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RECURRENT UTIs IN NON-PREGNANT WOMEN: NON-ANTIBIOTIC PREVENTION AND AN OUTPATIENT STEWARDSHIP ALGORITHM

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ABSTRACT

Introduction: Recurrent urinary tract infections (rUTIs) in non-pregnant women represent a major clinical and socioeconomic burden, increasingly complicated by antimicrobial resistance and limited antibiotic options.
Aim of the Study: This narrative review synthesizes current evidence on non-antibiotic prevention strategies and proposes a structured outpatient stewardship algorithm.
Methodology: A comprehensive literature search across PubMed, Scopus, Web of Science, and Cochrane Library (inception–September 2025) identified studies on behavioral, pharmacological, and immunological prophylaxis in adult women with recurrent uncomplicated UTIs.
Results: Evidence supports lifestyle optimization—adequate hydration, postcoital voiding, and intimate hygiene—as safe but variably effective measures. Cranberry-derived proanthocyanidins and D-mannose demonstrate moderate efficacy in reducing recurrences, while vaginal estrogen significantly benefits postmenopausal women by restoring mucosal integrity. Immunostimulants such as OM-89 and methenamine hippurate emerge as promising antibiotic-sparing options, supported by high-quality randomized trials. The proposed outpatient algorithm prioritizes elimination of modifiable risk factors, sequential non-antibiotic prophylaxis, and restricted antibiotic use guided by urine culture results. Non-antibiotic strategies have shown favorable cost-effectiveness and reduced healthcare utilization compared with continuous antibiotic prophylaxis. Future research should standardize outcome definitions, incorporate microbiome and immunological analyses, and evaluate long-term cost–benefit profiles through multicenter pragmatic trials.
Conclusions: Integrating non-antibiotic prevention into structured stewardship frameworks offers a sustainable, patient-centered model for rUTI management, mitigating resistance development while maintaining clinical efficacy.

KEYWORDS
Recurrent Urinary Tract Infection, Non-Antibiotic Prophylaxis, Women's Health, Review

CITATION

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1. Introduction

Recurrent urinary tract infections (rUTIs) in non-pregnant women are clinically defined as two or more episodes of acute uncomplicated cystitis within a six-month period or three or more episodes within one year, with complete resolution of symptoms and confirmed bacterial clearance between episodes [1]. A critical distinction must be made between relapse, which denotes the recurrence of symptoms caused by the same bacterial strain within approximately two weeks of initial treatment, and reinfection, which involves either a different strain or recurrence following a symptom-free interval exceeding two weeks. This differentiation holds important diagnostic and therapeutic implications [2].

Urinary tract infections (UTIs) are among the most common infections worldwide and represent a significant clinical and economic burden. They account for nearly 40% of all healthcare-associated infections and a notable proportion of community-acquired infections [3–5]. According to the Global Burden of Disease (GBD) Study, approximately 400–405 million UTI cases occurred globally in 2019, leading to roughly 273,000 deaths and 5.2 million disability-adjusted life years (DALYs). Between 1990 and 2019, a 2.4-fold increase in UTI-related deaths was reported, accompanied by a steady rise in the age-standardized mortality rate [3,4].

An increased incidence of UTIs has also been observed among women of higher sociodemographic status. Up to 10% of these women experience at least one episode of acute uncomplicated UTI annually, and approximately 50% will develop at least one episode during their lifetime. Recurrent infections occur in approximately 5–20% of affected women, depending on population characteristics and diagnostic definitions [5-7]. After the first year of life, UTIs occur 20–50 times more frequently in females than in males, with women accounting for roughly 80% of all cases. The highest incidence is observed among young, sexually active women aged 18–24 years [5,8].

The clinical burden of rUTIs extends beyond the immediate physical symptoms. Patients frequently report dysuria, urinary urgency, frequency, nocturia, and suprapubic discomfort, often accompanied by fatigue and malaise. The recurrent and unpredictable nature of these infections contributes to emotional distress, anxiety, sexual dysfunction, and limitations in both daily and occupational functioning, leading to a substantial reduction in health-related quality of life [9,10].

From a public health and economic perspective, rUTIs impose a substantial burden on healthcare systems worldwide. They account for a large number of outpatient consultations, microbiological investigations, antibiotic prescriptions, and in some cases, the use of long-term prophylactic antimicrobial regimens [6,11]. In the United States alone, direct healthcare costs associated with UTIs, including recurrent forms, are estimated to exceed 2–3 billion USD annually [6]. Indirect costs related to absenteeism, decreased work productivity, and diminished quality of life further underscore the socioeconomic significance of this condition [11]. The persistence of rUTIs despite standard management continues to challenge clinicians and underscores the need for individualized, evidence-based preventive and therapeutic strategies.

2. Methodology

Literature search strategy

This narrative review was conducted in accordance with the recommendations for evidence synthesis in narrative biomedical reviews, emphasizing transparency, reproducibility, and critical evaluation of included studies. A comprehensive literature search was performed across PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library from database inception to September 2025. Search terms combined controlled vocabulary (MeSH/Emtree) and free-text words related to recurrent urinary tract infections ("recurrent UTI," "rUTI," "recurrent cystitis"), non-antibiotic prophylaxis ("cranberry," "D-mannose," "probiotics," "immunostimulants," "vaginal estrogen," "behavioral modification"), and antibiotic stewardship ("outpatient stewardship," "antimicrobial resistance," "clinical algorithm"). Boolean operators and truncations were applied to maximize sensitivity and specificity.

Reference lists of relevant reviews and primary studies were manually screened to identify additional publications not captured by electronic search. Only full-text articles published in English were considered. Conference abstracts, opinion pieces, and duplicate records were excluded.

Inclusion and exclusion criteria for studies

Eligible studies met the following inclusion criteria:

1. **Population:** Non-pregnant adult women with recurrent uncomplicated urinary tract infections, defined as ≥2 episodes within 6 months or ≥3 within 12 months, with documented symptom resolution and negative urine culture between episodes.
2. **Interventions:** Non-antibiotic preventive strategies, including lifestyle modification, hydration, behavioral and hygiene interventions, probiotics, vaginal estrogen, immunostimulants, and D-mannose supplementation.
3. **Comparators:** Placebo, no treatment, or standard antibiotic prophylaxis.
4. **Outcomes:** Incidence or recurrence rate of UTIs, symptom duration, antibiotic consumption, quality of life measures, adverse effects, and cost-effectiveness.
5. **Study types:** Randomized controlled trials (RCTs), prospective or retrospective cohort studies, case-control studies, and high-quality systematic reviews or meta-analyses.

Exclusion criteria encompassed studies focusing on pregnant women, men, pediatric populations, complicated UTIs (e.g., associated with anatomical abnormalities, indwelling catheters, or neurogenic bladder), or those lacking explicit outcome measures. Where multiple reports described the same cohort, the most comprehensive or recent publication was included.

Data extraction was performed independently by two reviewers, with discrepancies resolved through discussion and consensus. Extracted information included study design, population characteristics, intervention details, comparator type, primary and secondary outcomes, and main conclusions. The risk of bias was qualitatively assessed based on study design, randomization procedures, blinding, and attrition. Evidence synthesis prioritized studies with robust methodology, clinically relevant endpoints, and real-world applicability.

3. Non-antibiotic prevention strategies

In the era of increasing antibiotic resistance, it is vital to identify a non-antibiotic approach to rUTIs.

The degree to which behavioral modifications influence the frequency of infection is not clear as there is a lack of relevant randomized trials conducted on the topic. A case control study found that infection rates were lower when patients:

1) wiped front to back after using the toilet,
2) avoided postponing micturition or defecation,
3) urinated after intercourse,
4) refrained from cleaning the genitals after micturition.

Even though there is little evidence of the efficacy of these behavioral changes, they are not harmful to the patients when implemented, therefore can be recommended by physicians [12].

Fluid intake is a behavioral change that could possibly influence the recurrence of UTIs. A meta-analysis found that increasing the daily fluid intake significantly lowers the infection rate over the short term, but the effect isn't prevalent at 12 months. Therefore, it is suggested that physicians should recommend an increase in water intake to women with rUTIs [12].

As far as diet is concerned, one study suggested that a vegetarian diet could lower the risk of UTIs in women, however, further research is needed to identify the pathogens necessary for the clarification of the relationship among UTI risk, pathogens and diet [13].

The supplementation of D-mannose was reported to be efficient in recurring UTIs by reducing bacterial adherence to urinary tract epithelium. Further research is necessary to determine the optimal dosage and duration of the treatment [14].

There exist many OTC medications containing proanthocyanidins - a vital substance in cranberries. They are thought to prevent the adhesion of bacteria to urothelium and in effect act as UTI prophylaxis. However, there seem to be many mixed studies on the efficacy of this substance. One study found that cranberry reduces the risk of symptomatic, culture-verified UTIs (*E. coli*, *Pseudomonas*, and *Klebsiella*) in women with rUTIs, children, and people susceptible to UTIs following interventions [15]. On the other hand, a Cochrane review updated in 2012 reported cranberry products did not significantly reduce the occurrence of symptomatic UTI overall or for any of the subgroups [16].

Probiotics did not show a significant benefit in reducing UTI recurrence in premenopausal women. Nonetheless, there is room for more conclusive data on the strengthening of the urogenital microbial barrier against bacteria [17].

Many studies reported the efficacy of vaginal estrogen products in preventing rUTIs. There seemed to be no difference between vaginal and oral estrogen. An estradiol ring appeared particularly effective. What is more, even an ultra-low-dose is safe and effective in preventing rUTI in postmenopausal women. [12]

Another form of rUTI prevention is an oral vaccine - OM-89 (Uro-Vaxom) made from a lysate of selected *E. coli* strains. Even though there seems to be compelling evidence as to the efficacy of this method, the limitations in availability and awareness may lead to OM-89 being underutilised [18].

Methenamine hippurate is a successful non-antibiotic strategy in rUTIs in women. It was also suggested that antimicrobial resistance may be higher in women taking prophylactic antibiotics [19.]

Non-antibiotic treatment options are crucial in the world where antibiotic resistance is increasing. There exist many different options, however, most of them require more research to verify their efficacy.

4. Outpatient stewardship algorithm

In some patients, the cause of rUTIs is never identified. In most cases, however, there is more than one risk factor present. In premenopausal women, sexual behaviors seem to be the most significant factor. Behaviors heightening the risk of rUTIs include having a new sexual partner, an increased frequency of sexual intercourse (more than times a week, triples the risk of a UTI), and the use of a spermicide-containing contraceptive. In postmenopausal women, sexual behaviors play a less significant role. Urinary tract disorders that have been associated with rUTIs include an increased postvoid residual urine volume, the presence of a cystocele, and urinary incontinence. Bowel dysfunction, such as chronic constipation, may be associated with incontinence, thus indirectly contributing to rUTIs. The treatment of asymptomatic bacteriuria has also been associated with the development of rUTIs. Drugs used in the treatment of overactive bladder may also predispose patients to rUTIs. Most authors agree that the use of the antimuscarinic subtype of anticholinergics agents is a risk factor, while it remains unclear what the impact of β3-adrenoceptor agonists might be. Diabetes itself is a risk factor for rUTIs; additionally, there is an ongoing debate concerning sodium-glucose cotransporter-2 (SGLT2) inhibitors used in the treatment of type 2 diabetes. One study showed an increase in the risk of UTIs by 30%-40%; however, other studies do not reveal a significant difference compared with other classes of anti-diabetic drugs. There is also an increased risk of rUTIs in patients who form calcium oxalate and urate stones [20]. Patients with a first UTI before the age of 16, or those with a sister or mother who has a history of rUTIs, are also at a higher risk. Hygiene risk factors that increase the likelihood of developing recurrent UTIs include washing the vaginal area without soap, reusing unclean washcloths, failing to clean the urethral area first, taking baths instead of showers, not washing hands before wiping, wiping or washing from back to front or repeatedly, not using vaginal estrogen when indicated, and inadequate fluid intake. If possible, risk factors should be eliminated. Lifestyle and personal hygiene changes are recommended; however their effectiveness in reducing recurrent UTIs remains inconclusive. Nonetheless, they carry no negative consequences and may provide some benefit [21].

If maximizing personal hygiene factors, avoiding spermicides, wiping correctly, increasing fluid intake and hydration, and using vaginal estrogens fail, non-antibiotic prophylactic therapies are recommended [21]. Only if those fail as well, antibiotic prophylaxis may be prescribed to decrease the risk of future UTIs in women of all ages [22], except for patients with permanent catheters or nephrostomies. This stepwise treatment

approach limits the development of bacterial resistance, minimizes antibiotic-related adverse effects, drug-drug interactions, allergies and reduces costs. Long-term low-dose antibiotic prophylaxis should last at least six months. Preferred antibiotic agents include: nitrofurantoin (50-100 mg before bed daily), sulfamethoxazole (40-200 mg daily) and trimethoprim (100 mg daily) [21].

According to the guidelines of the American Urological Association every case of acute UTI treatment should be preceded by obtaining a complete patient history and performing a pelvic examination in patients with rUTIs. Urinalysis, urine culture, and sensitivity testing should also be obtained prior to initiating treatment. Repeat urine studies should be performed when an initial urine specimen is suspected of contamination. Cystoscopy should not be routinely obtained [22] as it might induce an ascending lower urinary tract infection. Upper tract imaging (renal ultrasonography and a computed tomography scan) is advised for a select group of patients, including those presenting relapsing infections, persistent hematuria after treatment, a history of stone passage, or repeated isolation of Proteus from the urine [21]. First-line therapy, including nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomycin should be selected dependent on the local antibiogram, generally for no longer than seven days [22]. An alternative antibiotic agent should be prescribed to treat the infection if one is used prophylactically [21]. Acute cystitis episodes associated with urine cultures resistant to oral antibiotics should be treated with culture-directed parenteral antibiotics [22]. Post-treatment tests of urinalysis or urine culture in asymptomatic patients are unnecessary. Repeat urine cultures should, however, be obtained if UTI symptoms persist following antimicrobial therapy [21].

5. Efficacy and safety of non-antibiotic interventions

A review of studies showed some evidence of the long-term effects of untreated cystitis. It demonstrated that progression to pyelonephritis was rare, and most cases of cystitis resolved spontaneously, although symptoms sometimes persisted for several months [23]. According to the AAFP [24], immediate antibiotic treatment leads to better clinical outcomes, and delaying antibiotic therapy while awaiting culture results is not recommended. In contrast, the SSGO [25] recommends delaying antibiotic treatment for 48 hours. The SOGC [26] also promotes non-antibiotic management, such as the use of cranberry products. The NICE guidelines recommend providing advice on symptomatic treatment for all patients. The EAU guidelines concluded that symptomatic treatment may be an alternative for selected patients; however, antibiotics are still recommended based on evidence from randomized clinical trials, which have shown improved clinical success [27].

In 2012, Stapleton et al. demonstrated in a placebo-controlled trial that women assigned to cranberry treatment showed a concurrent but non-significant reduction in the number of P-fimbriated E. coli in the urine and in the incidence of symptomatic urinary tract infections (UTIs) [28]. The use of non-antimicrobial prophylactic agents does not lead to increased antimicrobial resistance in the commensal flora. Therefore, alternative preventive approaches have been considered, such as the use of topical vaginal estrogen, oral capsules containing L. rhamnosus GR-1 and L. reuteri RC-14 in postmenopausal women, and cranberry prophylaxis or intravaginal Lactobacillus crispatus in premenopausal women. Furthermore, it is important to continue research on other potential preventive methods, including D-mannose, acupuncture, and vaccination [29]. Compared with treatment without antibiotics, the use of antibiotics was clearly associated with adverse events. The rate of adverse events was higher in the antibiotic group than in the placebo group. In most studies, adverse events were classified as either severe or mild. There were also adverse events that led to discontinuation of treatment [30].

6. Implementation challenges and solutions

Effective management of recurrent UTIs necessitates a collaborative, interprofessional approach where healthcare providers work together to deliver patient-centered care, improve outcomes, and ensure safety. Physicians and advanced practitioners act as the primary contacts, performing detailed history-taking, physical examinations, and ordering diagnostic tests such as urinalyses and urine cultures. The use of clinic-specific urinary antibiograms, combined with treatment protocols, clinician education, and feedback on data, has successfully increased adherence to guidelines, shifting away from fluoroquinolones to alternative agents with narrower spectrum and fewer side effects—and has contributed to a decrease in UTI diagnoses [31]. Collaboration with specialists like urologists, infectious disease experts, and radiologists is crucial for complex cases, especially when urinary obstruction or unusual symptoms are present. Nurses play a critical role in monitoring vital signs, educating patients and families, and supporting treatment adherence. A nursing education program resulted in notable improvements in both clinical outcomes and cost savings, exceeding $1.5 million, thereby enhancing patient care and operational efficiency [32]. Effective interprofessional

communication is essential for bridging gaps in symptom interpretation, correcting misconceptions, building patient trust, and empowering individuals to participate actively in their care. In appropriate cases, engaged and reliable patients may benefit from self-diagnosis and treatment under supervision, which can streamline care without compromising quality. By coordinating efforts and sharing case details, the healthcare team ensures timely, accurate treatment, minimizes unnecessary procedures, and promotes optimal outcomes and team performance.

7. Economic considerations

Non-antibiotic prophylactic strategies for recurrent urinary tract infections (rUTIs) in nonpregnant adults are of increasing interest not only for their clinical effectiveness but also for their economic benefits. Several studies have shown that immunoprophylaxis and non-antibiotic agents can significantly reduce health care costs compared with continuous antibiotic prophylaxis.

A prospective real-world study evaluating the sublingual polymicrobial vaccine MV140 showed a marked reduction in average health care costs per patient, from approximately €21,171.87 to €20,763.73 after three months and from €32,980.35 to €23,629.19 after six months, indicating greater cost-effectiveness compared to long-term antibiotic prophylaxis [33]. Similarly, in 2023, MV140 was shown to not only reduce relapse rates and antibiotic use, but also reduced overall treatment costs, hospital visits, and laboratory testing frequency [34].In a multicentre randomised trial conducted in the United Kingdom, methenamine Hippurate- a non-antibiotic urinary antiseptic was found to be marginally less costly slightly more effective than continuous antibiotic prophylaxis over an 18-month period [35]. These findings suggest that, when effective in preventing rUTI episodes, non-antibiotic prophylaxis can achieve favourable incremental cost-effectiveness ratios (ICERs) and may even dominate antibiotic strategies, particularly when broader factors such as antimicrobial resistance and patient quality of life are considered.Although cost-effectiveness evidence is promising, it remains sensitive to key parameters including prophylaxis efficacy, adherence, time horizon, and the inclusion of indirect costs such as lost productivity.

Non-antibiotic preventive measures also have substantial potential to generate savings in healthcare expenditure by reducing healthcare resource utilisation. A multinational Markov-model analysis across seven countries estimated that promoting increased daily water intake in women with low baseline hydration could prevent a large proportion of rUTI episodes, leading to cumulative 10-year cost savings[36]. In addition to direct treatment costs, reducing the number of recurrent infections translates into fewer consultations in primary care, fewer antibiotics prescribed and fewer diagnostic tests, thus reducing the wider burden on health care. Additionally, by reducing antibiotic use, non-antibiotic prophylaxis may indirectly mitigate antimicrobial resistance, avoiding future costly hospitalizations and the need for advanced antimicrobial therapies. Although these subsequent savings are difficult to quantify precisely, they represent an important dimension of the long-term economic value of preventing rUTI without the use of antibiotics.

8. Future research directions

Despite growing evidence supporting non-antibiotic prophylaxis for recurrent urinary tract infections (rUTIs) in non-pregnant women, substantial knowledge gaps remain that limit the formulation of definitive, cost-effective prevention strategies. The pathophysiological mechanisms underlying recurrence are incompletely elucidated, particularly the roles of intracellular bacterial communities (IBCs), bladder mucosal reservoirs, and the urinary microbiome in relapse versus reinfection. Integrative mechanistic studies combining metagenomics, host transcriptomics, and bladder mucosal immune profiling are essential to delineate these processes and identify therapeutic targets [37,38]. Large, multicentre, double-blind randomized controlled trials (RCTs) with long-term follow-up are required to confirm the efficacy and durability of promising non-antibiotic interventions such as sublingual polybacterial vaccines (MV140), methenamine hippurate, and intravesical hyaluronic acid + chondroitin sulfate, with embedded microbiological substudies to determine their mechanism of benefit [39]. Furthermore health-economic evaluations should be prospectively integrated into such trials to assess incremental cost-effectiveness ratios (ICERs) and incorporate antimicrobial resistance (AMR) externalities using long-term Markov or microsimulation models, as short-horizon analyses may underestimate downstream costs [40,41]. Standardisation across studies is urgently needed; a core outcome set for rUTI research should define uniform case criteria, culture-confirmed recurrence, validated quality-of-life metrics, and economic endpoints to improve reproducibility and facilitate meta-analysis. Future innovation should also focus on rapid molecular diagnostics and strain-typing workflows to distinguish relapse from reinfection, enabling personalised management and precise endpoint ascertainment. Microbiome-directed

trials investigating probiotics, bacteriophage therapy, and microbiota modulation approaches represent another promising frontier, with pilot data suggesting modulation of vaginal and gut flora may reduce recurrence risk. Finally, global equity-focused research and patient-centred qualitative studies are needed to optimise adherence, assess feasibility across healthcare systems, and ensure generalisability to low- and middle-income settings [42].

9. Conclusions

Recurrent urinary tract infections in non-pregnant women represent a persistent clinical and psychosocial challenge that extends beyond the confines of microbiological recurrence. Despite decades of reliance on antibiotic prophylaxis, rising antimicrobial resistance and patient-centered care imperatives necessitate a paradigm shift toward non-antibiotic prevention and structured stewardship models.

Evidence accumulated over the past decade underscores the multifactorial nature of rUTI prevention. Adequate hydration, voiding behaviors, and intimate hygiene are low-cost interventions with favorable safety profiles, although their effect sizes vary across studies. Cranberry-derived proanthocyanidins demonstrate modest but reproducible benefit in reducing recurrence rates, particularly in women with low adherence to behavioral measures. D-mannose supplementation has emerged as a promising alternative, supported by RCTs demonstrating comparable efficacy to nitrofurantoin in preventing recurrences while avoiding microbiome disruption. Probiotic formulations containing *Lactobacillus crispatus* and *L. rhamnosus* show potential for vaginal recolonization, though strain-specific variability and formulation stability remain limitations. In postmenopausal women, topical vaginal estrogen restores urogenital mucosal integrity and reduces UTI frequency, supported by strong mechanistic and clinical evidence. Immunostimulants such as bacterial lysates offer an innovative approach through trained immunity and mucosal immune activation, warranting further mechanistic and clinical evaluation.

The outpatient stewardship algorithm proposed herein integrates individualized risk stratification, prioritization of non-antibiotic measures, and judicious antibiotic use guided by clinical and microbiological parameters. Such structured approaches can reduce unnecessary antibiotic exposure while maintaining clinical efficacy and improving patient-reported outcomes.

Ultimately, non-antibiotic preventive strategies, when embedded in a comprehensive outpatient stewardship framework, hold the potential to redefine rUTI management—shifting focus from repetitive treatment to durable prevention. Future research should emphasize multicenter pragmatic trials comparing combined interventions, standardized outcome definitions, and cost-effectiveness analyses to guide evidence-based implementation across diverse healthcare settings.

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