Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

State-of-the-Art Review: Recurrent Uncomplicated Urinary Tract Infections in Women

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Over 50% of adult women experience at least 1 urinary tract infection (UTI) in their lifetime, and almost one-quarter of them will experience a recurrent UTI (rUTI). Recurrent UTI is defined as ≥2 UTIs in a 6-month period or ≥3 UTIs in 12 months (at least 1 of these episodes should be culture-proven to confirm infectious etiology). In this narrative review, we discuss the epidemiology, pathogenesis, diagnosis, and treatment considerations for recurrent uncomplicated cystitis in the adult female population. We provide a focused overview of the comprehensive management of these patients, with input from infectious disease physicians, urogynecologists, and urologists with expertise in rUTI, highlighting updated recommendations by the Infectious Diseases Society of America, American Urologic Association, Canadian Urologic Association, and American Urogynecologic Society. Finally, given the variety of prevention strategies, different treatment goals, and the need for "preference sensitive" decisions, we highlight the need for shared decision-making with patients.

Keywords. recurrent UTI; recurrent cystitis; LUTS; asymptomatic bacteriuria; chronic UTI.

Urinary tract infections (UTIs) are one of the most common infections encountered in both inpatient and outpatient healthcare settings [1]. Over 50% of adult women experience at least 1 UTI in their lifetime, and almost one-quarter of them will experience a recurrent UTI (rUTI) [2–5].

Recurrent UTI is defined as 2 or more UTIs in a 6-month period or 3 or more UTIs in 12 months [6]. At least 1 of these infections should be culture-proven to confirm infectious etiology. While patients may recover fully from each UTI episode, the cumulative burden of rUTIs on healthcare costs and quality of life is substantial. Each UTI episode has, on average, 6.1 days of symptoms, 2.4 days of reduced activity, and 1.2 days of work or study lost [7]. Testing with formal quality-of-life instruments such as the RAND 36-Item Short Form Survey (SF-36) has shown that quality-of-life indices in all subsections are significantly decreased in patients with rUTIs [8, 9].

In this narrative review, we discuss the epidemiology, pathogenesis, diagnosis, and treatment considerations for recurrent uncomplicated cystitis in the adult female population. Data on transgender populations are lacking, and we will use the terminology "women" to inclusively refer to those with female anatomy. Furthermore, the impact of race, ethnicity, and socioeconomic factors is poorly understood as most studies involve White female patients or, in many instances, demographics are not reported [10]. We provide a focused overview of the comprehensive management of these patients with input from infectious disease physicians, urogynecologists, and urologists with expertise in rUTI, highlighting updated recommendations by the Infectious Diseases Society of America, American Urologic Association (AUA), Canadian Urologic Association (CUA), and American Urogynecologic Society. Finally, we offer suggestions for patient–clinician shared decision-making. This review is written from the perspective of US-based clinicians and intended primarily for infectious disease specialists.

EPIDEMIOLOGY OF rUTI

In a study of college-aged women with a single UTI, 19%–27% experienced recurrence within 6 months, while a study of Danish women aged 16–65 years showed a higher prevalence of recurrence between 25% and 35% within 3–6 months [11, 12]. The risk of rUTI among women varies by age, as there is approximately a 2-fold increased prevalence in postmenopausal women relative to premenopausal women [1, 13].

In premenopausal women, risk factors include sexual activity and spermicide-containing contraceptives [14, 15]. Genetic factors also seem to play a role. A history of a first UTI occurring before 15 years of age, maternal history of UTI, and having first-degree female relatives with rUTI are independent risk

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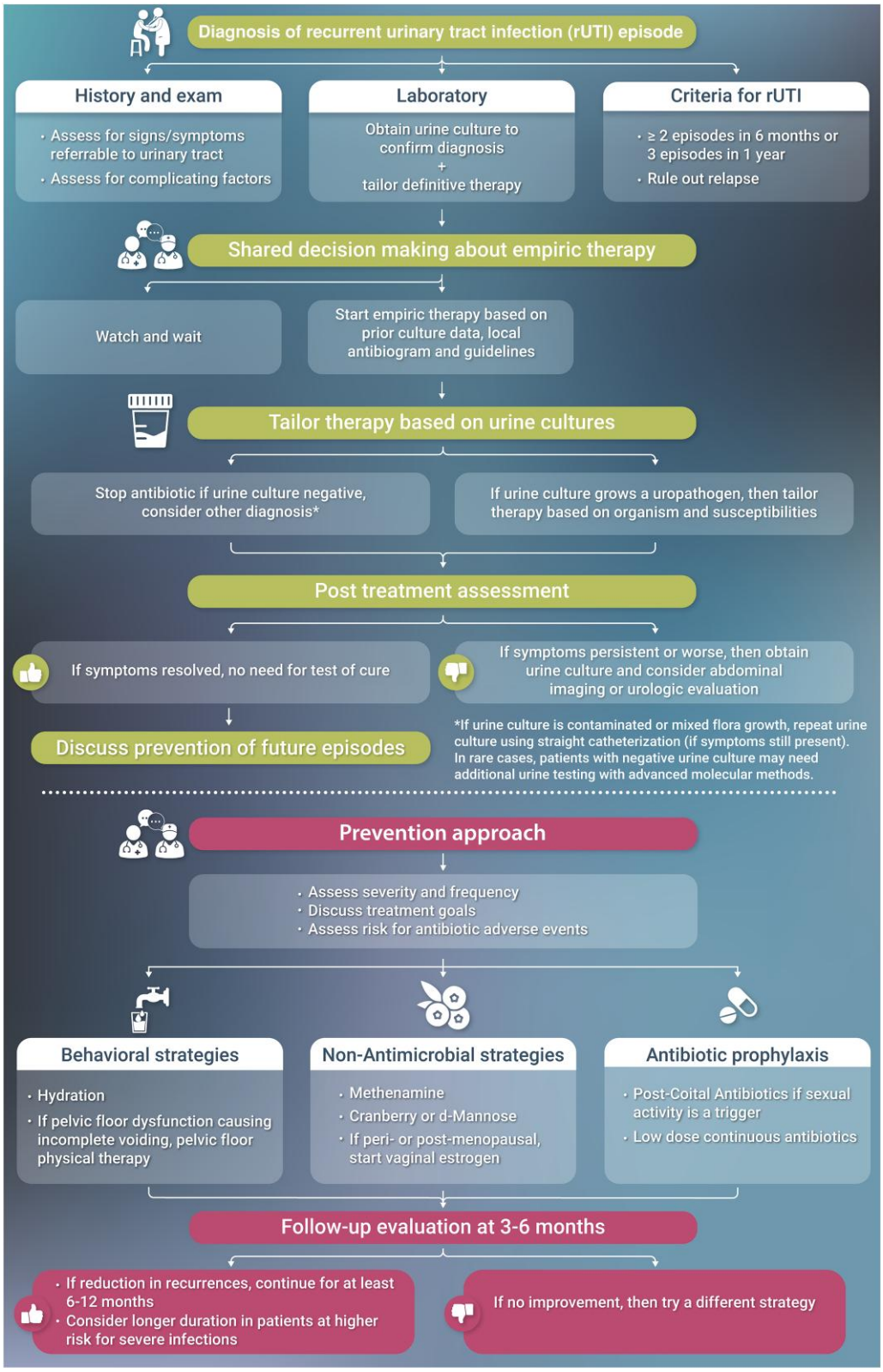

factors for recurrence [5]. Variations in the innate immune response, including polymorphisms in the Toll-like receptors that recognize pathogens in the urinary tract, are associated with adult susceptibility to rUTI [5, 16].

In postmenopausal women, urinary incontinence, premenopausal history of UTI, residual urine after voiding, and nonsecretor status (ie, those with the autosomal recessive trait that do not secrete blood group antigens into urine and bodily fluids) have been associated with rUTI in case-control studies [17, 18]. Vulvovaginal atrophy and changes in the urinary microbiome, both stemming from the physiological changes of menopause, are significant contributors to increasing rUTI in peri- and postmenopausal women. After menopause, decreased estrogen levels within the urogenital epithelium results in decreased *Lactobacillus* colonization, leaving the area more vulnerable to pathogens [17, 18].

PATHOPHYSIOLOGY OF rUTI AND EMERGING KNOWLEDGE IN THE MODERN ERA

Uropathogens are most commonly enteric gram-negative bacteria that have acquired the requisite virulence factors to thrive in the urinary environment. Historically, UTIs were thought to begin with pathogenic bacteria, usually originating from the gut or rectal area, colonizing the urethra and ascending into the bladder to cause infection [19]. Due to this thinking, clinicians have focused on eradicating "harmful bacteria" when found in the urine. However, we now know that pathogenic bacteria can be identified in the absence of urinary symptoms, either as asymptomatic bacteriuria on a standard urine culture or in low levels as part of the urinary microbiome [20]. As such, our understanding of rUTI pathogenesis has evolved [20]. In 1 model, there are repeated episodes of ascending infection from reservoirs outside of the urinary tract, which may include the vagina, vaginal microbiota, or gastrointestinal tract [21]. In another model, there is re-emergence of persistent intracellular bacterial colonies residing within the urinary tract itself [22, 23]. While both models may be true, the local ecology of other members of the urinary microbiome as well as host immune factors likely interact in both models of disease, leading to a multifactorial etiology of rUTIs (Figure 1) [22]. But, regardless of the cause of resulting bacteriuria, treatment is usually indicated for bacteriuria in symptomatic patients.

KEY COMPONENTS IN EVALUATION OF PATIENTS WITH rUTI

Management of recurrent episodes of uncomplicated cystitis in women involves a stepwise approach (as shown in Figure 2) starting with (1) initial evaluation of the acute UTI episode, (2) distinguishing rUTI from relapse, (3) treatment of the acute UTI episode, and (4) prevention of future episodes. In 2019, The AUA in conjunction with the CUA and the Society for Urodynamics and Female Urology (SUFU) published guidelines for the evaluation and management of rUTI in women [6]. These guidelines were most recently updated in 2022. The recommendations below are directed towards an otherwise healthy adult female with an uncomplicated rUTI.

Initial Evaluation of Acute UTI Episode in Patients Meeting Criteria for rUTI

An acute episode of cystitis is diagnosed primarily based on signs and symptoms localizing to the genitourinary tract [19, 24, 25]. The probability of cystitis is higher than 90% in women with dysuria and frequency in the absence of vaginal discharge or irritation (which may suggest other vulvovaginal entities) [19]. The initial evaluation of women with rUTI includes a focused history and physical examination to assess symptoms and frequency of infections, including UTI diagnostic testing results when available. Symptoms localizing to the genitourinary tract, such as dysuria, urinary frequency, urgency, suprapubic or flank pain, hematuria, and fever, should be documented, along with their duration and response to therapy [24]. Patients often attribute foul-smelling or cloudy urine to UTI; however, these symptoms are nonspecific for UTI, especially in the absence of other symptoms localizing to the genitourinary tract. Older women, especially those with frailty, may present with acute onset of general fatigue and/or confusion in the setting of pyuria and bacteriuria; however, antibiotic treatment is not recommended in the absence of localizing or systemic signs of infection [25]. The presence of fever, chills, rigors, marked fatigue, or malaise suggests that the infection has extended beyond the bladder and is regarded as acute complicated UTI [26]. The number and frequency of complicated and uncomplicated cystitis episodes should be determined.

Additionally, in patients meeting criteria for rUTI (≥2 UTIs in 6 months or ≥3 UTIs in 12 months), clinicians should document which diagnostic testing was used for symptomatic episodes. Urinalysis is used in many ambulatory settings and may support the diagnosis in those with urinary symptoms, but the presence of pyuria or nitrites is not diagnostic of UTI in otherwise asymptomatic patients. Similarly, in the absence of genitourinary symptoms, positive urine cultures do not require antibiotic therapy [25]. Notably, the absence of pyuria can rule out UTI in most nonneutropenic patients [27]. For those with recurrent symptoms, it is beneficial to order a urine culture to help direct antimicrobial therapy and differentiate rUTI from other genitourinary conditions that mimic UTI, such as overactive bladder, painful bladder syndromes like interstitial cystitis, vulvovaginal entities, or genitourinary syndrome of menopause, which are treated with different modalities [6, 28]. Even though urine culture thresholds greater than 100 000 colony-forming units (CFU)/mL are used for diagnosis of UTI, bacterial counts over 1000 CFU/mL may be diagnostic of UTI in a symptomatic woman [29, 30]. If, when cultured, clean catch urine is contaminated or grows mixed

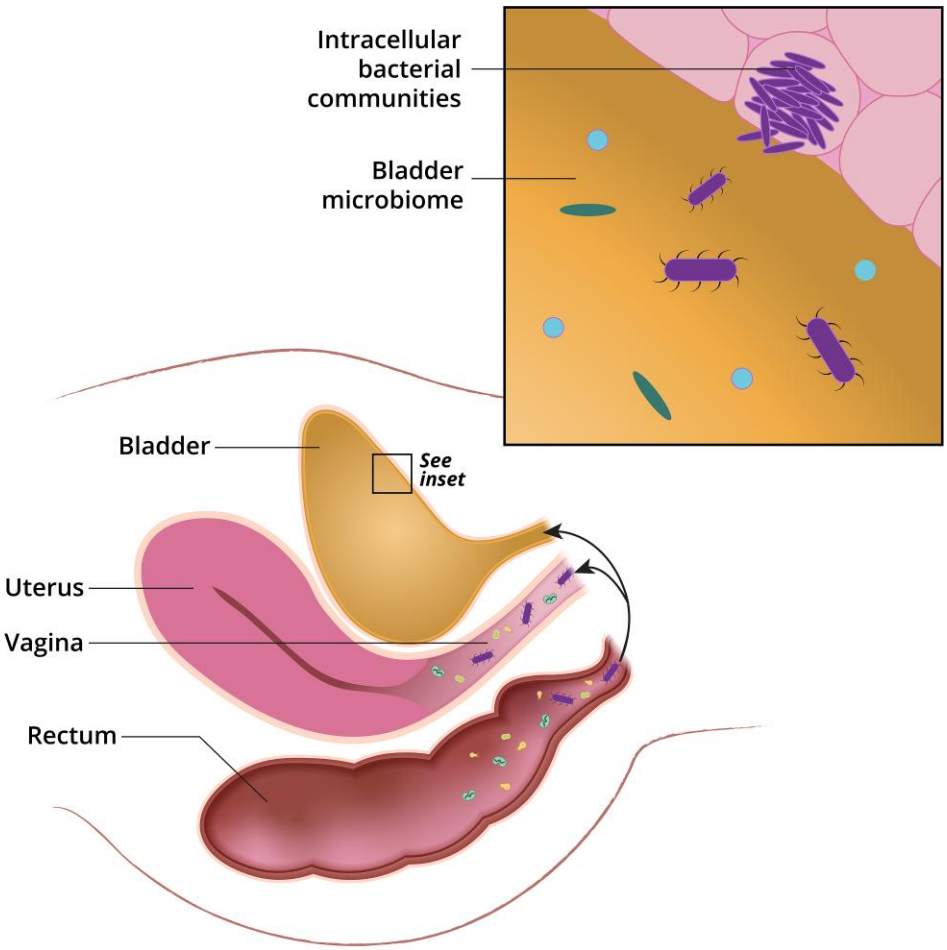

Figure 1. Evolving model of pathogenesis of uncomplicated recurrent urinary tract infection (showing re-emergence of persistent intracellular bacterial colonies residing within the urinary tract).

flora, then obtaining a catheterized urine specimen should be considered [6].

For women seeking initial evaluation for rUTI, we suggest asking probing questions to assess for other genitourinary conditions that present with symptoms similar to rUTI (eg, genitourinary atrophy, urethral diverticulum or strictures, bladder outlet obstruction, and vaginal prolapse). If symptoms are present, unclear, or uncertain, then the physical examination should include pelvic examination [6, 28]. As studies have shown that adequate bladder emptying is important for UTI prevention [31], assessment of bladder emptying should be considered, particularly in older women and those with neurologic disease, diabetes, vaginal prolapse, or symptoms of incomplete bladder emptying. We suggest asking probing questions to assess for urinary hesitancy and incomplete or interrupted bladder emptying. If symptoms are present or uncertain, bladder emptying can be assessed by checking the post-void residual (PVR) using either urethral catheterization or bladder scan within 30 minutes of a void. In neurologically intact women, a PVR above 150 mL is abnormal. In patients with neurogenic bladder, retained urine of more than 300 mL has been associated with a 4-fold risk of UTI [32]. Most women with rUTI do not warrant imaging or urologic evaluation (eg, cystoscopy or upper tract imaging) unless their symptoms do not improve with appropriate treatment, or unless their history or physical examination suggests structural or functional abnormalities of the genitourinary tract [33]. If these risk factors are suspected or diagnosed, a referral to urology or a urogynecologist would be beneficial for further management.

Distinguishing rUTI From Relapse

The next step is to determine if this acute episode represents recurrence or relapse. Clinically, relapse is classified as a recurrent episode within 2 weeks of a previous UTI, suggesting either failure of the antimicrobial therapy or a persisting nidus of infection. These patients need a repeat urine culture to assess for pathogen–drug mismatch and may need further evaluation for anatomical or functional abnormalities of the urinary tract [5].

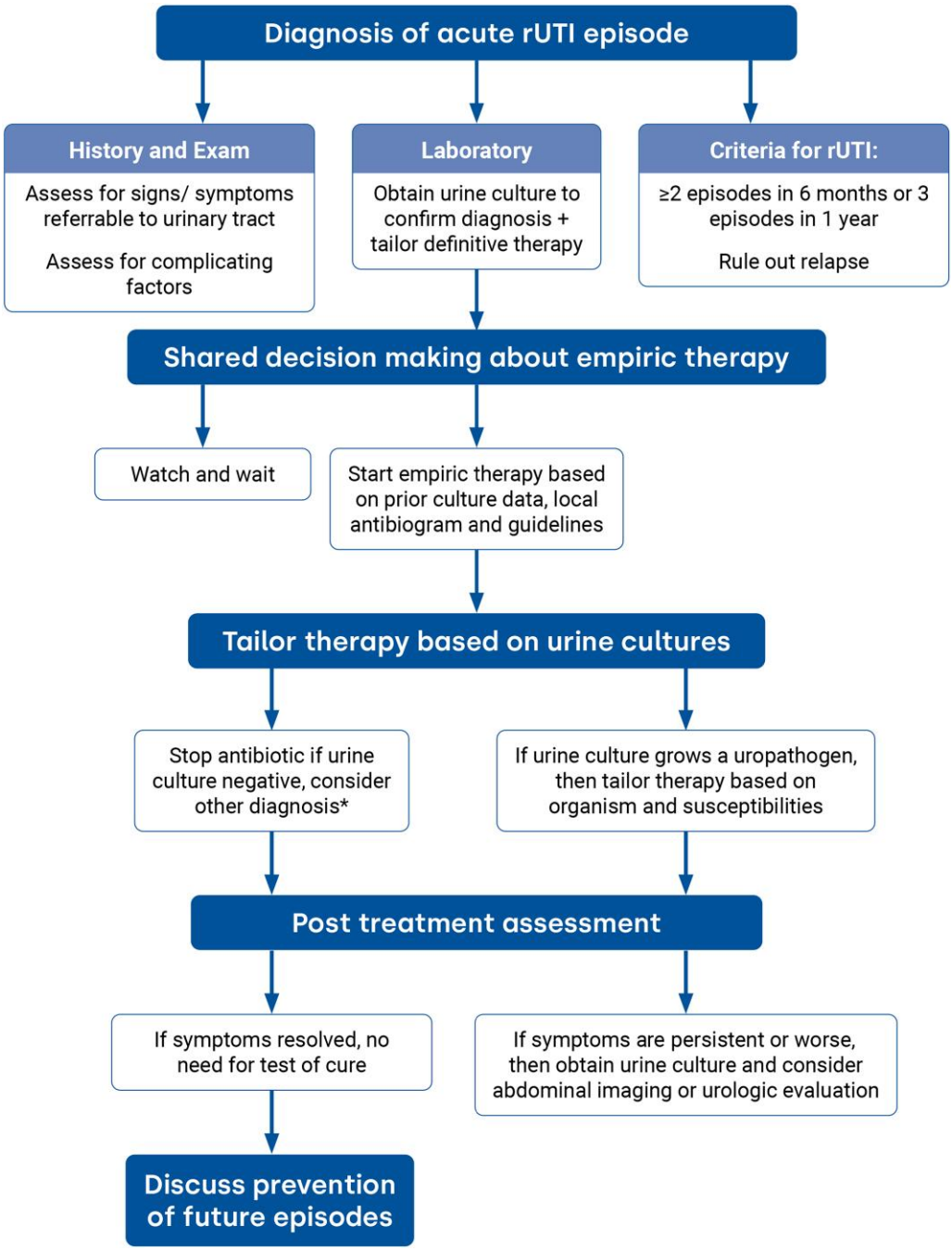

Figure 2. Stepwise approach to evaluation of recurrent urinary tract infection (rUTI). *If urine culture is contaminated or has mixed flora growth, repeat urine culture using straight catheterization (if symptoms still present). In rare cases, patients with negative urine culture may need additional urine testing with advanced molecular methods.

Treatment of an Acute rUTI Episode

In patients meeting criteria for rUTI (≥2 UTIs in 6 months or ≥3 in 1 year) and presenting with acute genitourinary symptoms, treatment should generally use first-line antibiotic therapy, in keeping with the local antibiogram, prior culture and sensitivity results, recent antibiotic use, and prioritizing a quinolone-sparing approach [5]. However, a watch-and-wait strategy could be offered to some patients with prescription for empiric antibiotics should symptoms persist or worsen while awaiting culture [34]. We suggest using a shared decision-making approach and leveraging a patient decision aid to discuss pros and cons of empiric antibiotics versus a watch-and-wait strategy [34]. If empiric therapy is used initially, it should be subsequently tailored according to urine culture results or clinical response. The duration of antibiotic regimens is the same as those used for sporadic uncomplicated

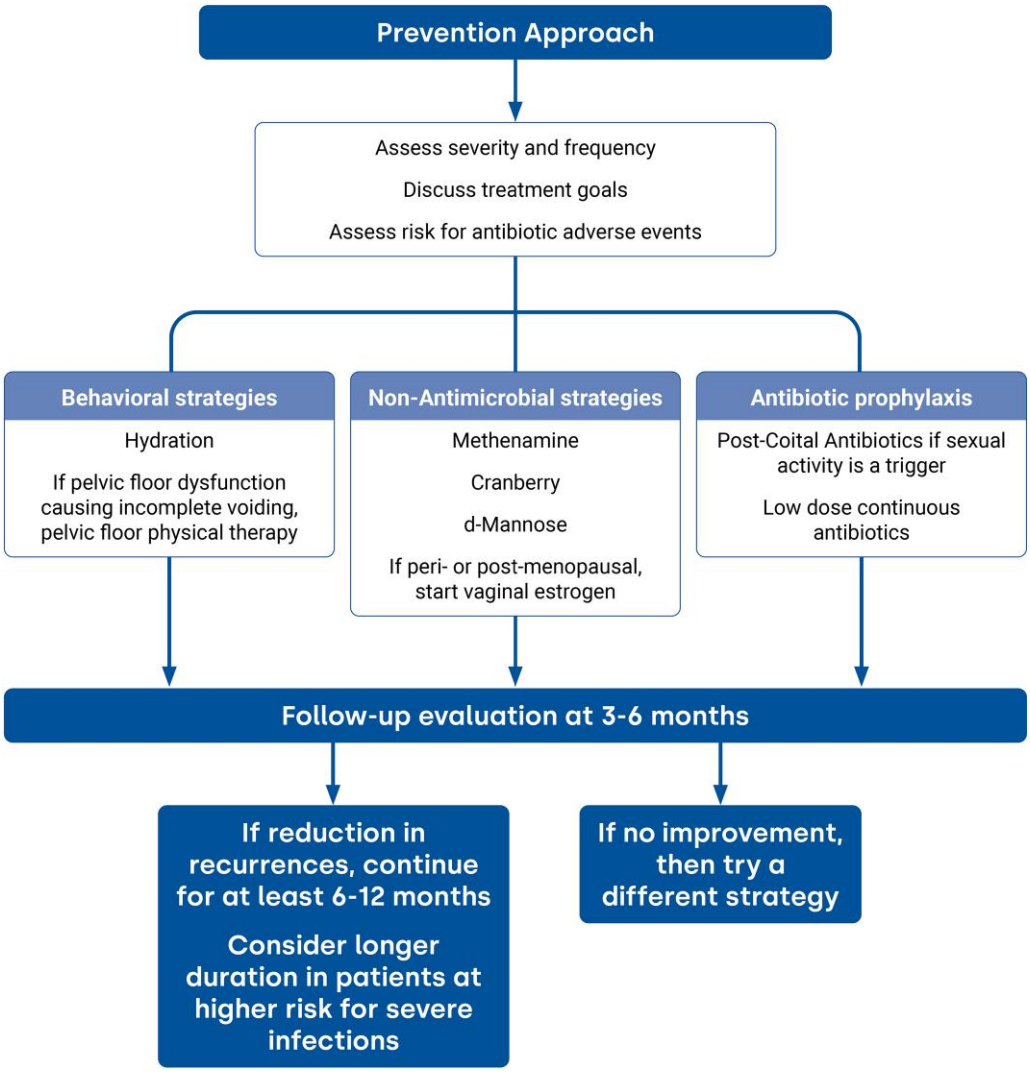

Figure 3. Prevention strategy for recurrent urinary tract infection (rUTI).

cystitis [5]. If symptoms resolve, a "proof of cure" culture is not necessary. If genitourinary symptoms persist after treatment or systemic symptoms develop, a repeat urinalysis (UA) and urine culture should be obtained [6, 35]. At this point, further evaluation to assess for structural or functional abnormalities of the genitourinary tract may be needed, if not already performed.

Strategies to Prevent Future Recurrence

After resolution of the acute UTI episode, the next step is to prevent further recurrences (Figure 3). There are multiple prevention strategies to prevent rUTIs, as shown in Table 1. These can be broadly broken down into the following: (1) behavioral strategies, (2) non-antimicrobial strategies, and (3) antimicrobial prevention strategies. Based on patient factors and patient preferences, behavioral and non-antimicrobial strategies should be optimized prior to pursuing antimicrobial strategies [36]. However, the timing and frequency of recent infections often guide the initial prevention strategy, with more frequent or higher acuity infections often requiring antimicrobial strategies initially. In many instances, several strategies are combined to help the local microenvironment, and to facilitate antimicrobial-sparing strategies long-term.

Behavioral Strategies

Increased hydration has been shown to prevent rUTIs, by increasing dilution and flushing of bacteria from the bladder. In a 2018 randomized controlled trial (RCT), women with rUTIs were assigned to drink an additional 1.5 L of water per day. During the 12-month study period, the mean number of cystitis episodes was 1.7 (95% confidence interval [CI]: 1.4–1.8) in the water group compared to 3.2 (95% CI: 3.0–3.4) in the control group, with a significant difference in mean UTIs of 1.5 (95% CI: 1.2–1.8; $P < .001$). The authors noted that, although increased hydration is not equivalent to daily antibiotic

Table 1. Prevention Strategies for Recurrent Urinary Tract Infection

	Strategies
Behavioral strategies	
Hydration	2–3 L of water daily
Pelvic floor physical therapy	If pelvic floor dysfunction causing incomplete voiding
Non-antimicrobial strategies[a]	
Vaginal estrogen	0.1 mg/g cream every night × 2 wk, then 2× weekly 4 or 10 μg suppository every night × 2 wk, then 2× weekly 2 mg/g ring (standard dose: 7.5 μg/24 h); change ring every 3 mo (off-label approach)
Cranberry	36–72 soluble PACs per day
Methenamine	1 g twice daily
D-Mannose	500 mg 1 to 3 times daily
Antibiotic prevention strategies[a]	
Postcoital (single dose)	PO nitrofurantoin 50 mg or 100 mg Trimethoprim/sulfamethoxazole 40/200 mg or 80 mg/400mg PO trimethoprim 100 mg PO cephalexin 250 mg
Low-dose continuous prophylaxis	PO nitrofurantoin 50 mg daily or 100 mg daily PO trimethoprim/sulfamethoxazole 40/200 mg daily or 3 times weekly PO trimethoprim 100 mg daily PO cephalexin 125 mg or 250 mg daily

Abbreviations: PAC, proanthocyanidin; PO, per oral.

[a]Adjust for renal and metabolic function, formulations, allergies, prior culture data, antibiogram, etc.

prophylaxis, water is "safe, inexpensive, and does not select for antimicrobial resistance" [37]. A subsequent meta-analysis of 7 RCTs, including this one, found that increased fluid intake reduced the risk of cystitis recurrence at 6 months (odds ratio [OR], .13; 95% CI: .07–.25) but not at 12 months.

Pelvic floor physical therapy (PT) has also been shown to decrease the incidence of UTI in patients with incomplete voiding due to high-tone pelvic floor dysfunction (overly constricted muscles contributing to aberrant neural signaling and poor bladder emptying) [38]. In 1 study of 86 women with voiding dysfunction, those who were assigned to pelvic floor PT and/or biofeedback had a lower prevalence of UTI at 12 months than those in the control group (20%–25% vs 90%; $P < .05$) [39].

Many prevention strategies for UTIs focus on perineal hygiene; however, there is little evidence to suggest that perineal hygiene contributes to UTI frequency. A study of 229 women demonstrated that there was no association between rUTI and pre- and postcoital voiding habits, wiping patterns, douching, use of hot tubs, frequent use of pantyhose or tights, or body mass index [14]. Indeed, perineal washing with antibacterial solutions has not been shown to prevent UTIs [40]. One perineal risk factor that has been associated with increased risk of rUTI is a urethral-to-anal distance of less than 4.5 cm [41], which is a nonmodifiable risk factor. Another modifiable risk factor is the use of spermicide. As such, spermicide use should be discouraged in patients with rUTIs [42]. Otherwise, clinicians should avoid perpetuating myths about behaviors contributing to rUTI and can instead educate patients with rUTI to reduce self-blame and non–evidence-based practices.

Non-Antimicrobial Strategies

There are several non-antibiotic prevention strategies for rUTI, as shown in Table 1. In postmenopausal women who are not having an escalating frequency of infections, treatment with vaginal estrogen should be considered prior to initiating antibiotic prophylaxis. Genitourinary syndrome of menopause (GSM) is a constellation of symptoms that can include vaginal dryness, irritation, increased risk of incontinence, and UTIs. Vaginal estrogen therapy (VET) is currently recommended by the National Association of Menopause and confirmed in an independent systematic review as the gold standard for GSM treatment [43, 44]. Vaginal estrogen therapy is also recommended as part of the AUA/CUA/SUFU guidelines for the prevention of rUTI [6, 35, 45]. Vaginal estrogen therapy in all commercially available formulations has been shown to be effective in decreasing rUTI [46, 47]. Clinicians and patients may have concerns about the safety of vaginal estrogen due to the package insert. However, multiple studies have shown low systemic absorption [44]. A large, population-based study in approximately 50 000 breast cancer survivors has shown that VET did not increase mortality, and the American College of Obstetricians and Gynecologists confirms that VET may be used under a shared decision-making model in women with a history of breast cancer [48, 49]. Studies of the urinary microbiome show that 3–6 months of VET results in increased lactobacilli in the bladder microenvironment [50, 51]. Lactobacilli, specifically the species *Lactobacillus crispatus*, have been associated with urogenital health in preclinical studies.

Given preclinical mechanistic data, *Lactobacillus* probiotics have been studied in several trials, but currently lack data to

support their role [7]. However, several different species, routes, and dosing regimens were used, resulting in substantial heterogeneity of trials and overall low quality of evidence [52]. While it is still not clear if they may be helpful, if patients choose to take a probiotic, we would consider one containing *L crispatus* as an active ingredient.

For premenopausal women, starting with antibiotic-sparing methods like methenamine or cranberry is preferable. Research indicates that both methenamine and cranberry products can effectively decrease the frequency of cystitis in females, with generally good tolerability and fewer side effects [53, 54]. The choice between them usually depends on patient and clinician preferences. Other commonly used antibiotic-sparing methods include D-mannose and probiotics. While not routinely recommended due to limited supporting data, they can serve as reasonable adjunctive options if patients choose to use them.

Methenamine is a non-antibiotic antiseptic strategy for the prevention of UTI, available in 2 formulations: hippurate or mandelate. These salts provide the acidic environment, where methenamine is hydrolyzed to ammonia and formaldehyde, which then act as bactericidal agents by denaturing bacterial proteins [54]. Due to the mechanism of action, bacteria cannot develop resistance to methenamine [55]. A 2012 Cochrane review showed that methenamine is effective in preventing UTIs [54], including in patients who require long-term catheterization [36]. More recently, a study showed that methenamine was as effective as trimethoprim prophylaxis in the prevention of rUTI [56]. This prescription medication is best utilized as a long-term prevention strategy and needs a minimum of 6–12 months to assess its efficacy in decreasing UTI recurrence [57].

Cranberry is a non-antibiotic option for the prevention of rUTIs in men and women of all ages. Proanthocyanidins (PACs), naturally occurring compounds in cranberries, are thought to prevent bacterial adherence to the bladder epithelium [58]. While large well-designed clinical trials examining cranberry supplements show conflicting results, the results of a recent Cochrane review supported the use of cranberry products in women with rUTI [6, 53]. Prior studies have shown that supplements must have 36 mg or more of soluble PACs to be effective [59]. It is important to counsel patients on these details, as supplements are not regulated via the US Food and Drug Administration (FDA) and effectiveness may be related to the potency and formulation of the cranberry supplement used.

D-Mannose is an inert monosaccharide that can be purchased over the counter and is popular with patients. Similar to cranberry, its metabolites are excreted into the urine and act to inhibit bacterial adhesion to the urothelium. While some meta-analyses have shown that D-mannose is comparable to daily antibiotic prophylaxis [60] in preventing UTIs, there is heterogeneity within the studies, which makes them difficult to compare. A 2022 Cochrane review was inconclusive as to whether D-mannose is effective in preventing UTIs [61]. However, in a recent randomized clinical trial of 598 women, D-mannose did not reduce the incidence of rUTI [62].

While each of these agents have small effect sizes, using them in combination may achieve better results and allow for an antibiotic-sparing approach, with few adverse events.

Antibiotic Prevention Strategies

Antimicrobial prophylaxis has the most robust data for the prevention of rUTIs and is an excellent option for the properly selected and counseled patient. Generally, for pre- or postmenopausal women with escalating frequencies of infection, starting with antimicrobial prophylaxis and transitioning to non-antimicrobial strategies after several infection-free months can be considered.

- Postcoital prophylaxis. For women in whom sexual activity is a trigger for UTI, the use of postcoital antimicrobial prophylaxis has been shown to be safe and effective. Dosing after sexual intercourse may help reduce UTI recurrence while limiting adverse events associated with long-term antibiotics [6, 35].
- Low-dose continuous antibiotic prophylaxis is another option for patients with rUTI without a clear trigger. In the 2019 AUA guideline, 11 trials were reviewed that compared different antibiotics head-to-head. All antibiotics had a decreased likelihood of experiencing 1 or more UTI as compared with placebo (11 studies; relative risk [RR], .26; 95% CI: .18–.37; $I^2 = 14\%$; absolute risk reduction [ARD], −46%; 95% CI: −56% to −37%) [63–72], with no significant differences between nitrofurantoin, fosfomycin, trimethoprim-sulfamethoxazole, norfloxacin, and cefaclor [71, 73–78]. Thus, the choice of prophylactic antibiotic depends on the local antibiogram, prior patient cultures, and tolerability of side effects. Given the FDA black box warning for tendon rupture with quinolones, they are not recommended as first-line daily prophylaxis [79]. The duration of therapy in most studies was 6–12 months, and patients generally returned to their baseline when discontinuing therapy.

While antibiotic prophylaxis has more extensive and consistent data supporting its efficacy, potential harms and adverse events related to prophylaxis must be weighed, especially in older adults. Antibiotics were associated with increased risk of any adverse event (6 studies; RR, 1.73; 95% CI: 1.08–2.79; $I^2 = 0\%$; ARD, 12%; 95% CI: 1% to 22%) [6, 35, 64, 66–68, 70, 72] and vaginitis (3 studies; RR, 3.01; 95% CI: 1.27–7.15; $I^2 = 0\%$; ARD, 18%; 95% CI: 5 to 32%). All antibiotics carry a risk of other side effects, such as gastrointestinal upset, skin rashes, and hepatic and renal toxicity, as well as medication interactions. No difference in the severity of adverse events was found between agents (4 studies; RR, 1.59; 95% CI: .58–4.42;

Table 2. Proposed Model for Shared Decision-Making

Shared Decision-Making Elements	Specific Considerations
Seek patient (and caregiver) participation	Weighing pros and cons, preferences, values
Explore and compare treatment options with your patient	Presenting risks and benefits of different options
Assess patient's values, treatment expectations, and preferences	Understanding the patient's goals of treatment
Decide with the patient and caregiver	Select a treatment option based on patient's treatment goals and preferences
Evaluate your shared decision	Assess the likelihood of desired outcome

$I^2 = 89\%$) [71, 74, 75, 77], so choice and duration of prophylactic antibiotic should be made considering patient-specific factors.

Strategy Selection

Patients experiencing rUTIs have a diverse understanding of the disease pathology and a variety of distinct treatment goals [80]. Many patients do not know that uncomplicated cystitis typically is self-limited and rarely progresses to more severe disease [15, 63, 64]. Similarly, clinicians should not assume that all patients have the same goals of treatment but should ask open-ended questions to better understand the patient's treatment goals and expectations (eg, symptom resolution, risk of antibiotic resistance, risk of sepsis or ascending infection). Clinicians should consider a shared decision-making approach as there are a variety of options for rUTI prevention, different treatment goals, and the ratio of benefits to harms is "preference sensitive" [81]. A key component to the success of shared decision-making is agreement upon a shared goal of treatment. Table 2 summarizes shared decision-making elements to consider while deciding between antibiotic and nonantibiotic prevention strategies.

Clinicians should be honest about the expected outcomes of treatment so that a shared goal can be realistic, measurable, and attainable [82]. Wish/Worry statements can be helpful in framing these expectations—for example, "I wish we could completely get rid of your UTIs, but I worry that a realistic outcome is reducing you to about two infections per year." Another helpful strategy can be asking patients their greatest fears in continuing to have rUTIs. A patient whose greatest concern is recurrent hospitalization may have different goals than one who is distressed by a particular symptom [83]. Additionally, helping educate patients about asymptomatic bacteriuria and risks of antimicrobials can be essential to identifying a shared goal. When discussing the role of suppressive antimicrobial therapy, the risks of future resistant infections, antibiotic adverse effects, and risk of *Clostridioides difficile* infection (CDI) should be clearly highlighted. If jointly agreeing on a course of suppressive antibiotics, clinicians should a priori define what outcomes would be defined as success and the timeline to reassess the risk/benefit of antibiotic suppression. While this approach can be time intensive upon the first visit, it establishes a strong foundation for a collaborative doctor–patient partnership moving forward.

INDICATIONS FOR UROGYNECOLOGIST OR UROLOGIST REFERRAL

Most patients with recurrent uncomplicated UTI may be treated successfully by primary care physicians. Urogynecologist referral for rUTI is indicated when risk factors for complicated UTI are present (anatomical or physiologic abnormalities of the urinary tract), when a surgically correctable cause of UTI is suspected, or when the diagnosis of UTI as a cause for recurrent lower urinary tract symptoms is uncertain.

FOLLOW-UP AND MONITORING

Patients with rUTI should be periodically assessed for the effectiveness of their prevention strategies. However, in the absence of distinct UTI symptoms, UA and urine culture should not be routinely collected [6, 35] as this can lead to the identification of asymptomatic bacteriuria and overtreatment with antibiotics if the bacteriuria is treated. Behavioral and non-antibiotic prevention strategies, in particular VET, need 3–6 months to reach full benefit. It is beneficial to follow-up within a few weeks of initiating prophylaxis to assess compliance, adverse events, or need to adjust strategy.

The duration of antibiotic prophylaxis in the literature ranges from 4 to 12 months. In clinical practice, the duration of prophylaxis can be variable, from 3 to 6 months to 1 year, with periodic assessment and monitoring. Some women stay on continuous or postcoital prophylaxis for years to maintain the benefit without adverse events.

There is emerging evidence that disruptions in the urinary microbiome contribute to rUTI [84, 85]. It can take 3–6 months to restore the microbiome after antibiotic treatment, so an appreciation for this broader time frame can often reassure patients who are frustrated with a series of rUTIs in close proximity. The goal is to partner with patients and develop an individualized treatment and prevention plan, and once the cycle of rUTI is broken, one can reassess in 6–12 months for continuation or discontinuation of prescription medications. As such, shared decision-making should be used to determine when to stop antimicrobial prophylaxis or if continuing daily prophylaxis is in the benefit of the patient and their goals.

EMERGING DIAGNOSTICS AND THERAPIES

There is increasing interest in exploring new methods for rapidly identifying and treating rUTI episodes. Molecular testing, such as polymerase chain reaction (PCR) and next-generation

sequencing (NGS), shows promise in providing comprehensive information about genitourinary microbes. While these tests may improve the identification of bacteria, they have the potential to increase the diagnosis of asymptomatic bacteriuria. Hence, caution is needed before widespread adoption due to potential antibiotic overuse [28].

Similarly, investigators continue to look for new, non-antibiotic treatment and prevention options for rUTI. Immunomodulating agents such as antibacterial vaccines have been studied since the 1990s, predominantly in female populations with rUTI [86]. The earliest iterations of vaccines had variable results. Newer iterations of vaccines utilize polyvalent heat-killed bacterial preparations. One such vaccine, called MV140 (Uromune®, Inmunotek S.L., Spain), has been studied in cohort studies and 1 randomized trial, suggesting beneficial effects that last for 6 months. Robust randomized trials are needed to understand if this vaccine is effective, and how often it may need to be re-dosed.

Another emerging therapy for rUTI involves bacteriophages, also referred to as phage therapy [87]. Bacteriophages are viruses that infect bacteria, resulting in quick bacterial cell death, thereby "re-shaping" the bacterial populations in an environment [88]. Custom bacteriophage preparations have been studied in 7 instances of complicated UTI with positive results, few side effects, and complete resolution of infections for up to 6 months [89]. Bacteriophages are specific to bacterial strains, and mass-produced products that are available "off-the-shelf" may have vastly different results than phage cocktails that are customized for a specific infection. However, there may be a role for phage cocktails in the treatment of recalcitrant infections, complicated rUTIs, or instances of colonization with multidrug-resistant bacteria [90].

Fecal microbiota transplantation (FMT) has been studied as a therapy for recurrent CDI. Many patients with CDI also have rUTI, and an incidental finding in early FMT studies was that rUTI improved concurrent with improvements in CDI. Follow-up studies have been limited by small sample sizes or retrospective study designs, without strong conclusions [91, 92]. There are now 2 FMT products approved by the US FDA for clinical use in CDI [93]. Further studies are needed to determine whether these are truly effective for UTI prevention in the absence of CDI.

Notes

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