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Review

Non-Antibiotic Prophylaxis for Recurrent Urinary Tract Infection: A Narrative Review & Clinical Guide for Primary and Hospital Care

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Abstract

Recurrent urinary tract infection (rUTI) is a common and distressing condition disproportionately affecting females. It also accounts for a substantial proportion of antibiotic prescribing in primary care. Repeated antibiotic exposure contributes to adverse effects, disruption of the urogenital microbiome and the accelerating global threat of antimicrobial resistance. Consequently, contemporary clinical guidelines increasingly emphasise non-antibiotic prophylactic strategies as a core component of rUTI management. This narrative review synthesises contemporary evidence and guideline recommendations from the European Association of Urology (EAU), the National Institute for Health and Care Excellence (NICE), and the American Urological Association (AUA) on non-antibiotic prophylaxis for rUTI. It places particular focus on practical implementation in primary care. Behavioural and risk-factor optimisation, methenamine hippurate, topical estrogen, D-mannose, probiotics, cranberry products, immunoactive prophylaxis and intravesical therapies are reviewed. These are appraised with respect to efficacy, safety, tolerability, accessibility and quality of evidence. This review highlights key differences in guideline positioning and identifies areas of ongoing uncertainty and future research. Additionally, this review explores the central role of general practitioners in confirming diagnosis and initiating first-line non-antibiotic prophylaxis. Moreover, their role in supporting shared decision-making and managing timely specialist referral, where appropriate, is highlighted. Considerations for both men and women with rUTI are discussed. To support the translation of evidence into practice, this article includes pragmatic clinical tools, such as a shared decision-making aid, a stepwise treatment algorithm, and a structured risk-factor checklist. By integrating evidence-based non-antibiotic strategies into routine care, clinicians can reduce antibiotic exposure, improve patient outcomes, and respond proactively to the global challenge of antimicrobial resistance.

Keywords: recurrent urinary tract infection; non-antibiotic prophylaxis; methenamine; estrogens; probiotics; cranberry; immunotherapy; primary health care

1. Introduction

Urinary tract infections (UTIs) are exceedingly common and constitute one of the leading indications for antibiotic prescribing, accounting for around a quarter of all prescriptions [1]. Recurrent urinary tract infection (rUTI) is defined by the European Association of Urology as two or more discrete episodes of UTI in 6 months or three or more in 12 months. It represents an enormous burden for both patients and healthcare systems alike, driving frequent antibiotic use and contributing to a multitude of problems. These include risk of adverse events (such as pyelonephritis), disruption of the microbiome and, importantly, as evidence suggests, accelerating antimicrobial resistance [2]. As has been represented with their inclusion in the most recent guidelines, the need for effective, sustainable non-antibiotic prophylaxis has become paramount [3,4,5]. Non-antibiotic prophylactic strategies offer a promising alternative to antibiotic measures, but thus far their implementation in primary and hospital settings remains inconsistent.

Whilst previous reviews have summarised the evidence for non-antibiotic prophylaxis in rUTIs [6], this article aims to additionally provide a practical, implementation-focused clinical guide. It aims to integrate contemporary guideline recommendations with decision-support tools tailored to primary care. This review combines 2024–2025 guideline recommendations from the European Association of Urology (EAU), the National Institute for Health and Care Excellence (NICE) and the American Urological Association (AUA). It approaches this common problem rigorously and proposes a practical clinical guide for primary care clinicians. The evidence base surrounding behavioural measures, methenamine hippurate, vaginal estrogen, D-mannose, probiotics, cranberry products, immunoactive prophylaxis and intravesical treatments will all be examined. Specifically, safety as well as barriers to use will be examined. By focusing on preventive, patient-centred strategies in primary care, this guide aims to support antimicrobial stewardship and enhance the quality of life for individuals living with rUTI.

A key objective of this review is to translate contemporary guideline recommendations into practical tools that clinicians can apply in routine care. To support this, the ar-

Table 1. Risk factor checklist for recurrent UTI.

Domain	Risk factors/Considerations
Patient characteristics	Age, sex; postmenopausal status; pregnancy; diabetes mellitus; immunosuppression/steroid use; neurological disease; urinary tract abnormalities; previous renal stones; pelvic radiotherapy
Lower urinary tract function	Frequency, urgency, nocturia; hesitancy, weak stream, straining; incomplete emptying/retention; incontinence; dysuria, suprapubic pain; post-void residual (if available)
Sexual & gynaecological factors	Intercourse frequency; spermicide/diaphragm use; vaginal atrophy; perineal irritants; recurrent candidiasis/BV; contraception type; HRT use
Behaviour & lifestyle	Hydration; bladder habits; constipation; hygiene practices; exercise
Medication-related factors	Recent antibiotics; SGLT2 inhibitors; anticholinergics; immunosuppressants; diuretics; contraceptives
Microbiological pattern	Culture-confirmed UTIs; organism type; resistance patterns; atypical organisms; contamination patterns
Male-specific factors	LUTS suggestive of BOO; prostatitis; epididymo-orchitis; catheter use; retention; PSA history
Red flags (refer to urology)	Haematuria; recurrent pyelonephritis; pneumaturia/faecaluria; atypical organisms; abnormal imaging; failure of $\geq$2 prophylaxis strategies

A concise clinical tool to be used in primary care consultation to support structured assessment and targeted intervention.
UTI, urinary tract infection; BV, bacterial vaginosis; HRT, hormone replacement therapy; SGLT2, sodium-glucose cotransporter 2; LUTS, lower urinary tract symptoms; BOO, bladder outlet obstruction; PSA, prostate specific antigen.

ticle incorporates a structured risk-factor checklist, a stepwise treatment algorithm, and a shared decision-making tool, all designed to facilitate implementation of guidelines in primary care settings.

1.1 The Role of the General Practitioner in Treating rUTI

UTIs are an extremely common presenting bacterial infection seen in general practice, with ~400 million worldwide diagnoses annually and 1 in 4 women suffering from recurrent UTIs in their lifetime [7,8]. General practitioners (GPs) play a central and sustained role in the management of uncomplicated and recurrent UTIs, acting as the first point of assessment, coordinator of ongoing care, and gatekeeper to specialist referral. Because most patients initially present in primary care, GPs are generally responsible for confirming the diagnosis. This involves using culture-proven infections, excluding alternative causes of lower urinary tract symptoms and, where appropriate, initiating first-line non-antibiotic prophylaxis in accordance with guideline recommendations. This can be challenging, as is discussed in a recent patient interview-based study in primary care; patients often have differing ideas surrounding their care, sometimes including an expectation of antibiotic treatment [9].

Determining optimal timing for a specialist urology review is equally important. GPs can play a key role in this, specifically preparing patients for further investigative tests. Urgent referral is indicated when there are red-flag features such as haematuria which does not settle on treatment of a UTI, recurrent pyelonephritis, suspected urinary tract obstruction, persistent atypical organisms, or failure of multiple prophylactic strategies. These are all scenarios in which specialist imaging or cystoscopic evaluation may become necessary [4]. Because such investigations can be anxiety-provoking for patients, GPs help maintain patient confidence and engagement by explaining what secondary-care assessment typically involves. This may include renal tract ultrasound, post-void residual measurement, or cystoscopy. In fact, a prospective study of 500 patients concluded that those who properly understood the indication for their cystoscopy had over 6 times the preference to go straight to cystoscopy without prior discussion in clinic [10]. The process of understanding future investigations should start in primary care.

For those patients who do require a specialist urology opinion, several investigations can be initiated prior to an outpatient urology appointment to streamline care. For patients with recurrent infections, upper tract imaging in the form of ultrasound or computed tomography (CT) can be useful to rule out stones, hydronephrosis or anatomical variations [11]. Moreover, patients with associated lower urinary tract symptoms (LUTS) could be given a bladder diary to complete in preparation for the urology clinic. Bladder diaries involve patients recording fluid intake, voiding frequency, volumes, urgency episodes, and nocturia over a period of two to three days. They can reliably improve diagnostic accuracy for lower urinary tract symptoms and help distinguish between polyuria, overactive bladder, and frequency due to infection or irritative behaviours, supporting targeted management [12].

To facilitate translation of evidence into clinical practice, this review provides three structured decision-support tools for primary care clinicians: a risk-factor checklist (Table 1), a stepwise treatment algorithm (Fig. 1), and a shared decision-making tool (**Supplementary Material**). The aim of these three is to provide an adjunct in primary care to help with the assessment and recognition of suitable patients for early specialist referral.

1.2 Key Points and Updates to the Most Recent Guidelines

NICE, EAU and AUA's most recent updates show convergent themes. Behavioural measures remain foun-

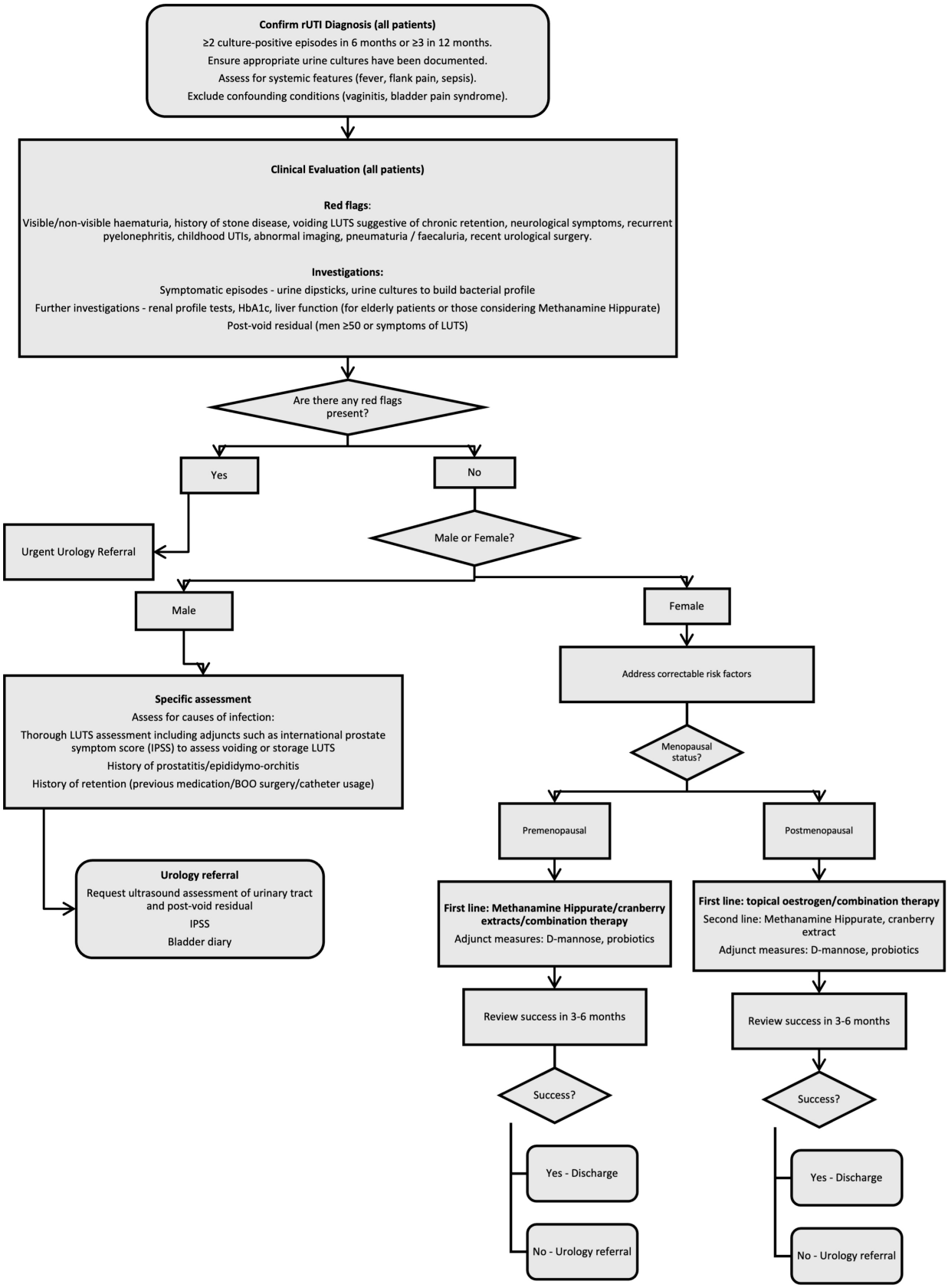

Fig. 1. A proposed treatment algorithm to be used by primary care clinicians. It highlights first-line options dependent on menopausal status and when to refer to specialist care. rUTI, recurrent urinary tract infection; UTIs, urinary tract infections; LUTS, lower urinary tract symptoms; HbA1c, glycated hemoglobin A1c; BOO, bladder outlet obstruction.

dational. Methenamine hippurate and vaginal estrogen have moved into more prominent, guideline-endorsed roles. Immunoprophylaxis is recognised as emerging evidence. Cranberry, probiotics and D-mannose are discussed more cautiously because of heterogeneity in trials and products. Finally, shared decision-making and regular review are now explicit components of best practice [3,4,5]. Below summarises the key new themes from each guideline:

1.2.1 NICE Guideline 112 (NG112) (Updated 2024)

NICE's December 2024 update places a stronger, explicit emphasis on non-antibiotic options within an antimicrobial-stewardship framework [3]. The guideline retains behavioural and self-care measures as the first-line foundation of prevention, but now explicitly recommends considering methenamine hippurate as a non-antibiotic prophylaxis for non-pregnant adults with recurrent lower UTI (with caveats about populations for whom evidence is limited). NICE further endorses topical vaginal estrogen for post-menopausal women with vaginal atrophy, asks clinicians to review any prophylaxis at 6 months and then annually, and stresses shared decision-making to better patients' understanding of the strengths and limits of the evidence.

1.2.2 EAU (2025)

The EAU 2025 Urological Infections guideline update broadens the non-antibiotic toolkit and ranks options by evidence strength [4]. Methenamine hippurate and local vaginal estrogen are supported as important prophylactic choices in appropriate patients with 'strong' recommendations. EAU also endorses immunoactive prophylaxis (bacterial-lysate vaccines) as a non-antibiotic strategy with limited but encouraging evidence. At present, this is only recommended 'in the context of a well-regulated trial'. Cranberry products, probiotics, and D-mannose are supported by limited or heterogeneous evidence, and clinicians should consider these interventions as adjuncts while counselling patients regarding variability in study results and product formulations. EAU further emphasizes that non-antimicrobial interventions should be optimised before initiating long-term antibiotic prophylaxis.

1.2.3 AUA/CUA/SUFU (2025)

The AUA (with partner societies—Canadian Urological Association [CUA] and Society of Urodynamic, Female Pelvic Medicine & Urogenital Reconstruction [SUFU]) frames its most recent updates around patient-centred, stewardship-focused decision-making [5]. AUA guidance acknowledges the expanding evidence base for non-antibiotic measures and recommends discussing options such as cranberry extracts (moderate strength evidence), D-mannose (with the proviso to tell patients it may not be effective as a sole agent) and methenamine hippurate. It also highlights the variable quality of evidence and the need for shared choices based on patient values, comorbidity and practicality. The AUA update also recognises immunoprophylaxis/vaccine approaches as emerging options, but notes access, licensing and longer-term outcome data remain variable across regions. Overall, AUA encourages clinicians to prioritise non-antibiotic measures where appropriate and to reserve continuous antibiotic prophylaxis for those who fail adequate non-antibiotic trials or have compelling indications.

Overall, these three major guideline bodies demonstrate broadly aligned principles with regard to recommending non-antibiotic approaches. On the other hand, they differ slightly in emphasis. EAU provides the most comprehensive and detailed framework, with graded recommendations across a wide range of non-antibiotic prophylactic strategies. These include emerging options such as immunoactive prophylaxis. In contrast, NICE adopts a more pragmatic, stewardship-focused approach within primary care, emphasising behavioural optimisation. Additionally, they mention methenamine hippurate as a key non-antibiotic option. AUA, alongside partner societies, highlights patient-centred decision-making and shared stewardship, acknowledging cranberry extracts, D-mannose and methenamine hippurate. AUA discusses the importance of individualised care and demonstrates uncertainties across available interventions, including immunoprophylaxis as an emerging option. Together, these guidelines reflect a convergent shift toward prioritising non-antibiotic prophylaxis, while differing in the breadth of recommendations and the degree of emphasis on emerging therapies and shared decision-making.

For consistency across this review, the strength of evidence for each intervention is described using standardised terminology aligned with guideline-based interpretation: 'Strong evidence' refers to data supported by high-quality randomized trials or consistent guideline recommendations. 'Moderate evidence' is supported by randomized or observational studies with some limitations. Finally, 'limited evidence' is based on small, heterogeneous, or low-quality studies.

2. Non-Antibiotic Prophylactic Strategies: Evidence, Advantages, Limitations, Implementation

Non-antibiotic prophylactic strategies can be broadly grouped into behavioural measures, pharmacological therapies, and adjunctive or specialist interventions.

2.1 Behavioural & Risk-Factor Optimisation

Behavioural and risk-factor optimisation is a low-cost, low-harm cornerstone of rUTI treatment. However, the modern evidence base remains somewhat heterogeneous. It is important to distinguish between guideline-supported measures and broader clinical considerations:

2.1.1 Guideline-Supported Behavioural Measures

The following behavioural modifications are explicitly supported or referenced within contemporary guideline recommendations:

- Increase fluid intake (unless contraindicated).
- Avoid delayed voiding, including habitual or post-coital delay.
- Post-coital voiding, where sexual activity is a trigger.
- Avoid vaginal douching.
- Avoid the use of spermicides.
- Avoid occlusive, non-breathable underwear.
- Consider perineal hygiene practices (e.g., wiping direction after defecation).

2.1.2 Additional Clinically Relevant Considerations

In addition to guideline-supported measures, several broader clinical factors may contribute to recurrent infection risk and are commonly addressed in practice, although they are not consistently listed as core guideline recommendations:

- Management of constipation.
- Addressing pelvic floor dysfunction.
- Optimisation of bladder emptying habits.
- Review of catheter use (hospital settings).
- Assessment for urinary retention.
- Optimisation of toileting protocols in dependent patients.

While these broader measures are biologically plausible and often clinically relevant, clinicians should counsel patients that the strength of supporting evidence varies and that these strategies are best considered as adjuncts to core guideline-recommended interventions.

The strongest and most actionable behavioural intervention supported by randomized data is increasing daily fluid intake in patients with poor intake. One trial showed that consuming ~1.5 L/day of water reduced recurrent cystitis episodes over 12 months in premenopausal women who were habitually low drinkers [13]. A 2024 systematic review of altering daily water intake concluded that, whilst few trials exist, single studies suggested possible benefit for UTI prevention, but overall evidence remains limited [14]. Beyond hydration, practical conservative measures described above are consistently recommended by guidelines [3,4,5]. This is mainly based on mechanistic plausibility, observational data and older trials, but high-quality contemporary data are largely lacking. For example, a widely cited case-control study of 1299 women from 1991–1993 found that spermicide-coated condoms were associated with UTI due to Staphylococcus saprophyticus (odds ratio 8.4 for those patients having sex weekly) [15]. Earlier behavioural intervention studies should be interpreted with caution, as they were conducted before current diagnostic standards, modern microbiological techniques, and contemporary guideline-based management approaches. The 2025 update from the AUA points out that, despite many risk-factor associations, there remains insufficient evidence to strongly recommend most behavioural strategies as stand-alone prophylaxis [5]. Whilst there is a lack of evidence for a comprehensive behavioural/hygiene intervention bundle, this remains consensus-based standard practice.

Lack of strong evidence for behavioural modification is easy to explain. It is difficult to randomize and blind behavioural interventions (hydration, voiding frequency, hygiene, bowel habits). This can lead to a high risk of bias in trials. Moreover, the multifactorial and patient-specific nature of rUTI (sexual behaviour, anatomy, hormones, microbiome, comorbidities) makes a “one-size-fits-all” behavioural strategy unlikely to succeed. Many studies avoid complexity by focusing on single factors, which may not reflect real-world situations.

In practice, guidelines therefore continue to recommend behavioural and hygiene-based risk-factor optimisation, even in the absence of high-level randomized evidence. The rationale is pragmatic, low-risk, low-cost interventions whereby the potential benefit outweighs the downside. Clinicians must counsel patients transparently about the limited quality of evidence and the possibility that behavioural optimisation alone may not suffice, especially in recurrent or complicated cases.

2.2 Methenamine Hippurate

Whilst behavioural and risk-factor optimisation form the foundation of management, many patients require additional pharmacological strategies to achieve sustained reduction in recurrence risk. Methenamine hippurate is one non-antibiotic prophylaxis for rUTI. It works in acidic urine by producing formaldehyde, which inhibits bacterial growth without being a traditional antibiotic. Recent high-quality evidence has strengthened guideline support for its use in selected adult patients. The largest pragmatic randomized trial (240 patients) to date, the UK ALTAR study, demonstrated non-inferiority of methenamine hippurate (1 g twice daily) compared with once-daily low-dose antibiotic prophylaxis over 12 months in women with recurrent UTI. They concluded that across the two groups, similar reductions in symptomatic, antibiotic-treated infections were seen, with overall lower selection pressure for antibiotic resistance during treatment [16]. Economic modelling alongside this trial suggested methenamine hippurate may also be cost-effective when benefits from reduced antibiotic use are considered [17].

Recent systematic reviews and narrative summaries consistently report that methenamine hippurate is supported by moderate- to high-quality evidence and generally well tolerated. Certainty of evidence, though, remains variable due to heterogeneity in older trials and limited data in some groups, with recommendations for further larger trials [18,19]. An earlier review similarly suggested potential benefit in people without significant urinary tract abnormal-

ities (not neuropathic patients or those with anatomical abnormalities) [20]. All of these highlighted that the data was largely based on small trials [18,19,20].

When considering methenamine hippurate in clinical practice, GPs and hospital clinicians should follow a few pragmatic pre-treatment checks and counselling points. Confirmation of diagnosis with recent urine culture(s) is hugely important. One must also ensure no current upper urinary tract infection and exclude complicating structural or functional factors. These may include significant post-void residual, obstruction, indwelling catheter or other known renal tract abnormalities that would favour specialist assessment rather than community prophylaxis [4,16]. Baseline renal function is essential because many formularies advise avoiding use when creatinine clearance is very low (e.g., creatinine clearance [CrCl] $<$10 mL/min) and avoiding use in severe hepatic insufficiency [21]. Concomitant medications that alkalinise urine (potassium citrate, acetazolamide, chronic bicarbonate) or interact (co-administration with certain sulfonamide antibiotics has a risk of crystalluria) should be checked. Finally, pregnancy status or intentions should be discussed. Treatment duration is for up to 12 months, and it is recommended that patients who are pregnant or planning to become pregnant should not start methenamine hippurate without specialist advice [3]. In fact, NICE explicitly recommend this as an area of future research [3]. Because methenamine hippurate's mechanism depends on acid hydrolysis to formaldehyde, clinicians should be aware that acidic urine (pH $\leq$5.5–6) optimises activity. Whilst guideline groups have noted urine acidity as biologically important, routine pH-testing before initiation is not universally mandated by guideline committees because of limited direct trial evidence [3,4]. Nevertheless, checking urine pH during follow-up and addressing factors that raise urinary pH can be useful if prophylaxis fails. Finally, setting expectations is incredibly important. Methenamine hippurate's benefit often accrues over months. Clinicians should review response and antibiotic usage at about 6 months and again at 12 months [3]. Side-effects should be monitored (gastrointestinal upset and rarely hypersensitivity), and patients re-assessed to check indications for continued prophylaxis. Referral to urology should be done if recurrences persist or if red-flag features emerge.

Overall, methenamine hippurate now sits strongly within contemporary guidelines as a legitimate non-antibiotic prophylaxis option for many adults with uncomplicated rUTI. EAU rates it strong, NICE now actively includes it, and AUA offers conditional support [3,4,5]. This is supported by the ALTAR trial [16] and recent systematic reviews, but its use should be individualised with appropriate baseline tests and ongoing monitoring.

2.3 Topical (Vaginal) Estrogen

In addition to pharmacological agents like methenamine hippurate, targeted therapies addressing specific mechanisms are also important in select populations. Topical (vaginal) estrogen is one of the best-evidenced non-antibiotic prophylactic options for recurrent urinary tract infection in post-menopausal women because it addresses a clear pathophysiological driver of recurrence. Hypo-estrogenism promotes vaginal atrophy, loss of lactobacilli, and an elevated vaginal pH that together facilitate uropathogen colonisation and ascension. Several randomized trials and meta-analyses have demonstrated that local estrogen therapy, in several forms (cream, pessary/tablet or ring) reduces UTI recurrence compared with placebo or no treatment and improves vaginal pH and flora. A comprehensive meta-analysis of 8 studies and 4702 patients concluded that vaginal estrogen significantly reduced rUTI rates (relative risk 0.42), whilst oral estrogen did not, when compared with placebo [22]. The same meta-analysis concluded that topical estrogen was associated with a reduction in vaginal pH (mean difference, –1.81) [22]. A recent multicentre study of 5600 retrospective patients concluded that UTIs fell by $>$50% in the year after topical treatment [23]. Another focused review reinforced findings and explored dose-response relationships, finding that weekly doses $\geq$850 µg were associated with greater efficacy [24].

Contemporary guideline panels reflect this evidence: the EAU, NICE and AUA updates now all recommend considering topical estrogen in post-menopausal women with recurrent UTI and signs of urogenital atrophy [3,4,5]. NICE specifically flags local estrogen as an option when behavioural measures alone are inadequate [3].

Clinically, choosing topical estrogen requires individualised assessment. Absolute contraindications are uncommon for low-dose local therapy but include known or suspected estrogen-dependent malignancy without specialist agreement. Unexplained post-menopausal bleeding mandates investigation before initiation. Although systemic absorption of low-dose vaginal preparations is minimal, oncological teams often advise a cautious shared approach in women with a recent history of breast cancer. Practical considerations include formulation and dosing (creams may require more frequent application and are less favoured by some patients; vaginal tablets or rings often result in higher adherence) [25]. Anticipated time to benefit (several weeks to months) should be discussed, and common local side-effects such as transient irritation or spotting. In addition, clinicians should document baseline symptoms and infection frequency so that the effect can be reviewed (a pragmatic review point is 6–12 months as per NICE) [3]. Counsel patients that topical estrogen is preventive rather than curative for an acute episode and combine therapy with behavioural risk-factor optimisation.

In summary, topical estrogen is supported by high-quality evidence and strong guideline recommendations in postmenopausal women. It is a targeted, generally well-tolerated first-line non-antibiotic option for postmenopausal women with rUTI and urogenital atrophy. It is a 'strong' recommendation by EAU and is recommended by NICE [3,4]. Clinicians should screen for contraindications, involve oncology/urology specialists where appropriate, set realistic expectations, and plan periodic review.

2.4 D-Mannose

Beyond established therapies such as methenamine hippurate and vaginal estrogen, several dietary supplements have been explored as potential adjunctive preventive strategies. D-mannose is a naturally occurring monosaccharide that has attracted substantial attention as a convenient over-the-counter prophylactic for rUTI. The proposed mechanism is that D-mannose binds to the FimH adhesin on uropathogenic *Escherichia coli*, inhibiting bacterial attachment to urothelial mannose residues, thereby promoting bacterial washout with voiding [26]. This anti-adhesion mechanism differentiates D-mannose from antimicrobial approaches and makes it an attractive adjunct.

Contemporary evidence has unfortunately tempered early enthusiasm. A 2024 double-blind, placebo-controlled trial in primary care (598 patients) found no statistically significant reduction in the proportion of participants presenting with UTI over the following six months with daily 2 g D-mannose versus matched placebo (51.0% vs 55.7%) [27]. Additionally, no reduction in the number or severity of UTIs across the two groups in the following 6 months [27]. An earlier (2014), single-centre, smaller (308 women across 3 groups) and widely cited secondary-care randomized control trial reported that the benefit of D-mannose was non-inferior to nitrofurantoin and better than no prophylaxis [28].

In addition to the large, contemporary primary-care randomized control trials, other studies on D-mannose have been limited by small sample sizes or highly selective populations. An example is a 2023 study, which investigated D-mannose as an adjunct to established vaginal estrogen therapy in post-menopausal women with rUTI [29]. This design restricts generalisability to a relatively narrow subgroup already receiving a proven prophylactic intervention. The study was terminated early after the interim analysis. It did not recruit its planned sample size and, as a result, produced wide confidence intervals around the effect estimates. These limitations make it difficult to draw firm conclusions about the independent efficacy of D-mannose, and the findings cannot be extrapolated to pre-menopausal women or to those not using topical estrogen.

Systematic reviews and evidence syntheses therefore reach cautious conclusions. A recent 2025 review concluded that the evidence base is heterogeneous and lacking high-quality evidence to support or refute routine use of D-mannose for prevention or treatment of UTIs [30]. Another meta-analysis of 6 papers found no significant reduction in recurrent urinary tract infections with D-mannose compared with control or antibiotic prophylaxis [31]. International urology guidelines reflect this by typically characterising D-mannose as an adjunctive option with weak support owing to limited and inconsistent evidence [4,5]. NICE's recent recurrent-UTI updates emphasise behavioural measures, methenamine and topical estrogen more strongly, and counsel that supplements such as D-mannose should only be considered after discussing limited evidence and cost with patients [3]. Finally, research gaps remain. Head-to-head comparisons of D-mannose regimens against methenamine, vaccine strategies or behavioural bundles, and mechanistic work on urinary D-mannose pharmacokinetics in high-risk groups (diabetes, renal impairment) are areas of future research.

From a pragmatic safety and prescribing perspective, D-mannose is generally well tolerated: trials report few adverse events, primarily mild gastrointestinal symptoms [32]. Important practical points include dosing. Most trials used about 2 g once daily or 2 g after sexual intercourse in event-driven regimens. However, there is a lack of regulatory oversight for many commercial preparations. Whilst D-mannose is poorly metabolised, there are also metabolic considerations in diabetic patients who should be counselled to closely monitor blood-glucose effects after initiation. On this note, NICE recommend that for D-mannose and cranberry extracts, the sugar should be "considered as part of the person's daily sugar intake" [3]. Whilst there are no major drug–drug interactions documented, clinicians should check supplements for added sugars, sweeteners or agents that might interact with other medications.

In practice, whilst D-mannose is a prophylaxis with limited evidence, it remains a reasonable, low-harm option for patients who prefer to try supplements and accept uncertainty. Clinicians should present the negative trial data and set expectations that benefit is not proven in broad primary-care populations. EAU rates the recommendation "weak" whilst AUA place its recommendation as "cautious" [4,5]. Because evidence now includes a robust negative primary-care trial, clinicians should document the shared-decision discussion, agree on a trial period (for example, 3–6 months), record baseline recurrence frequency, and reassess outcomes. This is acceptable for informed, preference-led trials by patients, but not supported as a sole first-line non-antibiotic prophylaxis.

2.5 Probiotics

In parallel with anti-adhesion strategies like D-mannose, interest in probiotics as a non-antibiotic prophylactic for rUTI has re-emerged in recent years. This is particularly as understanding grows around the vaginal and urinary microbiome. Lactobacillus species—especially *L. crispatus*, *L. rhamnosus*, and *L. reuteri* have been proposed

to reduce rUTI risk by restoring protective vaginal colonisation, lowering pH, and inhibiting uropathogen adherence [4,33,34]. Despite encouraging mechanistic data, clinical evidence remains limited.

Stapleton et al.'s [34] earlier findings on intravaginal *L. crispatus* remain one of the more robust demonstrations of benefit, yet replication has been limited. A recent (2023) randomized, double-blind, placebo-controlled trial enrolled 174 pre-menopausal women with a history of recurrent UTIs and compared oral, vaginal, combined, and placebo probiotic regimens over 4 months, with 12-month follow-up for symptomatic UTIs [35]. The study reported that those receiving vaginal probiotics (alone or combined with oral) had lower symptomatic UTI incidence at 4 months and prolonged time to first UTI compared to placebo, while oral-only probiotics did not confer a statistically significant benefit [35]. A recent randomized clinical trial (RCT) included 51 women who were given either a multistrain probiotic formulation or a placebo along with an antibiotic and were followed for 6 months [36]. 75% of those in the treatment arm remained recurrence-free, compared to 33% in the placebo arm but short duration and small population size are limiting factors of this study [36]. A 2022 review looking at 9 studies, however, concluded that whilst probiotics could potentially reduce UTI recurrence in select populations, the evidence base was small and heterogeneous with wide confidence intervals [37]. The same review found that the side-effect profile was low and mainly limited to localised vaginal side-effects such as itching [37]. One review also looked at the evidence base behind using probiotics to prevent UTI in children. They concluded that current data are not adequate to confirm this [38].

Guidelines reflect this uncertainty. The most recent NICE update states that evidence for probiotics remains insufficient for routine recommendation [3]. EAU classifies data on probiotics as "insufficient" with only limited evidence, advising that they should not replace proven therapies [4]. AUA similarly concludes that data are inadequate to support probiotics as a standalone prophylactic strategy [5]. Whilst safety is generally favourable, live organisms should be avoided in severely immunocompromised patients. Overall, while probiotic therapy aligns well with antimicrobial stewardship goals and remains attractive to patients seeking "natural" options, current evidence does not yet support its use as a first-line intervention. Ongoing work, including strain-specific RCTs, is needed to clarify its therapeutic role. In clinical practice, probiotics may be considered for motivated patients seeking non-antibiotic prophylaxis, but only with explicit shared decision-making, a defined trial period (e.g., 3–6 months), and careful monitoring for recurrence or side effects.

2.6 Cranberry Products

Cranberry products (juice, capsules or tablets) have been studied for decades as a non-antibiotic strategy to reduce rUTIs. This is on the biological premise that cranberry proanthocyanidins (PACs) inhibit P-fimbriae–mediated adhesion of uropathogenic *E. coli* to the urothelium. Its effectiveness has been debated for years.

The most comprehensive and up-to-date evidence syntheses present a cautiously positive picture. The fifth update 2023 Cochrane review (50 RCTs of which 26 were new, 8857 total participants) concluded with moderate-certainty evidence that cranberry products probably "reduce the risk of symptomatic UTIs in women with recurrent UTIs" [39]. There is also evidence of efficacy in children, which is a group which thus far have few prophylactic options [40]. Another group, often not considered in rUTI prophylaxis, are pregnant women. A recent systematic review of 30 papers demonstrated good effectiveness in pregnant women taking cranberry extract over 6 months [41]. Low-certainty evidence suggests cranberry products, compared with a placebo, may also reduce risk in people susceptible to UTIs following urological interventions (relative risk [RR] = 0.47) [39]. To the contrary, there was little or no evidence of benefit in pregnant patients, elderly patients or those with voiding dysfunction [39]. The review also found no major safety signals beyond mild gastrointestinal symptoms [39]. A 2024 RCT also found that over 12 months of cranberry prophylaxis reduced the incidence of UTI in women compared to placebo (incidence rate ratio 0.49) [42].

Subsequent and contemporary meta-analyses have attempted to refine these findings. A 2024 dose-focused meta-analysis reported that cranberry products reduced UTI risk only in those taking cranberry products with PAC $\geq$36 mg/day [43]. Moreover, subgroup analysis only found cranberry products effective in females and those who took prophylaxis for between 12 and 24 weeks [43]. Another recent review found a 49% reduction in antibiotic use with cranberry products [44]. However, due to heterogeneity between trials (formulation, PAC dose, outcome definition, patient population, and duration), the authors felt their conclusions were only of moderate to low certainty.

Major guideline bodies reflect the nuances of this evidence. NICE summarises the evidence as indicating possible benefit in women with recurrent UTIs but grades certainty as "very low" in some subgroups (children, young women and those who are not pregnant) [3]. They do not recommend cranberry prophylaxis in "older women, older trans men or non-binary people" [3]. NICE recommends cranberries as an option with shared decision-making rather than a standard of care and does not recommend a specific cranberry product [3]. EAU position cranberry as an adjunctive option with limited evidence compared with methenamine hippurate or topical estrogen, noting a favourable risk–benefit profile. While some of the

evidence cited within the guidelines includes juice-based preparations, the EAU does not explicitly recommend one formulation (e.g., juice versus capsules or tablets) over another [4]. AUA likewise recognises and recommends cranberry as a reasonable option for women with "moderate evidence" [5]. They stress variable evidence quality and the need to individualise decisions, but they recommend a daily dose $\geq$36 mg/day without preference on formulation [5]. In short, guidelines generally permit cranberry use for motivated patients (especially young women with recurrent, uncomplicated UTIs) but do not elevate it above interventions supported by stronger RCT data.

Safety and contraindications deserve explicit discussion when advising patients in primary care. Cranberry products are usually well tolerated. The Cochrane review found they only modestly increased gastrointestinal symptoms in some trials [39]. However, two areas require caution and counselling. First, the literature on cranberry–anticoagulant interaction (warfarin) is discordant. Early case reports suggested international normalized ratio (INR) destabilisation, but controlled studies have generally not confirmed a clinically important interaction [45,46]. Nonetheless, prudence and INR monitoring should be recommended for patients on warfarin starting regular cranberry consumption. Second, the relationship between cranberry intake and nephrolithiasis remains unresolved [47,48,49]. Older metabolic studies and supplement studies documented increases in urinary oxalate or lithogenic indices with concentrated cranberry tablets, whereas other work showed neutral or even protective changes in urinary chemistry. At present, this data is inconclusive, and for patients with a history of calcium oxalate stones, a specific discussion of the uncertain risk should be done with consideration of specialist input or metabolic testing if long-term high-dose cranberry use is contemplated.

Practical considerations in primary care are straightforward but important. Because RCTs differ widely in PAC content and many commercial products are unstandardised, clinicians should advise patients that if they wish to try cranberry, using standardised products with documented PAC content is prudent (~36 mg PAC/day). Juice preparations are easily accessible but vary enormously in PAC content and caloric load (relevant for diabetic patients). PAC-standardised treatment (tablets/capsules/sachets) is logically, therefore, the preferable choice for long-term prophylaxis. Patients should be counselled that cranberries are preventive, not therapeutic. Additionally, as clinicians, we must be clear that the benefit typically accrues over weeks to months. A pragmatic shared-decision approach is a short trial (e.g., 3–6 months) with defined outcome measures (symptomatic, culture-confirmed recurrences and antibiotic courses), after which the intervention should be reassessed and discontinued if ineffective. Cost, adherence, and product quality (independent testing and PAC quantification) are common real-world barriers and should be discussed. From an antimicrobial-stewardship perspective, cranberries are very attractive as a low-risk measure that may reduce antibiotic exposure in patients. Primary care clinicians are well placed to support informed trials of cranberry, monitor for adverse effects, and refer for alternative prophylaxis if recurrences persist.

In summary, cranberry products have a plausible mechanism and an accumulating body of randomized evidence showing modest benefit for some patient groups. In particular, women with uncomplicated recurrent UTI taking an appropriate $\geq$36 mg/day PAC are best placed for positive outcomes. The main limitations are heterogeneity of formulations and dosing and mixed safety signals in specific subgroups (warfarin users, stone formers). Fig. 1 demonstrates a proposed treatment algorithm, which can be used in primary care to direct treatment choices.

3. Further Treatments Available to Patients (After Referral to Urology)

Although this review targets clinicians in primary care, an important role of doctors is to clearly explain subsequent steps to patients, particularly when first-line treatments have been ineffective. This section describes two prophylactic measures that can be commenced only after specialist referral to the urology department.

3.1 Immunoactive Prophylaxis

Immune prophylaxis represents one of the newer non-antibiotic strategies for rUTI, aiming to enhance host defence against uropathogens rather than suppress bacterial growth. The most extensively studied agents are bacterial lysate–based immunostimulants, particularly oral *Escherichia coli* lysates (OM-89/Uro-Vaxom). These stimulate innate and adaptive immune responses through gut-associated lymphoid tissue, leading to increased urinary immunoglobulin A (IgA), immunoglobulin G (IgG) and cytokine-mediated antimicrobial activity. Unlike antibiotics, these agents do not exert selective pressure on bacterial resistance and therefore align closely with antimicrobial stewardship priorities.

Contemporary evidence continues to support a role for immunoprophylaxis in selected patients. A 2024 systematic review of 11 studies concerning 5 vaccines (StroVac, Uro-Vaxom/OM-89, ExPEC4V, Uromune, and Solco-Urovac) and 2822 patients, concluded that they were effective for adult female patients in the short term [50]. Specifically looking at their efficacy vs placebo, a pooled analysis of 8 studies demonstrated patients were roughly 50% more likely to remain free from UTI in the short term (pooled risk ratio 1.52) [50].

Uro-Vaxom (OM-89) remains one of the more researched immunoactive prophylaxis for rUTI and comes in oral form. Volontè et al. [51] have very recently reviewed the evidence of Uro-Vaxom (7 studies, 1005 patients), concluding that whilst it is both well-tolerated and

effective, variability and retrospective nature of studies are limiting factors in drawing good quantitative estimates of effectiveness. One of the earlier RCTs of 112 patients over 6 months demonstrated a 67.2% recurrence-free rate in the Uro-Vaxom group compared with 22.2% in the placebo group [52]. This has been reproduced in a more modern retrospective study, with patients' UTI episodes over a year roughly halving after starting treatment [53]. Tolerability of this agent is considered to be good, with side effects limited mainly to urethral and gastrointestinal effects, with no reports of anaphylaxis [51].

Beyond Uro-Vaxom, other immune strategies have been explored. StroVac is given as an intramuscular injection. A comparative study over 3-month treatment with StroVac compared to nitrofurantoin demonstrated non-inferiority over the first year (86.8% of patients had $\leq$1 UTI in the StroVac group compared with 91.8% in the Nitrofurantoin group, $p = 0.22$) [54]. Moreover, the StroVac group appeared to have a longer-lasting effect, with 79.3% of patients having $\leq$1 UTI in the second 12 months post-treatment (with booster injection) [54]. 2.3% of patients discontinued therapy due to side effects (swelling in the arm post-injection) [54]. Uromune is a sublingual administration. A study of 377 patients in Spain found that the vaccine groups had around 20% more efficacy than the group treated with prophylactic antibiotics at 3 and 6 months [55]. They also found Uromune treatment cheaper [55]. A similar study was replicated in Portugal, where 125 patients were followed prospectively after treatment with Uromune [56]. 38% of patients were UTI-free over the following 12 months, and good outcomes were found even in those patients with catheters, diabetes and paraplegia [56]. Another recent paper of 1104 women treated with Uromune found that patients who had $>$5 UTIs the preceding year had worse outcomes with the vaccine than those who had 3–4 UTIs [57].

Ongoing research continues with immunoprophylaxis. The NAPRUN study is an ongoing prospective, multicentre observational study assessing multiple non-antibiotic prophylaxis strategies in patients with neurogenic dysfunction on self-catheterisation [58]. These include immunoactive agents (Uro-Vaxom & StroVac) and supplements such as D-mannose; results are not yet available.

Guidelines reflect both the promise and the uncertainty of immune prophylaxis. The EAU 2025 guidelines give one of the strongest endorsements among international bodies, recommending immunoactive prophylaxis in women with rUTI, as part of a trial [4]. AUA recognise immune prophylaxis as a strategy with limited evidence but stops short of a firm recommendation due to limited availability and regulatory differences [5]. NICE does not currently recommend immune prophylaxis routinely, largely because Uro-Vaxom is not currently licensed in the UK.

From a safety and practical perspective, immune prophylaxis is generally well tolerated. Contraindications theoretically include hypersensitivity to bacterial lysate components and caution in patients with significant autoimmune disease or those receiving potent immunosuppression, where immune stimulation may be undesirable. As previously mentioned, side effects are typically mild and transient, and serious events are rare [50,59]. As per the other treatments, immune prophylaxis is preventive rather than therapeutic and should not be used to treat acute infection. Patients should understand the delayed onset of benefit, usually after completion of a 3-month induction course.

Looking ahead, immune prophylaxis is one therapy with the true potential to reshape the future rUTI landscape, particularly if ongoing trials of sublingual and next-generation multivalent vaccines demonstrate robust and durable efficacy. For primary care physicians, eventually, immune prophylaxis may occupy a role like vaccines in other chronic infectious conditions. Identifying suitable patients, counselling on expectations and safety, coordinating initiation and monitoring outcomes over time, with urology support for complex cases, may well be possible in future. However, at present, these therapies should be guided by specialist referral in the first instance, after a first-line prophylaxis has been tried. GPs currently play a key role in informing patients about emerging options.

3.2 Bladder Instillations (Intravesical Therapies)

In contrast to systemic immunomodulatory approaches, intravesical therapies aim to restore local bladder defences and represent an alternative strategy in selected patients. Intravesical bladder instillations have emerged as a specialist, non-antibiotic strategy for selected patients with rUTI. Those with refractory disease, underlying bladder pathology, or intolerance to systemic prophylaxis. The most studied agents include glycosaminoglycan (GAG) layer replenishment therapies such as hyaluronic acid (HA) alone or in combination with chondroitin sulfate (CS). These aim to restore the urothelial barrier, reduce bacterial adherence, and modulate local inflammation. Contemporary evidence supports a biological rationale for this approach, as disruption of the bladder GAG layer has been implicated in increased susceptibility to infection and chronic inflammation.

Recent data suggest that intravesical HA $\pm$ CS can reduce UTI recurrence rates and prolong time to recurrence, particularly in women with recurrent uncomplicated cystitis [60]. A 2025 systematic review reported a significant reduction in mean UTI episodes per year and improvement in symptom scores among patients receiving HA-based instillations compared with baseline or control treatments [61]. However, they also stated that the quality of studies limits the possibility of robust conclusions [61]. Another recent review found that HA $\pm$ CS not only reduced risk of infection (compared with placebo/standard care), with an odds ratio of 0.42, but also had positive effects on irritative symptoms, pain, voiding and even sexual function [62].

RCTs provide supportive but not definitive evidence. A European multicentre study evaluating rUTIs found that intravesical HA+CS improves recurrences compared with standard care [63]. They also concluded that $\geq$5 instillations were associated with better outcomes [63]. Another study comparing intravesical HA+CS to intravesical saline concluded that after 12 months of follow-up, HA+CS was 77% better at reducing UTI rates with improved quality of life compared with placebo [64].

Importantly, the benefits of intravesical therapies appear to also be applicable to those with bladder mucosal vulnerability, such as in post-radiation cystitis or interstitial cystitis [62]. Safety profiles are generally favourable [65]. Adverse events are usually mild and local, including transient dysuria, urgency, or discomfort related to catheterisation, with serious adverse events being rare [60]. Bladder instillations are contraindicated in active urinary infection, untreated urethral stricture, or patients unable to tolerate catheterisation [4,66]. Repeated catheterisation introduces a theoretical infection risk, and patients with poor mobility, significant cognitive impairment, or high procedural anxiety may be unsuitable. From a practical perspective, instillation therapy requires repeated clinic visits, trained personnel, and healthcare resources. This may make it an option that is not suitable for certain patients, which would be discussed at the time of initial clinic.

Guideline positioning reflects this. Latest EAU guidelines acknowledge intravesical GAG-layer replenishment as a potential option for prevention of rUTI but assign a weak recommendation [4]. NICE and AUA guidelines do not currently recommend bladder instillations for rUTI prevention. For primary care physicians, bladder instillations are not a treatment initiated in the community, but awareness of their role is important. GPs play a key role in identifying patients who may benefit from referral. In particular, those with recurrent infections despite optimised behavioural measures, or those with features suggesting bladder barrier dysfunction. Clear explanation to patients that instillations are preventive rather than curative, require repeated procedures, and have variable response rates helps manage expectations and supports informed shared decision-making. Explanation that this treatment will require multiple trips to the hospital for instillation is an imperative early discussion point. As research continues, particularly with better phenotyping and standardised regimens, intravesical therapies may evolve into a more defined niche within rUTI management. At present, they remain a specialist, second- or third-line option rather than a primary-care intervention.

One additional measure that ought to be mentioned but is only given in specialist care is intravesical gentamicin. One review, which looked at 5 studies (168 patients), demonstrated a short-term reduction of UTIs in 78% of patients [67]. Intravesical gentamicin prophylaxis is referenced in European urological guidance as a potential last-line option for highly selected patients with complex or neurogenic bladders who have failed standard prophylactic strategies [4]. However, it is not recommended for routine management of recurrent uncomplicated UTI and is absent from NICE guidance and AUA recommendations. Its use should remain confined to specialist urology services, reflecting the limited evidence base and antimicrobial stewardship considerations.

3.3 Recurrent UTI in Men

While the above strategies largely focus on recurrent UTI in women, it is important to consider the distinct clinical considerations in male patients. Recurrent urinary tract infection in men is less common than in women and should be regarded as a potential marker of underlying pathology rather than a benign recurrent condition. Contemporary guidelines consistently emphasise that, unlike uncomplicated rUTI in women, recurrent infection in men is rarely idiopathic and warrants structured evaluation to exclude anatomical, functional or prostatic causes [4]. In primary care, the general practitioner plays a critical role in recognising this distinction early, ensuring microbiological confirmation, initiating appropriate initial management, and arranging timely referral where indicated.

From a diagnostic perspective, all episodes of suspected UTI in men should be culture-confirmed, as symptoms alone are insufficiently specific and may overlap with prostatitis, urethritis, bladder outlet obstruction, or non-infective LUTS. rUTIs should routinely prompt assessment for chronic bacterial prostatitis, which is the most frequent cause of this presentation in men and often under-recognised in primary care [68,69]. Simultaneous history of perineal discomfort, ejaculatory pain, bacterial persistence of the same organisms on culture, or relapse shortly after treatment completion should raise suspicion of prostatitis.

All men with rUTI should undergo urological evaluation for bladder outlet obstruction (BOO), which is where a good initial history of storage and voiding LUTS in primary care is important. Evaluation in specialist care would be to rule out incomplete emptying and structural abnormalities. As part of primary care assessment, as well as a focused LUTS history, medication review (including anticholinergics and opioids), digital rectal examination when appropriate and if possible, assessment of post-void residual volume is important. Urinalysis and repeat cultures should be reviewed longitudinally to identify patterns of relapse versus reinfection. Routine prostate specific antigen (PSA) testing is not recommended solely for rUTI but may be appropriate if prostate cancer is suspected based on age, examination or symptoms [4]. Imaging in the form of ultrasound in the first instance is a useful adjunct. Cystoscopy is not a first-line diagnostic test, but should be anticipated and explained to patients when referral thresholds are met.

With respect to prophylaxis, evidence for non-antibiotic strategies in men is limited, as most trials of

methenamine hippurate, cranberry, D-mannose, probiotics and vaginal estrogen either exclude men or include too few to permit meaningful subgroup analysis. NICE guidance recommends seeking specialist advice if considering methenamine hippurate in men [3]. Continuous or post-treatment antibiotic prophylaxis in men should be undertaken with caution. Ideally, under specialist guidance, given the higher likelihood of complicated infection and the need to ensure adequate prostatic penetration where relevant (e.g., fluoroquinolones or trimethoprim, balanced against resistance and safety concerns) [3,4].

Failure of initial management, evidence of relapse, haematuria, abnormal imaging, elevated post-void residual, suspected chronic prostatitis, or infection with atypical or resistant organisms are pointers for specific referral to urology. The GP's role includes preparing patients for this pathway, explaining that further investigations may include invasive techniques, and reassuring patients that referral reflects standard best practice rather than disease severity. Before referral, patients can be encouraged to complete bladder diaries, validated symptom scores such as the International Prostate Symptom Score (IPSS) and ensure cultures are obtained before antibiotics, improving diagnostic yield.

In summary, rUTI in men should prompt a systematic, cause-focused approach, rather than reflex prophylaxis. Primary care clinicians are central to confirming diagnosis, recognising red flags, avoiding repeated empiric antibiotic courses, and coordinating early specialist input. While non-antibiotic prophylaxis is increasingly supported in women, its role in men remains uncertain. Reinforcing the importance of identifying and correcting underlying pathology is the cornerstone of management.

3.4 Areas of Future Research

Despite increasing interest in non-antibiotic prophylaxis for recurrent urinary tract infection, several important evidence gaps remain that limit optimal implementation in clinical practice. Firstly, a lot of evidence in guidelines is based upon older studies, highlighting the need for contemporary data. There is presently a lack of high-quality evidence in key patient subgroups, particularly men. As discussed in earlier sections, most randomized and observational studies focus on female populations. rUTI in men is more likely to reflect underlying pathology such as chronic bacterial prostatitis or bladder outlet obstruction. Future research should prioritise well-designed studies specifically addressing stepwise prevention strategies in male populations. In addition, while immunoactive prophylaxis has shown promising short-term outcomes, robust long-term data evaluating the durability of response and sustained reduction in recurrence are limited. Variability in study design, population selection, and availability across regions further complicates interpretation. These gaps highlight the need for well-designed, long-term randomized trials to better define the role of these therapies in clinical practice.

There also remains limited comparative evidence between non-antibiotic prophylactic strategies. While interventions such as methenamine hippurate, cranberry products, D-mannose, probiotics, and immunoactive prophylaxis have been evaluated individually, there is a lack of head-to-head trials to guide optimal selection or sequencing of therapies in routine care. Furthermore, there is scope to evaluate combination and multimodal approaches. rUTI carries a multifactorial nature, so combining behavioural optimisation with pharmacological or immunological strategies may offer greater benefit compared with single interventions. One recent Italian paper, for example, demonstrated that combination therapy of D-mannose with antibiotics led to a greater reduction in rUTI episodes over a year than respective monotherapies [70].

Thirdly, the durability of the treatment effect remains uncertain for many interventions. Some therapies are supported by short- to medium-term randomized data. However, longer-term follow-up is lacking, particularly for emerging strategies. An area for future studies should be the incorporation of extended follow-up periods to better assess sustained benefit and relapse patterns.

Finally, future research should prioritise patient-centred and pragmatic outcomes. These include quality of life, treatment acceptability, adherence, and reduction in antibiotic use. Standardisation of outcome measures, including definitions of recurrence and microbiological endpoints, would improve comparability across studies and strengthen guideline development. Addressing these gaps will be essential to refine clinical pathways, support evidence-based decision-making, and optimise the role of non-antibiotic prophylaxis in both primary and specialist care.

4. Conclusion

Non-antibiotic prophylaxis for rUTIs represents a paradigm shift in clinical care, aligning with principles of antimicrobial stewardship and patient-centred practice. Evidence and guidelines support options such as methenamine hippurate, vaginal estrogen and behavioural measures. Moreover, immunoactive therapies are an area with a limited but increasing research base. By integrating these into routine clinical pathways, clinicians in both primary and hospital settings can reduce antibiotic burden, support patient quality of life, and respond to the rising threat of antimicrobial resistance. This review integrates contemporary guideline recommendations with practical clinical tools to support the management of recurrent urinary tract infection. By combining non-antibiotic strategies with our structured decision-support tools, clinicians can more effectively translate evidence into practice. This approach has the potential to reduce unnecessary antibiotic exposure, improve

patient outcomes, and strengthen antimicrobial stewardship across healthcare settings.

Key Points

• Recurrent urinary tract infection (rUTI) is a major contributor to antibiotic use and antimicrobial resistance, driving interest in effective non-antibiotic preventive strategies.

• Contemporary NICE, EAU and AUA guidance include behavioural optimisation, methenamine hippurate and topical vaginal estrogen as first-line non-antibiotic prophylactic options in appropriately selected patients.

• Other interventions, including cranberry products, probiotics, D-mannose and immunoactive prophylaxis, may be considered in selected cases but require careful counselling due to heterogeneity and limitations in the evidence base.

• General practitioners play a central role in diagnosing rUTI, initiating preventive strategies, supporting shared decision-making and coordinating timely referral for specialist assessment.

• A structured, patient-centred approach to rUTI management can reduce unnecessary antibiotic exposure, improve quality of life and support antimicrobial stewardship across healthcare settings.

Availability of Data and Materials

Not applicable.

Author Contributions

VA: conceptualisation, literature review, and manuscript drafting. BS: made substantial contributions to conception and design of the project as well as supervision. Both authors contributed to revising the manuscript critically for important intellectual content. Both authors have read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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The authors declare no conflicts of interest.

Supplementary Material

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