoprotein, produced exclusively by tubular epithelial cells of the thick

ascending limb of the loop of Henle, and plays a pivotal role in innate defense against UTIs. UMOD binds type 1 fimbriae expressed by selected *Escherichia coli* strains, competing with urothelial receptors and thereby preventing bacterial adherence to the urothelium [35]. Recent cryo-electron microscopy studies have further clarified this mechanism, showing that uromodulin forms highly ordered extracellular filaments with glycan-rich side chains that provide multivalent binding sites for the type 1 fimbrial adhesin of uropathogens. This multivalent interaction promotes bacterial aggregation, limits bacterial-urothelial contact, and facilitates pathogen clearance through urinary flow. Collectively, these findings support uromodulin as a natural anti-adhesive barrier that limits bacterial colonization and reinforces intrinsic host defenses [36]. The functional relevance of this mechanism is corroborated by murine models: THP knockout mice exhibit prolonged bacteriuria and significantly greater bladder colonization compared with wild-type controls [37]. A recent editorial also highlighted that patients with CKD display reduced urinary uromodulin levels, proportional to the loss of functioning nephrons, suggesting that anti-adhesive activity against uropathogens may be compromised in this population [38]. Beyond its anti-adhesive role, uromodulin can directly bind neutrophils and enhance their capacity to generate neutrophil extracellular traps (NETs)—large extracellular networks that trap and neutralize microorganisms [39]. In this context, uromodulin acts as a regulator of urinary neutrophil immunity: it modulates neutrophil activation, amplifies NETosis in response to infectious stimuli, and integrates with extracellular structures released by granulocytes, generating NET-UMOD complexes that substantially strengthen innate urinary tract defenses against uropathogens [40]. In conditions characterized by intense NETosis—such as acute UTIs, pyelonephritis, or severe infections in transplant recipients—the UMOD-NET interaction may contribute to a dense, highly adhesive physical barrier that is particularly effective in bacterial trapping. From a diagnostic standpoint, neutrophil degranulation releases esterases; however, during NET release, large amounts of granular enzymes are discharged into the urine. As a consequence, the leukocyte esterase dipstick may be strongly positive even when microscopic leukocyturia appears relatively modest [41]. Overall, THP/UMOD represents a model of natural defense that current preventive strategies aim to replicate or potentiate, with the shared goal of reducing bacterial colonization and the subsequent risk of infection.

SGLT2 INHIBITORS AND UROMODULIN

It is well established that SGLT2 inhibitors affect glomerular hemodynamics and tubular reabsorption [42] and can effectively reduce proteinuria in kidney transplant recipients [43]. In an EMPA-KIDNEY substudy, urinary biomarkers from 2,752 patients were analyzed to better understand which nephron segments are influenced by sodium-glucose co-transporter 2 (SGLT2) inhibition. The most striking finding was a marked effect on tubular biomarkers, with a substantial reduction in uromodulin production—decreasing by approximately 63% and remaining stable at both 2 and 18 months of empagliflozin

therapy. The observation that an SGLT2 inhibitor, whose primary target resides upstream in the proximal tubule, produces such a pronounced reduction in UMOD suggests a downstream functional impact, plausibly reflecting reduced activity of the thick ascending limb, the main site of uromodulin synthesis. Empagliflozin may induce a state of “metabolic rest,” with profound modulation of tubulo-glomerular biomarkers, reduced nephron workload, and functional reprogramming, thereby attributing a central role to the thick ascending limb in nephroprotection. Given the protective role of uromodulin and these emerging data, it becomes even more relevant to clarify to what extent such effects may contribute to UTI risk. Specifically, it remains to be determined whether the increased susceptibility to UTIs observed in some patients is driven primarily by a glucose-enriched urinary milieu or by a potential attenuation of the anti-adhesive barrier mediated by uromodulin [44].

SGLT2 INHIBITORS AND URINARY TRACT INFECTIONS

A recent study involving more than 61,000 patients with type 2 diabetes treated with SGLT2 inhibitors reported that the occurrence of a UTI may serve as an indirect marker of metabolic and immunological frailty, with a relevant impact on adverse outcomes. In the initial analysis, patients who developed a UTI, compared with those without infectious episodes, experienced significantly worse cardiovascular and renal outcomes and higher all-cause mortality; this association persisted after balanced comparisons between groups, supporting the robustness of the finding. In the second part of the study, approximately one-third of patients discontinued SGLT2 inhibitor therapy after the infectious episode, and treatment discontinuation was associated with significantly worse cardiovascular, renal, and survival outcomes—possibly reflecting the interplay between infection-related inflammatory burden and the loss of cardio-renal protection conferred by therapy. In patients who discontinue the drug, the critical issue is therefore not an increased susceptibility to UTIs or recurrence risk, but rather the loss of organ-protective effects during a phase of heightened systemic vulnerability. Overall, a UTI occurring during SGLT2 inhibitor therapy should be interpreted as an intercurrent event rather than an automatic indication to discontinue treatment. In the absence of specific clinical circumstances, continuing therapy appears to be the preferable strategy, and the study findings support a continuity-oriented clinical approach even after a UTI episode [45].

CLINICAL APPROACH IN KIDNEY TRANSPLANT PATIENTS

Not all UTIs require treatment, and heightened clinical attention is warranted in kidney transplant recipients. In this subgroup, UTIs arise within the context of a broad—and often multidrug-resistant—pathogen spectrum, making it essential to characterize infection phenotypes and microbial behavior. Urine culture results should therefore be interpreted within the framework of immunosuppression, taking into account the time elapsed since transplantation and the patient’s clinical presentation. Despite

the immunocompromised status of these patients, indiscriminate antimicrobial treatment is not recommended, as it may promote colonization with resistant organisms without providing clear clinical benefit; accordingly, this practice should be avoided beyond the first 2 months after transplantation [46]. Conversely, in the presence of key symptoms and/or complicated presentations—particularly in patients at high clinical risk—prompt initiation of empiric antibiotic therapy is crucial. Treatment should then be tailored based on microbiological identification and antimicrobial susceptibility testing, in order to maximize efficacy while minimizing the selection of antimicrobial resistance [47]. In the study by Mee et al. in kidney transplant recipients, screening for and treating asymptomatic bacteriuria (ASB) within the first 2 months after transplantation was not associated with a reduction in UTI incidence; rather, the results suggested a possible increase in events in the treated group. Specifically, during the early postoperative period—traditionally considered the phase of greatest infectious vulnerability—the protocol included scheduled urine-culture screening at key time points during early follow-up (bladder catheter removal, ureteral stent removal, and the period of peak immunosuppression between weeks 3 and 4). Patients with ASB were then randomized to antibiotic therapy or observation. The analysis showed no benefit of antibiotic treatment in reducing symptomatic UTIs or allograft pyelonephritis; instead, the

antibiotic arm displayed a trend toward a higher rate of clinically relevant infectious events [48]. Overall, these data suggest that even within the first 60 days post-transplant—despite intense immunosuppression—systematic treatment of ASB does not provide measurable clinical benefit and may predispose to unfavorable outcomes, supporting the need for a critical reassessment of traditional practices during this phase. Nonetheless, further adequately powered studies remain desirable to definitively consolidate the evidence supporting the non-indication for ASB treatment in kidney transplant recipients.

PREVENTIVE MEASURES AS THERAPEUTIC STRATEGIES

In clinical practice, preventive measures primarily aim to impair bacterial adhesion and limit bacterial growth. Among the most effective interventions are adequate hydration [49], which promotes sufficient diuresis, supports complete bladder emptying, and facilitates the physiological “washout” of microorganisms; appropriate urogenital hygiene; and the use of agents that interfere with uropathogen adhesion mechanisms, such as cranberry derivatives with a high content of proanthocyanidins (PACs) [50,51] (Table 3). According to the guidelines authored by Nelson Z. et al., the available evidence is sufficient to provide a clear recommendation supporting the role of cranberry juice

Table 3. Nonantibiotic Strategies to Prevent UTIs in Kidney Transplant Recipients (KTRs)

KTR-focused Strategy	Efficacy in KTRs	Recommendation in KTRs
Early ureteral stent removal (ideally ≤ 14 –21 days, and not later than 3 weeks, when clinically feasible)	Reduces UTI incidence without clear increase in major urologic complications (moderate certainty, meta-analyses) [14,71]	Strong (perioperative practice optimization)
Timing of Foley catheter removal (early vs late)	Uncertain effect on bacteriuria/UTI; evidence very low certainty and outcomes incompletely reported [72,73]	No recommendation (individualize by surgical/urologic risk)
Methenamine hippurate (commonly 1 g BID; requires urinary acidification for activity)	Likely beneficial in recurrent UTI (reduced UTI episodes/antibiotic exposure in observational transplant cohorts) [66,74]	Conditional (selected KTRs with rUTI; antibiotic-sparing option)
Cranberry products (prefer standardized PAC content when available; transplant evidence largely non-standardized formulations)	Possible benefit (limited transplant data; formulation heterogeneity) [61]	Conditional
Urine acidification (L-methionine)	Possible benefit (limited, retrospective transplant data; often evaluated with cranberry) [61]	Conditional
D-mannose ($\pm$ PACs)	No preventive benefit demonstrated in de novo KTR RCT (no meaningful reduction in UTI/ASB) [63]	Not recommended for routine prophylaxis
Vaginal estrogen (postmenopausal women)	No KTR-specific RCTs; efficacy supported in non-transplant rUTI RCTs $\rightarrow$ extrapolation [75,78]	Conditional (postmenopausal KTRs with rUTI, after contraindication review)
Increased water/fluid intake	Commonly advised, but limited KTR evidence for UTI prevention; should be individualized [76]	No recommendation (expert opinion; personalize)
Probiotics (eg, <i>Lactobacillus</i>)	Insufficient KTR-specific evidence for UTI prevention [77,78]	No recommendation

Abbreviations: ASB, asymptomatic bacteriuria; KTR, kidney transplant recipient; PAC, proanthocyanidins; rUTI, recurrent urinary tract infection.

and PAC-containing supplements in UTI prevention. Most prospective studies indicate that these products may reduce the risk of symptomatic infection in women with recurrent episodes, as well as in children and in individuals susceptible to post-procedural infections [52]. Mechanistically, PACs bind P fimbriae on the surface of *Escherichia coli*, thereby hindering bacterial entry into urothelial cells of the bladder wall [53–55]. PACs also represent a distinctive source of polyphenols with high antioxidant activity, known for broader beneficial effects on general health [56], and increasingly considered as preventive measures in acute uncomplicated UTIs. Early clinical trials, including the study by Stothers (2002), reported a significant reduction in recurrent UTI episodes in women treated with cranberry preparations, highlighting that standardized dosing and the actual PAC content across formulations were more important than the specific formulation itself [57]. In subsequent years, however, the literature yielded heterogeneous and often discordant results, likely due to substantial variability in PAC content across the products used in clinical trials. In this context, the 2012 Cochrane Review by Jepson et al. contributed to widespread skepticism regarding cranberry efficacy. Across the 24 included studies, formulations were highly variable (juices, capsules, tablets, and combined extracts) and, critically, no standardized method was used to quantify PACs, precluding meaningful comparability. Most preparations contained <10 to 18 mg of PACs, and only a few studies used formulations exceeding 20 mg, dosages now recognized as sub-therapeutic. Despite these limitations, the review still suggested a possible—albeit uncertain—preventive effect of cranberries against UTIs [58]. More recently, Mantzorou and Giaginis again emphasized that the benefit of cranberry products depends on the dose and type of PACs administered [55], given that the heterogeneity of preparations across trials makes it difficult to define a uniform, comparable regimen. The importance of PAC dosing is further supported by the 2024 meta-analysis by Moro et al. (≈ 3000 participants), which reported a clear superiority of cranberry juice over capsules and other formulations. This apparently counterintuitive advantage was attributed to the higher PAC content of the administered juice, enabling attainment of an effective therapeutic threshold, whereas alternative formulations provided substantially lower amounts of the active component [59]. A decisive step forward came from Xiong et al., whose meta-analysis included ten randomized controlled trials (RCTs) using standardized PAC dosing. This work identified, for the first time, a minimum effective threshold of 36 mg/d, to be taken for at least 12 to 24 weeks, to achieve a clinically meaningful preventive effect. With this regimen, studies conducted in healthy women showed an approximately 18% reduction in the risk of a UTI episode [60]. Overall, current evidence indicates that cranberry efficacy in UTI prevention depends primarily on the actual PAC dose ingested, more than on the route/form of administration (juice vs capsules), provided that the product is adequately standardized. Therefore, cranberry represents a promising and safe prophylactic option; however, the substantial heterogeneity in doses and formulations used to date has limited the strength of conclusions. Further studies are needed to better define the benefits of cranberry

preparations using evidence-based, therapeutically effective PAC dosing, in order to generate recommendations that can more reliably inform clinical practice. In kidney transplant recipients, 2 additional challenges must be considered: the potential impact on allograft integrity and the growing burden of antimicrobial resistance. In this setting, the exploration of non-antibiotic strategies applicable both in the early postoperative phase and during long-term follow-up becomes central. Among alternative approaches, cranberry has shown encouraging results in reducing UTI episodes. Notably, Pagonas et al. conducted one of the few studies specifically in transplant populations. In this retrospective study, cranberry juice and L-methionine were evaluated in 82 recipients with recurrent infections; intake of either product alone or in combination was associated with a 63.9% overall reduction in annual UTI incidence. In addition to fewer infectious episodes, more than half of patients reported symptomatic improvement, and a substantial proportion showed normalization of pyuria and nitrituria. These findings suggest that, even in transplant recipients, cranberry-based preparations may represent an effective and safe prophylactic option, offering a valuable non-antibiotic alternative in a context at high risk for resistance development [61]. D-mannose is also believed to inhibit bacterial adhesion to urothelial cells by mimicking mannose residues and binding type 1 fimbriae on uropathogens. *E. coli*, responsible for the vast majority of UTIs, expresses the virulence factor FimH, which facilitates bacterial binding to the bladder mucosa. By trapping microorganisms, D-mannose may promote their elimination through urinary flow, reducing colonization and infection risk without antibiotics [62]. However, the Manotras study (2024) did not demonstrate clinically meaningful benefit. This prospective, randomized, double-blind trial enrolled 60 de novo kidney transplant recipients to test whether adding sustained-release D-mannose to PACs could reduce UTI and ASB incidence during the first 6 post-transplant months. Participants were assigned to D-mannose+PACs vs PACs alone. No significant differences emerged: cystitis occurred in 7% vs 4%, pyelonephritis in 4% vs 5%, and ASB in 17% vs 14%, respectively. These results indicate that adding D-mannose did not provide a significant clinical advantage over cranberry-based prophylaxis alone [63]. Although the proposed mechanism of D-mannose—antagonizing FimH-mediated adhesion—has strong biological plausibility, this does not necessarily translate into clinical efficacy in transplant recipients or in the general population. Indeed, clinical data are also inconsistent among otherwise healthy women with recurrent UTIs: a recent placebo-controlled RCT published in *JAMA Internal Medicine* ($n = 598$) did not confirm a significant benefit of D-mannose. Specifically, 303 participants were assigned to D-mannose and 295 to placebo; the proportion seeking outpatient care for suspected UTI was 51% in the D-mannose group versus 55.7% in the placebo group (risk difference -5% ; 95% CI -13% to 3% ; $P = .26$). These findings support the conclusion that, despite a solid rationale, D-mannose has not demonstrated clinically meaningful prophylactic efficacy, consistent with the limited and heterogeneous evidence in the post-transplant setting [64]. Within non-antibiotic strategies, methenamine hippurate (MH) is a urinary antiseptic of growing interest.

Its mechanism relies on hydrolysis in an acidic urinary environment, releasing formaldehyde, a broad-spectrum compound with non-specific bactericidal activity through protein denaturation and nucleic acid inactivation. The non-selective nature of this mechanism is particularly advantageous in kidney transplant recipients, where MDR organisms are common and increasing: MH does not exert selective antimicrobial pressure and does not promote resistance. In transplant recipients—often characterized by urogenital dysbiosis, persistent colonization, and recurrent UTIs—methenamine may reduce antibiotic burden and the selection of MDR strains, representing an additional option in patients with adequate renal function and urinary pH amenable to acidification. In the general population, the ALTAR trial compared MH with continuous antibiotic prophylaxis in women with recurrent UTIs and demonstrated non-inferiority of methenamine in reducing symptomatic episodes [65]. Similarly, Botros et al. compared MH and trimethoprim over 12 months in women with recurrent UTIs, reporting identical recurrence proportions (65% in both groups; $P = 1.00$) in both intent-to-treat and per-protocol analyses, with no significant differences in adverse events [66]. Although evidence in transplant recipients remains limited, retrospective data are emerging: a study of 60 kidney or kidney–liver transplant recipients found that MH use for ≥ 180 days was associated with a significant reduction in UTI rate compared with controls (0.6 vs 1.3 episodes per 180 patient-days; $P = .0005$), along with decreased ASB, antibiotic utilization, hospitalizations, and isolation of MDR organisms. Despite the methodological limitations inherent to retrospective designs and small sample sizes, these findings suggest MH may represent a promising prophylactic strategy in transplant recipients [67]. Importantly, while methenamine has no role in treating acute infections, it may be useful as a non-antibiotic option to contain recurrent UTIs and antimicrobial selective pressure in this population, pending prospective controlled studies to better define efficacy and safety. Finally, topical vaginal estrogen in peri- and postmenopausal women is supported by a clear recommendation, as it can reduce vaginal atrophy, restore the microbiome, and decrease infection frequency [68]. In contrast, evidence regarding the preventive efficacy of locally administered probiotics remains inconclusive, and current studies do not provide sufficient support for their routine use [69,70].

CONCLUSION

UTIs remain one of the major threats to allograft survival, exacerbated by the immune frailty inherent to CKD and by the expanding burden of multidrug-resistant (MDR) organisms within a broad and opportunistic microbial spectrum. Indiscriminate antimicrobial treatment provides no tangible benefit and fosters the emergence and expansion of resistant strains. Therefore, in patients with CKD and in kidney transplant recipients, clinical decision-making should rely on a pragmatic and judicious assessment of the true risk–benefit balance. In this setting, timely initiation of appropriately targeted empiric therapy remains essential and should be promptly refined after microbiological identification and susceptibility testing to maximize

effectiveness while limiting selective antimicrobial pressure. Within this framework, the need to move beyond an exclusively antibiotic-centered model is increasingly evident—not only because of its limited efficacy in preventing recurrences, but also to reduce infectious burden without amplifying selection pressure—through the adoption of adjunctive non-antibiotic strategies such as adequately standardized cranberry preparations with effective PAC content and methenamine hippurate. In parallel, an indispensable goal is the development of personalized protocols based on biomarkers, immunological profiling, and microbiological risk stratification. At the same time, the pathophysiological landscape is evolving. Uromodulin is emerging as a key regulator of urothelial defense, while SGLT2 inhibitors—through tubular “metabolic rest” and established cardio-renal protection—are reshaping our understanding of infectious vulnerability in both CKD and kidney transplant populations. Ultimately, the future management of UTIs after kidney transplantation is moving toward an integrated model that combines prevention, immunomodulation, and non-antibiotic interventions in a synergistic strategy aimed at curbing antimicrobial resistance, reducing recurrence risk, and preserving long-term allograft longevity.

DATA AVAILABILITY

No data was used for the research described in the article.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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