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2734 17 Avenue SW,
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+15878858911
editorial-office@sciformat.ca

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NON-ANTIBIOTIC PREVENTION STRATEGIES FOR RECURRENT URINARY TRACT INFECTIONS IN WOMEN: A SYSTEMATIC REVIEW

Maciej Krzesimir Kuświk (Corresponding Author, Email: mkkuswik@gmail.com)

Student Scientific Association of Lifestyle Medicine; The Student Scientific Society of Poznan University of Medical Sciences; Poznań University of Medical Sciences; Poznań, Poland
ORCID ID: 0009-0006-1925-204X

Paweł Zdebski

Poznan University of Medical Sciences, Poznan, Poland
ORCID ID: 0009-0004-9718-157X

Dominika Dmowska

HCP Medical Center, John Paul II Hospital, Poznań, Poland
ORCID ID: 0009-0002-9269-5577

Mikołaj Lewandowski

Regional Hospital in Poznań, Poland
ORCID ID: 0009-0001-8533-0660

Karolina Rymska

University Clinical Hospital Jan Mikulicz-Radecki, Wrocław, Poland
ORCID ID: 0009-0009-8826-8899

Alicja Serafin

Lower Silesia Oncology, Pulmonology and Haematology Center, Wrocław, Poland
ORCID ID: 0009-0000-1060-7437

Wiktoria Bajek

National Medical Institute of the Ministry of the Interior and Administration in Warsaw, Poland
ORCID ID: 0009-0004-6200-2471

Dominik Chrzanowski

National Medical Institute of the Ministry of the Interior and Administration in Warsaw, Poland
ORCID ID: 0009-0000-7793-6315

Marcelina Kaczmarek

Faculty of Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland
ORCID ID: 0009-0009-0114-0607

Kinga Żmuda

University Clinical Hospital of Opole, Opole, Poland
ORCID ID: 0009-0007-0948-3642

ABSTRACT

Recurrent urinary tract infections (rUTIs) in women represent a frequent and burdensome clinical problem, often leading to repeated antimicrobial exposure, reduced quality of life, and increased healthcare utilization. Although antibiotic prophylaxis can reduce recurrence, long-term or repeated antibiotic use contributes to adverse effects, disruption of the urogenital microbiota, and antimicrobial resistance. This systematic review summarizes current evidence on non-antibiotic prevention strategies for rUTIs in adult women, with emphasis on methenamine hippurate, vaginal estrogen, cranberry products, D-mannose, probiotics, increased fluid intake, immunoprophylaxis, and intravesical glycosaminoglycan therapies. A structured literature search was performed in PubMed/MEDLINE and PubMed Central for studies and reviews published up to September 2026. Relevant randomized trials, systematic reviews, meta-analyses, clinical reviews, and guideline documents were included. The strongest contemporary evidence supports methenamine hippurate as an antibiotic-sparing alternative in selected women, vaginal estrogen in peri- and postmenopausal women, cranberry products as an option with modest benefit, and increased water intake in women with low baseline fluid intake. Evidence for D-mannose and probiotics is inconsistent, while immunoprophylaxis and intravesical therapies remain promising but require further standardization. Non-antibiotic prevention should be individualized according to menopausal status, recurrence pattern, comorbidities, preferences, and local antimicrobial stewardship priorities.

KEYWORDS

Recurrent Urinary Tract Infection, Non-Antibiotic Prophylaxis, Methenamine Hippurate, Vaginal Estrogen, Cranberry, Antimicrobial Stewardship

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Introduction

Urinary tract infections are among the most common bacterial infections encountered in adult women. A substantial proportion of women experience at least one symptomatic episode during their lifetime, and many develop recurrent disease. Recurrent urinary tract infection is commonly defined as at least two symptomatic episodes within six months or at least three episodes within one year, preferably with documentation of at least one culture-proven infection (Anger et al., 2019; NICE, 2024). Although uncomplicated episodes often resolve with short-course antimicrobial treatment, repeated recurrences create a cumulative clinical, psychological, and socioeconomic burden that is frequently underestimated in routine practice.

For many patients, rUTI is not merely a sequence of isolated infections. Repeated symptoms may interfere with sexual activity, work, travel, sleep, exercise, and social functioning. Women may develop anticipatory anxiety, avoid triggers, and repeatedly seek urgent consultations. From a healthcare perspective, rUTIs generate repeated urine testing, antimicrobial prescriptions, telephone consultations, emergency visits, specialist referrals, and occasional imaging or invasive investigations. The burden is therefore both biomedical and social, which makes prevention an important component of patient-centered care.

For decades, continuous low-dose antibiotic prophylaxis, post-coital antibiotic prophylaxis, or patient-initiated antibiotics have been used to prevent or manage recurrent episodes. Antibiotic strategies remain clinically useful in selected patients, particularly when non-antibiotic options fail or when recurrences are frequent and culture-confirmed. However, the increasing importance of antimicrobial stewardship has changed the way clinicians approach long-term prevention. Guidelines now emphasize shared decision-making, confirmation of diagnosis, identification of modifiable risk factors, and consideration of antibiotic-sparing strategies before initiating prolonged antimicrobial prophylaxis (Anger et al., 2025; NICE, 2024).

The rationale for non-antibiotic prevention is strong. Recurrent antimicrobial exposure may select resistant uropathogens, cause adverse drug reactions, promote gastrointestinal and vaginal dysbiosis, and increase the likelihood of future treatment failure. The problem is particularly relevant in women with repeated

infections due to *Escherichia coli* and other Enterobacterales, but also applies to patients exposed to nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin, fluoroquinolones, and beta-lactams across multiple episodes. Even when resistance does not develop in an individual patient, widespread antibiotic use contributes to population-level antimicrobial resistance.

At the same time, non-antibiotic prevention is not a single intervention. It includes behavioral measures, increased fluid intake, cranberry products, D-mannose, probiotics, topical vaginal estrogen, methenamine hippurate, immunoactive prophylaxis, vaccines, and intravesical therapies. These interventions differ substantially in mechanism, evidence quality, target population, safety profile, cost, acceptability, and guideline support. Some are supported by randomized trial evidence, whereas others remain biologically plausible but clinically uncertain. Therefore, clinicians need a balanced understanding of what can reasonably be offered, to whom, and with what expectations.

The aim of this systematic review is to summarize evidence regarding non-antibiotic prevention strategies for recurrent urinary tract infections in adult women. The review focuses on clinical effectiveness, mechanisms of action, patient selection, safety considerations, and practical implications for antimicrobial stewardship. Particular attention is given to interventions that are currently discussed in guidelines or supported by recent systematic reviews and randomized clinical trials.

Methodology

This manuscript was developed as a systematic literature review following the general structure recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The review was designed to identify and synthesize evidence on non-antibiotic strategies for the prevention of recurrent urinary tract infections in adult women. Because the topic includes multiple intervention categories with heterogeneous study designs, the synthesis was narrative rather than quantitative.

A structured search was performed in PubMed/MEDLINE and PubMed Central for publications available up to September 2026. Search terms included combinations of: recurrent urinary tract infection, recurrent UTI, women, female, prevention, prophylaxis, non-antibiotic, methenamine hippurate, vaginal estrogen, cranberry, D-mannose, probiotics, *Lactobacillus*, immunoprophylaxis, vaccine, MV140, OM-89, intravesical therapy, hyaluronic acid, chondroitin sulfate, increased water intake, and antimicrobial stewardship. Boolean operators AND and OR were used to combine intervention-specific and disease-specific terms.

Eligible publications included randomized clinical trials, systematic reviews, meta-analyses, guideline documents, and clinically relevant narrative reviews. Priority was given to studies involving adult women with recurrent uncomplicated lower urinary tract infections. Studies focusing exclusively on children, catheter-associated infections, neurogenic bladder, structural urinary tract abnormalities, recurrent pyelonephritis, pregnancy, or animal models were excluded unless they provided essential background information relevant to mechanisms or guideline interpretation. Case reports, conference abstracts without full text, and studies unrelated to prevention were not included.

Data were extracted regarding intervention type, population characteristics, comparator, main outcomes, safety profile, limitations, and clinical applicability. Outcomes of interest included symptomatic recurrence, culture-confirmed recurrence, time to recurrence, antibiotic use, adverse events, patient adherence, antimicrobial resistance, and quality-of-life implications. Evidence was organized thematically according to intervention categories rather than pooled statistically. This approach was chosen because interventions differed in mechanism and because many reviews included heterogeneous definitions, dosing schedules, outcome measures, and follow-up durations.

The main limitation of this methodology is that the review was not registered in PROSPERO and does not include a formal risk-of-bias table for each included trial. Therefore, conclusions should be interpreted as a structured clinical synthesis rather than a new meta-analysis. Nevertheless, the review relies primarily on PubMed-indexed trials, systematic reviews, meta-analyses, and guideline documents to support clinically relevant conclusions.

Results

Burden and Definition of Recurrent Urinary Tract Infection

Across guidelines and clinical reviews, recurrent UTI is generally defined by frequency of symptomatic episodes: at least two infections in six months or at least three infections in twelve months (Anger et al., 2019; NICE, 2024). The definition appears simple, but its clinical application requires caution. Symptoms alone may overlap with genitourinary syndrome of menopause, overactive bladder, interstitial cystitis/bladder pain syndrome, vulvovaginal irritation, sexually transmitted infections, or noninfectious dysuria. For this reason, recurrent symptoms should not automatically be interpreted as repeated bacterial infection without appropriate clinical and microbiological assessment.

The literature consistently emphasizes the importance of confirming at least one symptomatic episode with urine culture. Culture confirmation supports antimicrobial stewardship by distinguishing true recurrence from persistent noninfectious symptoms and by identifying resistant or atypical pathogens. At the same time, excessive testing in asymptomatic patients may lead to unnecessary treatment of asymptomatic bacteriuria. Therefore, prevention begins with accurate diagnosis, symptom assessment, and avoidance of unnecessary antibiotic exposure.

Recurrent UTIs in women are commonly categorized as relapse or reinfection. Relapse suggests persistence of the same organism despite treatment and may prompt consideration of inadequate eradication, an anatomic reservoir, stones, or complicated infection. Reinfection, more common in otherwise healthy women, indicates a new infection after resolution of the previous episode. This distinction matters because non-antibiotic prevention strategies are more appropriate for recurrent uncomplicated cystitis than for complicated or upper tract infections.

Behavioral Measures and Increased Fluid Intake

Behavioral counseling is often recommended as the first step in prevention because it is safe, inexpensive, and consistent with patient-centered care. Common recommendations include adequate hydration, avoidance of delayed voiding, post-coital voiding when intercourse is a trigger, avoidance of spermicides, and review of personal hygiene practices. However, many traditional behavioral measures are supported more by biological plausibility and clinical experience than by strong randomized evidence. This distinction is important when counseling patients: advice should be practical and nonblaming, and women should not be made to feel responsible for recurrence because of unproven behavioral assumptions.

Among behavioral interventions, increased fluid intake has one of the stronger evidence bases. In a randomized clinical trial of premenopausal women with recurrent cystitis and low baseline fluid intake, increasing daily water intake reduced the frequency of recurrent episodes and antibiotic use (Hooton et al., 2018). This effect is biologically plausible because increased urine volume may dilute bacterial concentration and promote more frequent mechanical flushing of the bladder. The intervention is also inexpensive and generally safe, although it may not be appropriate for patients with conditions requiring fluid restriction.

The clinical implication is that hydration should be discussed particularly in women who report low daily fluid intake. However, universal advice to drink excessive water is not evidence-based and may be poorly tolerated. A practical approach is to assess baseline intake, urinary frequency, comorbidities, and patient preference before recommending a specific increase.

Methenamine Hippurate

Methenamine hippurate has become one of the most important antibiotic-sparing options for rUTI prevention. It is converted in acidic urine to formaldehyde, which has nonspecific antibacterial activity. Because its mechanism is antiseptic rather than conventional antibiotic, it is attractive from an antimicrobial stewardship perspective. Methenamine does not treat an active infection and should only be considered after current UTI has been adequately treated (NICE, 2024).

The ALTAR randomized non-inferiority trial substantially influenced contemporary practice. In this multicenter trial, methenamine hippurate was compared with daily low-dose antibiotic prophylaxis in women with recurrent UTIs. The trial concluded that methenamine hippurate was non-inferior to daily antibiotic prophylaxis for prevention over twelve months, supporting its role as an alternative in women who wish to avoid long-term antibiotics or when stewardship concerns are prominent (Harding et al., 2022).

Guideline recommendations have increasingly incorporated methenamine. NICE recommends considering methenamine hippurate as an alternative to daily antibiotic prophylaxis in nonpregnant women when behavioral measures, vaginal estrogen when appropriate, and single-dose antibiotic prophylaxis have not adequately improved recurrence (NICE, 2024). The AUA/CUA/SUFU 2025 update similarly reflects a growing role for non-antibiotic options and increased attention to antimicrobial-sparing prevention (Anger et al., 2025).

Several clinical issues require attention. Methenamine is most useful for prevention, not acute treatment. Patients should be instructed to seek medical assessment if acute UTI symptoms develop during prophylaxis. Alkalinizing agents may reduce effectiveness because acidic urine is required for formaldehyde generation; this is specifically highlighted in guidance (NICE, 2024). Renal function, hepatic disease, pregnancy status, and drug interactions should also be considered. Follow-up is necessary to assess recurrence frequency, tolerability, adherence, and ongoing need for therapy.

Table 1. Main Non-Antibiotic Prevention Strategies for Recurrent UTI in Women

Strategy	Proposed mechanism	Best-supported population	Key clinical considerations
Increased fluid intake	Increased urine dilution and bladder flushing	Premenopausal women with low baseline fluid intake	Low cost and safe for many patients; avoid excessive intake in fluid-restricted conditions
Methenamine hippurate	Urinary antiseptic activity through formaldehyde generation in acidic urine	Selected nonpregnant adult women with rUTI	Not for acute UTI; avoid alkalinizing agents; review response and tolerability
Vaginal estrogen	Restoration of vaginal epithelium, lower pH, increased lactobacilli, reduced uropathogen colonization	Peri- and postmenopausal women or hypoestrogenic women	Local therapy preferred; discuss contraindications and patient preferences
Cranberry products	Proanthocyanidins may reduce bacterial adhesion to urothelium	Women with recurrent uncomplicated UTI	Modest benefit; product formulation and adherence vary
D-mannose	Competitive inhibition of bacterial adhesion via FimH-mediated pathways	Evidence uncertain; adult women with rUTI	Large recent trial did not support routine use in primary care
Probiotics	Restoration of urogenital microbiota and lactobacilli dominance	Uncertain; selected women interested in microbiome-based prevention	Strain, route, dose, and duration vary widely
Immunoprophylaxis/vaccines	Stimulation of mucosal/systemic immune response to uropathogens	Selected women in settings where products are available	Promising but heterogeneous evidence and availability
Intravesical glycosaminoglycans	Replenishment of bladder protective layer	Refractory cases or specialist settings	Invasive, resource-intensive, and less suitable as first-line prevention

The table summarizes commonly discussed non-antibiotic interventions, their mechanisms, and practical clinical considerations.

Vaginal Estrogen

Vaginal estrogen is among the most clinically important preventive options in postmenopausal women. Menopause is associated with estrogen deficiency, thinning of the urogenital epithelium, increased vaginal pH, reduction in lactobacilli, and increased colonization by Enterobacterales. These changes may contribute to recurrent cystitis and overlap with genitourinary syndrome of menopause. Local estrogen therapy aims to restore a more protective vaginal environment rather than directly eradicate bacteria.

The classic randomized trial by Raz and Stamm demonstrated that intravaginal estriol reduced recurrent UTI in postmenopausal women, probably through modification of vaginal flora (Raz & Stamm, 1993). Later evidence and meta-analytic work suggest that local vaginal estrogen is more relevant than systemic estrogen for UTI prevention. A meta-analysis of randomized trials found that oral estrogen did not significantly reduce recurrent UTIs compared with placebo, whereas vaginal estrogen showed preventive benefit in postmenopausal women (Chen et al., 2020).

Contemporary guidelines recommend considering vaginal estrogen in peri- or postmenopausal women when behavioral measures are insufficient or inappropriate (NICE, 2024). Counseling should include discussion of formulation, expected time to benefit, local irritation, adherence, and the distinction between local vaginal estrogen and systemic hormone replacement therapy. For many women, the benefit may extend beyond UTI prevention because local estrogen can improve vaginal dryness and other symptoms of genitourinary syndrome of menopause.

Vaginal estrogen should not be presented as a universal treatment for all women with rUTI. It is most relevant in hypoestrogenic states and may have limited value in young premenopausal women without estrogen deficiency. Shared decision-making is important, particularly in patients with a history of estrogen-sensitive malignancy, where coordination with the oncology team may be appropriate.

Cranberry Products

Cranberry products are among the most widely used non-antibiotic interventions for UTI prevention. The proposed mechanism involves proanthocyanidins, which may reduce adhesion of uropathogenic *E. coli* to urothelial cells. This mechanism is attractive because it targets bacterial adherence rather than bacterial killing, theoretically reducing selective pressure for antimicrobial resistance. However, clinical translation has been complicated by differences in cranberry formulation, proanthocyanidin content, dose, adherence, and outcome definitions.

The updated Cochrane review of cranberry products found that cranberry products probably reduced the risk of symptomatic, culture-verified UTIs in women with recurrent UTIs, although the magnitude of benefit was modest and heterogeneity was present (Williams et al., 2023). This supports cranberry as an option rather than a guaranteed preventive therapy. The AUA guideline permits offering cranberry prophylaxis, but clinicians should acknowledge that no specific formulation has been clearly established as superior (Anger et al., 2019).

In practice, cranberry products may be reasonable for women who prefer low-risk self-care strategies and understand that benefit is uncertain or modest. Potential drawbacks include gastrointestinal intolerance, cost, sugar content in juice preparations, variable supplement quality, and adherence challenges. Capsules or tablets may be preferable for some patients, but standardization remains a problem.

D-Mannose

D-mannose is a naturally occurring sugar that has been proposed to prevent UTI by inhibiting FimH-mediated adhesion of uropathogenic *E. coli* to urothelial receptors. This mechanism created substantial interest because uropathogen adhesion is a key early step in cystitis pathogenesis. Earlier small trials and meta-analyses suggested potential benefit, but the quality of evidence was limited by small sample sizes, heterogeneity, and variable comparators.

A large randomized clinical trial published in JAMA Internal Medicine provided important new evidence. In women with recurrent UTI in primary care, daily D-mannose did not reduce the proportion experiencing a subsequent clinically suspected UTI over six months compared with placebo (Hayward et al., 2024). The authors concluded that D-mannose should not be recommended for prophylaxis in this population. This study shifted the interpretation of D-mannose from promising to uncertain or unsupported for routine use.

Clinically, D-mannose remains popular among patients because it is available over the counter and perceived as natural. Physicians should respond with balanced counseling rather than dismissal. Patients can be told that the biological rationale exists, but high-quality contemporary evidence does not support routine recommendation for prevention in women similar to those studied in primary care. Sugar content, cost, and expectations should also be discussed.

Probiotics and Urogenital Microbiota

The concept of probiotic prevention is based on the protective role of lactobacilli in the vaginal and periurethral microbiota. Lactobacilli may inhibit uropathogen colonization by maintaining an acidic environment, producing antimicrobial substances, competing for adhesion sites, and supporting mucosal barrier function. Antibiotic exposure, menopause, sexual activity, and other factors can disrupt this protective ecology, creating a theoretical rationale for probiotic restoration.

Despite this rationale, clinical evidence for probiotics remains inconsistent. Trials differ by *Lactobacillus* strain, dose, oral versus vaginal route, duration of therapy, comparator, and diagnostic criteria. A Cochrane review of probiotics for prevention of UTIs in adults and children found insufficient evidence to draw firm conclusions, partly because of methodological limitations and heterogeneity (Schwenger et al., 2015). More recent reviews continue to view probiotics as promising but not definitively established as a standard prophylactic intervention.

In clinical practice, probiotics may be considered for selected women who prefer microbiome-oriented approaches and understand that evidence is not as strong as for methenamine hippurate or vaginal estrogen in appropriate populations. If used, counseling should include realistic expectations, attention to product quality, and avoidance of substitution for appropriate assessment when symptomatic infection occurs.

Immunoprophylaxis and Bacterial Vaccines

Immunoprophylaxis seeks to reduce recurrent infection by enhancing host immune responses to common uropathogens. Products such as oral bacterial lysates and sublingual inactivated whole-cell vaccines have been studied in women with rUTI. This approach is mechanistically appealing because recurrent cystitis may reflect not only bacterial exposure but also host susceptibility, mucosal immune response, and repeated colonization patterns.

Earlier meta-analytic evidence suggested that oral immunostimulants such as OM-89 may reduce recurrence, but study designs, products, and endpoints varied (Naber et al., 2009; Beerepoot et al., 2013). Newer systematic reviews of bacterial vaccines suggest potential benefit over six to twelve months, but certainty is limited by heterogeneous products, limited long-term data, and variation in availability across countries (Mak et al., 2024).

The practical limitation is that immunoprophylaxis is not uniformly available and is not always incorporated into national guidelines with equal strength. It may be more relevant in specialist urology or urogynecology settings than in routine primary care. Future research should clarify optimal candidate selection, durability of protection, booster schedules, safety, and comparative effectiveness against established options such as methenamine hippurate and vaginal estrogen.

Intravesical Glycosaminoglycan Replacement and Specialist Therapies

The bladder urothelium is protected by a glycosaminoglycan layer that may reduce bacterial adherence and mucosal irritation. Intravesical therapies using hyaluronic acid, chondroitin sulfate, or combined preparations aim to restore this protective barrier. These approaches are usually considered in specialist settings, particularly for women with frequent recurrences, bladder pain features, or failure of simpler preventive strategies.

Systematic reviews and meta-analyses suggest that intravesical hyaluronic acid with or without chondroitin sulfate may reduce recurrence in adult women with rUTI, but evidence includes observational designs and heterogeneous protocols (Goddard & Janssen, 2018). A more recent systematic review of intravesical therapies further supports potential efficacy, while emphasizing the need to consider safety, invasiveness, cost, and applicability across patient groups (Kwon et al., 2026).

These therapies are not ideal first-line prevention. They require bladder instillation, trained personnel, patient time, and repeated visits. For selected patients, however, they may provide an antibiotic-sparing option when oral or local vaginal approaches are insufficient or inappropriate.

Table 2. Evidence Strength and Practical Positioning of Selected Interventions

Intervention	Relative evidence support	Practical role	Important limitations
Methenamine hippurate	Moderate to strong contemporary support	Antibiotic-sparing alternative to daily prophylactic antibiotics in selected nonpregnant women	Requires preventive rather than acute use; urine pH considerations; follow-up required
Vaginal estrogen	Strongest in peri/postmenopausal women	First-line non-antibiotic option in hypoestrogenic women with recurrent UTI	Not relevant to all patients; local irritation; cancer history may require specialist input
Cranberry products	Moderate but heterogeneous support	Optional self-care/prophylaxis strategy	Variable preparations and adherence; modest expected benefit
Increased water intake	Good trial support in low fluid intake subgroup	Simple first-step intervention for appropriate premenopausal women	Not generalizable to all; avoid in fluid-restricted patients
D-mannose	Weakened by recent large RCT	Not routinely recommended based on current evidence	Patient popularity may exceed evidence; cost and sugar intake
Probiotics	Inconclusive/heterogeneous	Optional adjunct in selected motivated patients	Strain-specific uncertainty; variable product quality
Immunoprophylaxis	Promising but variable	Specialist or country-specific option	Availability, standardization, long-term durability
Intravesical HA/CS	Potential benefit in refractory cases	Specialist-level antibiotic-sparing option	Invasive, cost, heterogeneous protocols

The table provides a practical synthesis for clinicians rather than a formal grading of evidence.

Antimicrobial Stewardship and Patient-Centered Prevention

The growth of non-antibiotic prevention reflects a broader shift from episode-by-episode antimicrobial prescribing toward longitudinal management. A stewardship-oriented strategy does not mean avoiding antibiotics at all costs. Rather, it means confirming diagnosis, matching treatment intensity to risk, avoiding treatment of asymptomatic bacteriuria, minimizing unnecessary prophylaxis, and offering antibiotic-sparing alternatives when evidence supports them.

Patient-centered prevention is essential because rUTI management often involves preference-sensitive decisions. Some women prioritize avoiding antibiotics because of previous adverse effects or fear of resistance. Others prioritize maximum recurrence reduction and may prefer antimicrobial prophylaxis after discussing risks. Some may accept modest benefit from cranberry or hydration because the interventions are low-risk, whereas others may find daily tablets burdensome. Shared decision-making therefore helps align prevention with individual values and improves adherence.

The reviewed evidence suggests that the most practical non-antibiotic pathway begins with confirmation of recurrent uncomplicated cystitis, assessment of triggers and menopausal status, optimization of hydration if low, avoidance of spermicides when relevant, consideration of vaginal estrogen in peri/postmenopausal women, and consideration of methenamine hippurate for suitable nonpregnant patients. Cranberry may be offered as an optional adjunct, while D-mannose and probiotics require more cautious counseling. Specialist therapies should be reserved for refractory or complex cases.

Table 3. Suggested Clinical Approach to Non-Antibiotic Prevention in Adult Women with rUTI

Step	Clinical action	Rationale
1	Confirm diagnosis with symptom history and at least one culture-proven episode	Avoid mislabeling noninfectious urinary symptoms as recurrent bacterial infection
2	Identify complicated features, pregnancy, upper UTI, hematuria, stones, or atypical symptoms	Patients with complicated disease may require specialist assessment rather than routine prophylaxis
3	Assess triggers and modifiable factors, including fluid intake, spermicide use, and postmenopausal symptoms	Prevention should be individualized and nonblaming
4	Recommend increased water intake when baseline fluid intake is low and no contraindication exists	Supported by randomized trial evidence in selected premenopausal women
5	Consider vaginal estrogen in peri- or postmenopausal women	Targets hypoestrogenism, vaginal pH, lactobacilli, and uropathogen colonization
6	Consider methenamine hippurate in suitable nonpregnant women after acute infection is treated	Antibiotic-sparing alternative supported by contemporary trial evidence and guidance
7	Discuss cranberry as an optional adjunct with realistic expectations	Evidence suggests modest benefit but formulation variability remains
8	Use caution with D-mannose and probiotics as routine recommendations	Recent evidence does not support routine D-mannose; probiotic evidence remains heterogeneous
9	Refer or seek specialist advice in refractory, complicated, or diagnostically uncertain cases	Allows consideration of imaging, cystoscopy when indicated, intravesical therapies, or alternative diagnoses

This table translates the evidence into a practical stepwise approach for routine clinical care.

Safety, Adherence, and Implementation Considerations

The success of non-antibiotic prevention depends not only on biological efficacy but also on tolerability, adherence, cost, and the ability to integrate the intervention into daily life. A strategy that is effective in a clinical trial may fail in routine practice if it requires frequent dosing, causes bothersome adverse effects, is expensive, or is poorly understood by the patient. Conversely, modestly effective interventions may have meaningful value when they are safe, inexpensive, and acceptable to women who prefer to avoid long-term antimicrobial prophylaxis.

Safety profiles differ markedly between interventions. Increased water intake is generally low risk, but it should be avoided or individualized in patients with heart failure, advanced kidney disease, hyponatremia risk, or other conditions requiring fluid restriction. Cranberry products are usually well tolerated, but gastrointestinal symptoms, sugar content, and potential interactions should be considered. D-mannose is also commonly perceived as safe, yet its routine use is not strongly supported by current evidence and it may add cost without clear benefit. Vaginal estrogen has a primarily local safety profile, but counseling should address irritation, discharge, adherence, and patient concerns about hormones. Methenamine hippurate requires attention to renal function, hepatic status, urine alkalinization, and the need to treat breakthrough symptomatic infections separately.

Adherence is particularly important because most preventive strategies require sustained use over months. Women may discontinue prophylaxis if the rationale is unclear or if benefit is not immediate. Follow-up should therefore be built into the prevention plan. At review visits, clinicians should assess the number of symptomatic episodes, culture results, additional antibiotic use, adverse effects, adherence, patient satisfaction, and whether the original diagnosis remains convincing. If symptoms persist despite negative cultures, the treatment plan should be reconsidered rather than escalated automatically.

Implementation also depends on healthcare setting. In primary care, the most feasible options are education, hydration assessment, cranberry counseling, vaginal estrogen when indicated, and methenamine hippurate where available and appropriate. In specialist care, additional strategies such as intravesical therapy, investigation for anatomical or functional abnormalities, and detailed assessment of bladder pain or genitourinary syndrome of menopause may be considered. This distinction is clinically useful because it prevents first-line care from becoming overly complex while ensuring that refractory patients are not left without further options.

Clinical Subgroups and Individualized Prevention

Women with rUTI are not a homogeneous group. Premenopausal women with intercourse-associated recurrences, postmenopausal women with hypoestrogenic symptoms, older women with multimorbidity, and women with diabetes or urinary retention may have different mechanisms of recurrence and different tolerance for preventive interventions. A single prevention algorithm may therefore be less useful than a structured assessment that identifies the dominant clinical pattern.

In premenopausal women, recurrence is often temporally related to sexual activity, spermicide exposure, low fluid intake, or previous antimicrobial exposure. For women with low fluid intake, hydration may be a particularly appropriate first-line measure. If recurrences are strongly post-coital and non-antibiotic strategies fail, post-coital antibiotic prophylaxis may still be appropriate, but this decision should be made after discussing alternatives and resistance concerns. In this group, vaginal estrogen is generally not relevant unless there is a specific hypoestrogenic state.

In peri- and postmenopausal women, genitourinary syndrome of menopause should be actively assessed. Symptoms such as vaginal dryness, irritation, dyspareunia, urinary urgency, and recurrent lower urinary symptoms may coexist. Local vaginal estrogen can address a plausible underlying mechanism and may reduce recurrent infections while improving related symptoms. For women who continue to have culture-confirmed recurrences despite estrogen or for those without hypoestrogenic features, methenamine hippurate is a reasonable antibiotic-sparing option when not contraindicated.

Women with diabetes, immunosuppression, renal impairment, recurrent upper urinary tract infection, hematuria, stones, or atypical symptoms require more cautious evaluation. Some may not fit the category of recurrent uncomplicated cystitis. In such patients, non-antibiotic prevention should not replace investigation for complicated disease. Referral or specialist advice is appropriate when recurrence pattern is unusual, cultures are repeatedly negative, resistant organisms are frequent, or symptoms suggest an alternative diagnosis.

Discussion

This review highlights a central clinical message: non-antibiotic prevention of rUTI is no longer a marginal topic, but it should not be treated as a uniform category of equivalent interventions. The evidence is strongest for specific strategies in specific populations. Methenamine hippurate is best supported as an antibiotic-sparing prophylactic alternative for selected nonpregnant adult women; vaginal estrogen is most relevant in peri- and postmenopausal or hypoestrogenic women; increased fluid intake is most appropriate for women with low baseline fluid intake; and cranberry products may be offered as a modest-benefit option. In contrast, D-mannose and probiotics require more cautious interpretation because recent high-quality data or persistent heterogeneity limit routine endorsement.

Methenamine hippurate is clinically important because it directly addresses one of the major problems in rUTI management: repeated antibiotic exposure. The ALTAR trial demonstrated that methenamine can be a reasonable alternative to daily antibiotic prophylaxis for women with recurrent UTIs, particularly when patient preference and stewardship priorities favor an antibiotic-sparing approach (Harding et al., 2022). This does not mean methenamine is superior to antibiotics or appropriate for every patient. Instead, it provides a practical middle ground between purely behavioral advice and continuous antimicrobial prophylaxis.

Vaginal estrogen represents a different preventive logic. Rather than acting as an antiseptic, it modifies the postmenopausal urogenital environment. The mechanism is coherent with known changes in vaginal microbiota and pH after menopause. The key clinical task is selecting the appropriate population. A young premenopausal woman with intercourse-associated cystitis does not have the same mechanism of recurrence as a postmenopausal woman with vaginal dryness, increased pH, and recurrent lower urinary symptoms. Therefore, menopausal status should be routinely documented when planning prevention.

Cranberry illustrates the difference between statistical benefit and clinical expectations. The updated Cochrane review supports a probable reduction in symptomatic culture-verified UTIs among women with recurrent UTIs, but product variability remains substantial (Williams et al., 2023). Patients often view cranberry as harmless, but clinicians should discuss sugar content, gastrointestinal side effects, medication interactions when relevant, and the possibility of no individual benefit. The strongest role for cranberry may be as an adjunctive self-care option rather than as a replacement for evidence-based prevention in high-burden disease.

D-mannose is a useful example of why biologically plausible interventions require rigorous testing. The mechanism of inhibiting *E. coli* adhesion is attractive, and earlier smaller studies generated enthusiasm. However, the large randomized clinical trial by Hayward et al. found no meaningful preventive benefit in primary care women with rUTI (Hayward et al., 2024). This finding should influence counseling. Patients who already take D-mannose and perceive benefit may require individualized discussion, but routine recommendation is difficult to justify on current evidence.

Probiotics and immunoprophylaxis both reflect increasing interest in host-microbiome interactions and mucosal immunity. However, they also demonstrate the difficulty of translating mechanistic concepts into reliable clinical interventions. Probiotic studies vary widely by strain and route; immunoprophylaxis studies vary by product, schedule, and geographic availability. Future research should focus on standardized outcomes, culture-confirmed recurrences, patient-reported outcomes, microbiome endpoints, and comparative trials against established options.

A major practical issue is diagnostic certainty. Non-antibiotic prophylaxis should not be used to mask diagnostic uncertainty. Women with persistent dysuria but negative cultures may have bladder pain syndrome, overactive bladder, vulvovaginal atrophy, dermatologic disease, sexually transmitted infection, pelvic floor dysfunction, or other noninfectious causes. Repeated empiric treatment in such cases may perpetuate symptoms, increase antimicrobial exposure, and delay correct diagnosis. A prevention plan should begin with careful history, urine culture during symptomatic episodes when appropriate, and reassessment if the pattern changes.

The social dimension of rUTI also deserves attention. Women with recurrent infections often report frustration, fear of recurrence, sexual avoidance, embarrassment, and feeling dismissed by healthcare professionals. Prevention strategies should therefore be discussed in a way that validates symptoms and avoids blaming the patient. This is especially important when discussing behavioral measures, because advice about hygiene or intercourse can easily be perceived as moralizing if not framed carefully.

From a public health perspective, the appeal of non-antibiotic prevention is closely tied to antimicrobial resistance. Daily antibiotic prophylaxis can be effective but may select resistant organisms. Antibiotic-sparing strategies may reduce antimicrobial use, but only if they are implemented thoughtfully. A poorly effective supplement that delays appropriate care is not stewardship; neither is reflexive long-term antibiotic use without diagnostic confirmation. Good stewardship balances efficacy, safety, patient experience, and resistance risk.

The findings of this review support a stepwise, individualized approach rather than a single universal protocol. Initial evaluation should confirm recurrent uncomplicated cystitis and identify red flags. Behavioral and hydration measures can be discussed first, particularly when low fluid intake is present. Vaginal estrogen should be considered for hypoestrogenic women. Methenamine hippurate is a key option for women seeking an antibiotic-sparing prophylactic therapy. Cranberry may be offered with realistic expectations. D-mannose and probiotics should be discussed as uncertain rather than established. Refractory or complicated cases should prompt specialist assessment.

Several limitations of the available evidence remain. Definitions of rUTI and outcome measures vary across studies. Some trials use symptomatic recurrence, while others require culture confirmation. Follow-up duration may be short, and adherence is often difficult to measure. Many interventions are sensitive to dose, formulation, and patient behavior. In addition, studies often underrepresent pregnant women, older women with multimorbidity, women with diabetes, and patients with complicated urinary tract anatomy. These limitations restrict generalizability and should be clearly communicated.

Future research should prioritize pragmatic comparative effectiveness trials. The most clinically useful studies would compare methenamine, vaginal estrogen where appropriate, cranberry, immunoprophylaxis, and antibiotic strategies in clearly defined subgroups. Trials should include patient-reported outcomes, antibiotic consumption, resistance patterns, adverse events, cost, and quality of life. Research should also explore whether microbiome profiling or host susceptibility markers can identify which women benefit most from specific non-antibiotic interventions.

Conclusions

Recurrent urinary tract infections in women are common, burdensome, and often managed with repeated antibiotic exposure. Non-antibiotic prevention strategies offer an important opportunity to reduce recurrence while supporting antimicrobial stewardship, but their evidence base is heterogeneous. Current literature supports methenamine hippurate as a meaningful antibiotic-sparing alternative in selected nonpregnant women, vaginal estrogen in peri- and postmenopausal women, increased water intake in women with low baseline fluid intake, and cranberry products as an optional intervention with modest benefit. Evidence for D-mannose and probiotics remains inconsistent, while immunoprophylaxis and intravesical therapies may have roles in selected or specialist populations.

The most appropriate clinical approach is individualized rather than universal. Prevention should begin with diagnostic confirmation, exclusion of complicated features, and discussion of patient priorities. Non-antibiotic strategies should be selected according to menopausal status, recurrence triggers, comorbidities, safety considerations, adherence likelihood, and local antimicrobial stewardship goals. Further high-quality trials are needed to standardize intervention protocols and determine which patient subgroups benefit most from each preventive strategy.

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