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Diagnosis and Management of Recurrent Urinary Tract Infections in Women: Comparison and Interpretation Based on Existing Guidelines (Postprint)

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Abstract

Background Recurrent urinary tract infection (rUTI) is a common condition in female patients that severely impacts quality of life, increases healthcare burden, and is associated with global antibiotic resistance. Currently, European and American countries have developed independent clinical guidelines addressing the clinical problems posed by female rUTI, but there remains a lack of relevant consensus in China. Objective To summarize existing evidence and guideline recommendations regarding diagnostic evaluation, treatment strategy selection, and preventive protocols for rUTI, and to explore diagnostic and therapeutic strategies that can be applied in China. Methods Systematic searches were conducted in Chinese and English databases including CNKI, VIP, Wanfang Data, PubMed, and Web of Science, as well as official society webpages of urology, nephrology, and obstetrics and gynecology. Guidelines on female rUTI published between 2014 and 2024, along with major randomized controlled trials and observational studies mentioned in these guidelines, were included. Results A total of 274 articles were included for review and summary, comprising 98 systematic reviews and meta-analyses, 129 randomized controlled trials, 15 observational studies, and 32 expert opinions/guidelines. Comparison of current domestic and international clinical guidelines for rUTI reveals that, at the symptom management level, all guidelines generally recommend routine midstream urine culture during acute episodes. For antibiotic treatment during acute episodes, guidelines recommend nitrofurantoin, fosfomycin, and trimethoprim-sulfamethoxazole (TMP-SMX), among others. Adequate hydration, estrogen replacement, continuous low-dose antibiotic therapy, immunostimulant therapy, and methenamine hippurate are currently preventive measures with relatively

sufficient evidence. Conclusion Currently, most guideline recommendations primarily target female populations with uncomplicated cystitis, and guidelines from various countries are relatively consistent in their antibiotic regimens for acute infection, but differ in their recommendations for preventive measures. Future guideline versions should consider broader populations, particularly rUTI patients with complicating factors such as diabetes mellitus and renal disease, in order to optimize the evaluation and management of rUTI.

Full Text

Diagnosis and Management of Recurrent Urinary Tract Infections in Women: A Comparison and Interpretation Based on Existing Guidelines and Evidence

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Abstract

Background: Recurrent urinary tract infections (rUTI) are a common condition among female patients that severely impacts quality of life, increases

healthcare burden, and contributes to global antibiotic resistance. While European and American countries have developed independent clinical guidelines for rUTI, China currently lacks a dedicated consensus on this condition.

Objective: To summarize existing evidence and guideline recommendations regarding diagnostic evaluation, treatment strategies, and preventive measures for rUTI, and to explore applicable management strategies for domestic clinical practice.

Methods: We conducted systematic searches of Chinese and English databases including CNKI, VIP, Wanfang Data Knowledge Service Platform, PubMed, and Web of Science, as well as official websites of urology, nephrology, and obstetrics and gynecology societies. Guidelines related to female rUTI published between 2014 and 2024 were included, along with major randomized controlled trials and observational studies cited within these guidelines.

Results: A total of 274 articles were included in the review, comprising 98 systematic reviews and meta-analyses, 129 randomized controlled trials, 15 observational studies, and 32 expert opinions/guidelines. For symptom management, most guidelines universally recommend routine midstream urine culture during acute episodes. For acute-phase antibiotic therapy, guidelines recommend nitrofurantoin, fosfomycin, and trimethoprim-sulfamethoxazole (TMP-SMX). Evidence-based preventive measures include adequate hydration, estrogen replacement, continuous low-dose antibiotic therapy, immunoactive prophylaxis, and methenamine hippurate.

Conclusion: Most current guidelines primarily target non-pregnant women with uncomplicated cystitis. While guidelines from various countries demonstrate consistency in antibiotic regimens for acute infection management, they diverge in their recommendations for preventive strategies. Future guideline versions should consider broader populations, particularly rUTI patients with complicating factors such as diabetes and kidney disease, to optimize assessment and management of rUTI.

Keywords: Recurrent urinary tract infections; Urinary tract infections; Female patients; Guidelines; Interventional measures

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Urinary tract infection (UTI) is one of the most common bacterial infections, affecting approximately 150 million people globally each year. Due to unique microbial flora in the periurethral area and physiological differences, women are significantly more susceptible to UTIs than men, with over 60% experiencing at least one UTI during their lifetime [1-2]. Recurrent urinary tract infection (rUTI) is defined as the occurrence of bladder irritation-related symptoms at least twice within six months or three times within one year [2]. The repeated episodes of rUTI not only severely impact patients' quality of life but also impose substantial socioeconomic burden [3]. In the United States alone, rUTI accounts for over 7 million medical consultations annually, with associated healthcare

expenditures reaching $2 billion per year [4]. Repeated infections and inappropriate antibiotic use have exacerbated the public health challenge of antibiotic resistance [5-6].

European and American countries have established specific guidelines and consensus statements for managing female rUTI, though recommendations vary. Currently, China lacks independent guidelines or consensus specifically addressing female rUTI [7-8]. This article aims to summarize and analyze existing evidence, compare relevant clinical guidelines/consensus statements from Europe and America, and provide references for rUTI clinical diagnosis and treatment. As rUTI guidelines and evidence continue to evolve, clinical decision-making should incorporate patient preferences and local practice environments.

1. Methods

1.1 Inclusion and Exclusion Criteria We included guidelines/consensus statements regarding female rUTI patients and major randomized controlled trials (RCTs) and observational studies cited within these guidelines. After retrieval, titles and abstracts were screened initially, followed by full-text review for final inclusion. Inclusion criteria were: (1) Original clinical studies (RCTs, crossover trials, prospective cohort studies, and retrospective cohort studies) conducted in female patients with rUTI (defined as at least two UTIs within six months or at least three UTIs within 12 months); (2) Age 18 years; and (3) Studies referenced in the guidelines. Exclusion criteria included: (1) Basic research; (2) Non-Chinese or non-English publications; (3) Duplicate publications; (4) Prospective study protocols; (5) Case reports or conference abstracts; (6) Pregnant or lactating patients; (7) History of urological surgery; (8) Urogenital system malformations; (9) Urinary incontinence; (10) Catheter use; and (11) Severe renal impairment.

1.2 Search Strategy Chinese databases (CNKI, VIP, Wanfang Data Knowledge Service Platform) were searched using "复发性尿路感染" (recurrent urinary tract infection) as subject or free-text terms. English databases (PubMed, Web of Science) were searched using terms including "Recurrent Urinary Tract Infections," "prevention," and "prophylaxis." Official websites of professional societies were also reviewed, including the Chinese Medical Association, European Association of Urology (EAU), Wiki Guidelines Group (WGG), American Urological Association/Canadian Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (AUA/CUA/SUFU), Swiss Society of Gynaecology and Obstetrics (SSGO), National Institute for Health and Care Excellence (NICE), Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), Association of Scientific Medical Societies in Germany (AWMF), and American Academy of Family Physicians (AAFP). To reflect recent developments, the search was limited to November 2014–November 2024.

1.3 Literature Screening and Data Extraction Two authors independently screened literature, reviewed full texts, and extracted data according to inclusion and exclusion criteria. Disagreements were resolved through collaborative re-review or consultation with corresponding authors. Data were extracted regarding diagnosis, treatment, and prevention as highlighted in various national clinical guidelines. Information extracted from RCTs and observational studies included first author, publication year, study type, sample size, diagnostic criteria, and main findings.

The initial systematic search identified 1,764 relevant articles, with 274 ultimately included: 98 systematic reviews and meta-analyses, 129 RCTs, 15 observational studies, and 32 expert opinions/guidelines. The literature screening process is shown in Figure 1 [Figure 1: see original paper].

2. Results

2.1 Diagnosis of rUTI

2.1.1 Diagnostic Evaluation for rUTI Guidelines from various countries [9-14] define rUTI diagnostic criteria as including both A and B:

A: Typical UTI clinical manifestations and signs, including urinary frequency, urgency, dysuria, difficulty urinating, with or without hematuria, with or without urge incontinence, and generally mild or absent systemic symptoms. The primary physical sign is mild suprapubic tenderness.

B: Multiple episodes within a short period: at least three UTIs within one year or at least two UTIs within six months, with at least two weeks of asymptomatic interval between episodes [15]. Initial diagnosis requires confirmation through midstream urine bacterial culture, while subsequent infections can be diagnosed with assistance from typical symptoms.

2.1.2 Is Midstream Urine Culture Required for rUTI Diagnosis? Guidelines differ on whether clean-catch midstream urine culture is necessary for each rUTI episode. In China, urine culture remains the gold standard for diagnosing rUTI, with >10^{5} CFU considered positive from clean midstream urine, sterile catheterization, or suprapubic aspiration [7]. Most guidelines emphasize midstream urine culture for definitive diagnosis. However, EAU [9] and AAFP guidelines [14] note that urine culture is typically unnecessary when typical rUTI symptoms recur, considering that repeated cultures increase unnecessary healthcare costs and patient waiting time. Nevertheless, urine culture should be performed when UTI symptoms persist after 48 hours of antibiotic therapy.

Based on EAU recommendations and considering evolving antibiotic resistance trends, we suggest that urine culture with susceptibility testing is mandatory for initial diagnosis. For recurrent cases, midstream urine culture should be

performed whenever possible to confirm diagnosis, particularly when identifying resistance patterns or when treatment is ineffective, to assist in adjusting antibiotic use.

2.1.3 Is Routine Cystoscopy, Urinary Imaging, or Gynecological Examination Required for rUTI? Most society guidelines consider routine cystoscopy to have low diagnostic yield in practice [9-10,14]. A systematic review evaluating cystoscopy in women with rUTI found that <1.5% of patients had life-threatening lesions [16-17]. Therefore, cystoscopy is generally not recommended for initial diagnosis in rUTI patients without risk factors. However, cystoscopy and imaging should be performed for recurrent UTIs unresponsive to antibiotics, or when painless gross or microscopic hematuria is present, to exclude bladder lesions or urinary system structural abnormalities. Additionally, when urinary obstruction, stones, foreign bodies, or suspected space-occupying lesions are suspected, cystoscopy can identify obstruction location and severity and determine stone position, size, and quantity, providing important diagnostic value [7,10]. Ultrasound, as a non-invasive and convenient imaging method, can measure post-void residual urine volume and assess bladder emptying function, particularly suitable for initial screening and repeated measurements [7]. For patients suspected of urinary obstruction, intravenous urography (IVU) is simple to perform with minimal risk [10,18]. Computed tomography urography (CTU) has become more commonly used due to its high resolution and comprehensive information, clearly displaying urinary system structures and lesions, especially in diagnosing obstructive conditions like ureteral stones [9].

Gynecological examination can help exclude anatomical or functional factors contributing to rUTI, such as uterine prolapse [19]. For postmenopausal rUTI patients, gynecological examination also helps identify and treat menopause-related vaginal or urinary issues. Gynecological examination is a primary basis for diagnosing genitourinary syndrome of menopause (GSM), including observation of vulvar and vaginal atrophy symptoms and assessment of urinary tract atrophy [20].

We recommend that rUTI patients consider urinary system color Doppler ultrasound, while patients with non-Escherichia coli cultures, suspected urinary stones, cystitis glandularis, or urinary tumors may undergo cystoscopy or CT urography with contrast based on recommendations from SSGO 2020 [11] and AWMF 2017 [21]. When evaluating patients with prior pelvic surgery history, cystoscopy serves as an important diagnostic tool to identify anatomical variations from surgery, including urethral strictures or obstruction, urinary fistulas, and urethral or bladder diverticula. However, as cystoscopy is an invasive procedure, performing it during the acute phase of bladder and urethral infection may increase infection dissemination risk. Additionally, anesthesia complications including allergic reactions and cardiopulmonary depression may occur. For postmenopausal rUTI patients, we recommend collaborative gynecological evaluation.

Guideline comparisons regarding rUTI diagnosis are presented in Table 1 [9-14,21-22].

2.2 Acute-Phase Treatment Measures for rUTI Currently, most societies indicate that antibiotics for acute rUTI episodes should align with those for acute uncomplicated cystitis. The latest EAU, AUA, and Chinese urology guidelines recommend antibiotics including nitrofurantoin, fosfomycin, TMP-SMX, and levofloxacin for acute rUTI episodes (Table 2) [7,9-10,22]. Domestic recommendations still mention quinolones, but these may cause cardiac QTc interval prolongation, tendon rupture, and aortic dissection. In recent years, the U.S. Food and Drug Administration (FDA) has issued the highest-level black box warnings for these drugs [23]. Consequently, some guidelines have excluded levofloxacin from recommendations. Additionally, antibiotic-related gastrointestinal adverse reactions and candidiasis may cause patient reluctance toward antibiotic therapy.

A 2024 meta-analysis by HADIDI et al. [24] included 13 RCTs (n=3,856) comparing fosfomycin with nitrofurantoin, TMP-SMX, and ciprofloxacin for UTI treatment. Results showed fosfomycin was superior in both clinical and microbiological cure compared to other antibiotics, while ciprofloxacin was inferior in adverse event rates and recurrence rates. These findings support fosfomycin as the most effective antibiotic for uncomplicated UTI in terms of clinical cure, microbiological cure, and adverse events.

Based on this evidence, we believe that although guidelines recommend nitrofurantoin, fosfomycin, and TMP-SMX as first-line treatments for acute rUTI episodes, clinicians should comprehensively consider local antibiotic susceptibility patterns and potential adverse reactions when selecting appropriate antibiotics [25-26]. Long-term antibiotic use may also promote super-resistant bacteria and even refractory urosepsis [2]; therefore, antibiotic treatment duration should follow guideline recommendations whenever possible.

2.2.1 Should NSAIDs Be Used During Acute rUTI Episodes? NSAIDs primarily treat acute UTI by inhibiting inflammatory responses and reducing urinary symptoms [27-28]. Most guidelines suggest that for mild-to-moderate cystitis symptoms, NSAIDs may be used as an alternative or adjunct to antimicrobial therapy after patient consultation [29-31]. One RCT (n=494) compared ibuprofen versus fosfomycin in women with acute uncomplicated UTI [29]. At day 28, women receiving ibuprofen had significantly reduced antibiotic needs (35% vs. 100%; $P<0.0001$), with 67% recovering without antibiotics. However, compared to antibiotic-treated women, ibuprofen-treated women had higher symptom burden at day 7 and increased risk of developing pyelonephritis. The SSGO guideline notes that although diclofenac can reduce antibiotic use in uncomplicated cystitis, it increases pyelonephritis risk [31]. Therefore, the efficacy of NSAIDs in treating UTI requires careful evaluation.

We suggest that NSAIDs may be considered as adjunctive therapy before mid-

stream urine culture and susceptibility results are available when significant urinary irritation symptoms are present. However, NSAIDs should be used cautiously in patients with prior pyelonephritis history to avoid masking symptoms and delaying treatment.

2.2.2 Should Self-Diagnosis and Treatment Be Recommended During Acute rUTI Episodes? Most guidelines [9-10,12,14] recommend that if patients are well-informed, have high adherence, can communicate effectively, and self-assess symptoms, they may self-diagnose and initiate empirical treatment before obtaining midstream urine culture results (Table 3). An RCT by SCHAEFFER et al. [32] evaluating self-initiated antibiotic therapy for rUTI patients (n=34, with 28 patients followed for 355 months and 84 symptom episodes) showed that intermittent self-initiated therapy allows patients to start short-course antibiotics when symptoms appear, reducing long-term antibiotic exposure and consequently lowering resistance risk and adverse effects. The SEIMC guideline [12] notes that for patients with fewer than three UTIs per year, prophylactic self-initiated antibiotic therapy can reduce long-term antibiotic use.

We recommend that community and outpatient clinicians strengthen patient education for rUTI, helping patients accurately assess their condition, identify acute episodes promptly, and reasonably initiate intermittent antibiotic therapy based on prior urine culture results. Patients should contact physicians promptly if symptoms persist or worsen. Clinicians should document patients' self-diagnosis and treatment frequency and symptom resolution while recording urine culture data to assist in developing and adjusting personalized treatment plans.

2.3 Preventive Measures During rUTI Remission During rUTI remission, preventive measures should be considered to prevent recurrence, including behavioral modifications, oral non-antibiotic agents, topical therapies, UTI vaccines, intravesical agents, and oral antibiotics (Table 4) [9-14,21-22,33].

2.3.1 Increased Fluid Intake All guidelines recommend increased fluid intake as the first-line preventive measure [9-12,14,21]. In dehydrated states, urine concentration increases and voiding frequency decreases, creating more favorable conditions for bacterial proliferation in the urinary system. A 12-month RCT in premenopausal women with rUTI found that daily fluid intake >1.5 L reduced cystitis episodes and antibiotic use compared to <1.5 L/day [34].

2.3.2 Oral Non-Antibiotic Agents 2.3.2.1 Cranberry Products: Cranberry contains proanthocyanidins that interfere with bacterial adhesion (e.g., E. coli) to uroepithelial cells by preventing bacterial fimbriae from binding to uroepithelial receptors, thereby reducing bacterial colonization. Additionally, cranberry components may alter bacterial morphology (e.g., from rod-shaped to spherical), increasing bacterial expulsion [35-36].

Current evidence regarding cranberry product efficacy remains uncertain, with most guidelines [9-10,12,14,33] providing weak-to-moderate recommendations. The AUA guideline provides no recommendation due to limited and conflicting evidence. The NICE guideline recommends cranberry products for non-pregnant women and children/adolescents under 16 based on favorable benefit-risk ratio and reduced antimicrobial resistance. The EAU guideline, considering adverse effects and potential preventive benefits from seven meta-analyses, provides a moderate recommendation. A 2024 systematic review of 20 intervention trials (n=3,091, including 18 RCTs and 2 non-RCTs) showed cranberry intake significantly reduced UTI incidence (RR=0.73, 95%CI=0.59-0.91), representing a 27% reduction compared to placebo and 54% compared to no treatment, while reducing antibiotic use (RR=0.51, 95%CI=0.30-0.87) and alleviating UTI-related symptoms [37].

We believe that despite low-quality evidence, cranberry may be recommended for rUTI-susceptible populations due to minimal adverse effects, potential benefits in reducing antimicrobial resistance, and favorable risk-benefit profile. Future clinical research should focus on evaluating stable formulations and effective dosages.

2.3.2.2 D-Mannose: D-Mannose is an isomer of glucose involved in protein glycosylation [38]. Enterobacteria such as uropathogenic E. coli (UPEC) attach to uroepithelium via FimH adhesin molecules on type 1 fimbriae binding to mannosylated host proteins [39]. D-Mannose can competitively bind to FimH, preventing bacterial attachment to uroepithelial glycoprotein receptors and reducing infection risk [40-41].

Currently, due to insufficient evidence quality, most guidelines [9,11-13,24,33] provide conditional recommendations for D-mannose in rUTI prevention. However, a recent RCT showed D-mannose did not reduce the proportion of women with prior rUTI who developed subsequent UTIs requiring outpatient treatment [42].

We believe D-mannose shows potential as an antibiotic-sparing therapy for preventing female rUTI, but existing evidence remains low-quality. Further research is needed to confirm its clinical value and specific role in rUTI prevention. The recommended dosage is 2 g D-mannose dissolved in 200 mL water for six months.

2.3.2.3 Methenamine Hippurate: Methenamine hippurate decomposes into ammonia and formaldehyde in acidic environments. Formaldehyde inhibits cell division and blocks synthesis of 1,3-thiazine-4-carboxylic acid, interfering with methionine synthesis—a key metabolite for cytoplasmic synthesis—thereby inhibiting nucleic acid and cytoplasmic synthesis to achieve antibacterial effects. If urine pH >6.5, concurrent urine acidification and vitamin C supplementation (100 mg) is recommended for maximum efficacy.

Before the 2022 update, EAU and AUA/CUA/SUFU guidelines considered methenamine hippurate evidence limited or conflicting and could not provide clear recommendations. The SEIMC guideline did not recommend methenamine

hippurate due to potential carcinogenic risk and limited evidence. The 2022 ALTAR trial, a multicenter non-inferiority RCT, compared methenamine hippurate with low-dose antibiotics for UTI prevention, demonstrating non-inferiority [43]. A 2023 RCT (n=205) comparing methenamine hippurate with low-dose antibiotics for preventing female rUTI showed methenamine hippurate serves as an effective alternative [17]. Current NICE guidelines recommend twice-daily dosing (one tablet per dose), which may be combined with high-dose vitamin C (1,000 mg) daily, though this is not yet standard treatment.

We believe methenamine hippurate serves as an effective, cost-efficient alternative to low-dose antibiotics without antibiotic resistance risk. While no direct evidence exists for preventing catheter-associated rUTI, further clinical exploration in patients with complicating factors is warranted.

2.3.3 Topical Therapies **2.3.3.1 Probiotics:** Lactobacillus is the predominant commensal microorganism in the vaginal and periurethral area, preventing pathogen attachment and migration to bladder urothelium and maintaining urogenital health. Lactobacillus prevents pathogen colonization by occupying epithelial adhesion sites and produces antimicrobial substances including hydrogen peroxide, lactic acid, and bacteriocins that inhibit pathogen growth [44-47]. Significant reduction in Lactobacillus levels correlates with increased vaginal E. coli colonization [48].

Due to limited and conflicting evidence, most guidelines provide no clear recommendation. Only the EAU guideline provides a weak recommendation based on available data, but notes that evidence quality is too low to specify administration routes, optimal dosage, or treatment duration. A 2024 meta-analysis of five RCTs (n=552) comparing probiotics with placebo for adjunctive UTI treatment showed probiotics achieved better Nugent scores (3) than placebo (RR=1.38, 95%CI=1.01-1.89, P<0.04, I^{2}=72%), but sensitivity analysis excluding the lowest-weight study did not support probiotics as adjunctive UTI therapy [49]. The EAU guideline specifically notes that only certain strains may effectively prevent UTI, with potentially effective strains including L. rhamnosus GR-1, L. reuteri RC-14, L. reuteri B-54, L. casei shirota, and L. crispatus CTV-05 [50-53].

We believe that although some studies and meta-analyses support the role of specific Lactobacillus strains in preventing rUTI, evidence quality and consistency remain insufficient for definitive guideline recommendations. Future research should focus on clinical applications of specific effective strains, optimize dosing regimens, and provide more precise evidence to ensure probiotic efficacy and safety in UTI prevention.

2.3.3.2 Local Vaginal Estrogen Replacement Therapy: Local vaginal estrogen replacement therapy (VERT) maintains vaginal epithelial integrity, regulates vaginal pH, and promotes an acidic environment that inhibits harmful bacterial growth [54-55]. Most guidelines recommend local vaginal estrogen for postmenopausal patients with recurrent rUTI. The AUA guideline recommends

that clinicians offer vaginal estrogen to all postmenopausal women with rUTI to reduce infection risk. EAU, SSGO, and SEIMC specifically propose that local vaginal estrogen effectively reduces rUTI incidence in postmenopausal patients with vaginal atrophy. Although current evidence shows vaginal estrogen is less effective than antibiotics, it still provides benefits compared to placebo. A 2023 systematic review of 10 RCTs (n=2,608) summarized the benefits of vaginal estrogen in reducing rUTI risk and associated urinary symptoms in postmenopausal women, supporting its use for improving urinary symptoms and reducing rUTI risk [56].

We believe local vaginal estrogen replacement therapy is recommended by most guidelines for preventing rUTI in postmenopausal women. Before initiating treatment, clinicians should note contraindications including history of endometrial or breast cancer, thromboembolic disease (e.g., deep vein thrombosis or ischemic stroke), and acute liver disease due to cholestasis exacerbation risk [57]. Common vaginal estrogen formulations include vaginal creams, vaginal estrogen tablets (e.g., 17 -estradiol vaginal tablets), and vaginal estrogen rings (e.g., estradiol-releasing vaginal ring Estring) [58-59]. Specific usage and regimens are detailed in Table 5 . Each formulation has specific administration methods and dosages that can be selected based on individual patient needs. Currently, no clear evidence indicates differential efficacy among various vaginal estrogen formulations for rUTI prevention.

2.3.3.3 Immunoactive Prophylaxis for UTI: Immunoactive prophylaxis activates dendritic cells, neutrophils, and helper T cells, triggering B lymphocytes to release IgA that forms a protective layer on mucosal surfaces [60-61]. AUA, SSGO, SEIMC, and AWMF guidelines recommend OM-89 for immunoactive prophylaxis, though evidence quality is limited and does not support strong recommendations.

OM-89 (Uro-Vaxom) is an oral capsule containing extracts from 18 heat-killed UPEC strains that stimulates the host immune system through mucosa-associated lymphoid tissue in the gastrointestinal, respiratory, and urogenital tracts, increasing bacterial-specific antibody concentrations [62]. Meta-analysis shows OM-89 is effective in reducing rUTI in adult women (RR=1.94, 95%CI=0.65-5.86), though evidence quality is low [63]. The guideline expert panel strongly recommends OM-89 for rUTI prevention, but it is only effective against UPEC strains. The recommended regimen is 6 mg OM-89 daily for 90 days, followed by a 3-month drug-free interval, then 10-day booster treatments during the first 10 days of months 7, 8, and 9 [64].

MV140 (Uromune) is a novel sublingual immunomodulator containing inactivated uropathogenic strains including E. coli, Klebsiella pneumoniae, Proteus vulgaris, and Enterococc faecalis. Administered via the sublingual route, it induces T cell-specific adaptive immune responses in urogenital tissues [65-66]. A systematic review of two retrospective and three prospective cohort studies showed MV140 reduced rUTI episodes and/or increased UTI-free periods [67]. LORENZO-GÓMEZ et al. [68] published a 2022 RCT evaluating MV140 in 240

women with UTI, demonstrating that annual UTI frequency decreased from six episodes pre-treatment to zero during the 9-month observation period. MV140 has minimal adverse effects and shows promising clinical efficacy in reducing rUTI. It is currently available as a sublingual spray, with recommended usage of two sprays daily under the tongue for three months.

StroVac is a vaccine for long-term rUTI prevention containing 10^{9} inactivated pathogens from five bacterial species (E. coli 7.5×10^{8}, Morganella morganii 3.75×10^{7}, Proteus mirabilis 3.75×10^{7}, K. pneumoniae 1.5×10^{8}, and Enterococcus faecalis 2.5×10^{7}). StroVac activates gut-associated lymphoid tissue (MALT) and systemic immunity, enhancing urinary tract mucosal immune defense and reducing pathogen adhesion to urothelium. A 2023 RCT randomized 173 participants to StroVac vaccination or 100 mg nitrofurantoin daily for three months, showing StroVac provides a potential non-antibiotic option for rUTI prevention with lower adverse event rates than nitrofurantoin [69]. The recommended regimen is three injections of 0.5 mL at 1-2 week intervals, followed by a 12-month drug-free period, then a 0.5 mL booster injection [70].

We believe immunomodulators show potential for rUTI prevention, but heterogeneous and limited evidence warrants cautious clinical application. Different immunomodulator types may suit different patient needs. OM-89 capsules have gained wider acceptance but are limited to short-term prevention with insufficient long-term evidence. Before considering immunomodulators, clinicians should note potential contraindications including allergic reactions, severely compromised immune function (e.g., undergoing immunosuppressive therapy), and acute exacerbations of certain chronic diseases (e.g., asthma, COPD, diabetes, autoimmune disorders). Additionally, use in pregnant or lactating women should be deferred when necessary.

2.3.3.4 Intravesical Therapy: The glycosaminoglycan (GAG) layer is a protective barrier on the bladder mucosal surface composed of negatively charged polysaccharides that prevents bacterial adhesion [71]. GAG deficiency is considered a common initial step in the pathogenesis of many chronic inflammatory bladder diseases including rUTI and may increase bacterial internalization into urothelial cells, leading to intracellular bacterial community (IBC) formation [72]. Intravesical instillation of hyaluronic acid (HA) and chondroitin sulfate (CS) forms a physical barrier on the bladder mucosal surface, repairing the GAG protective layer covering bladder urothelium [73], thereby preventing bacterial adhesion and invasion and reducing recurrence risk. SSGO and EAU guidelines recommend HA and CS for rUTI prevention; other guidelines do not mention or recommend this approach. The EAU guideline suggests considering intravesical therapy (IVA) when less invasive treatments are ineffective, noting this therapy can reduce UTI frequency and prolong intervals between infections. A 2022 systematic review by REDDY et al. [74] including 13 studies (n=764, comprising 2 RCTs and 11 non-RCTs) showed IVA therapy (including gentamicin combined with hyaluronic acid and chondroitin sulfate) demonstrated good efficacy in reducing rUTI for patients failing oral antibiotic therapy. Ialuril is a

commonly used GAG therapy for rUTI, with a recommended regimen of weekly instillations for the first month, followed by a 5-month maintenance phase with monthly instillations [75-76], providing continuous protection and reducing UTI recurrence.

We believe intravesical GAG therapy prevents rUTI recurrence by repairing the GAG layer and has been recommended in some guidelines with demonstrated clinical efficacy. However, optimal treatment frequency and duration remain undetermined, and more high-quality research is necessary to validate long-term efficacy and safety.

2.3.3.5 Continuous Low-Dose Antibiotic Prophylaxis: Guidelines consider continuous low-dose antibiotics the most effective method for preventing UTI recurrence [19,21,77-85]. An RCT including 404 rUTI patients using clean intermittent self-catheterization (CISC) compared continuous low-dose antibiotic prophylaxis with no prophylaxis, showing significantly lower UTI incidence in the prophylaxis group during 12-month follow-up (RR=0.52, 95%CI=0.44-0.61, P<0.0001), representing a 48% reduction [86]. Another systematic review and meta-analysis of 23 RCTs (n=1,572) evaluating antibiotic prophylaxis for rUTI showed significantly lower UTI risk compared to placebo (RR=0.15, 95%CI=0.08-0.29, P<0.0001, I^{2}=57%), demonstrating antibiotic prophylaxis as an effective risk-reduction strategy. Head-to-head comparisons of different antibiotics showed similar efficacy among nitrofurantoin, trimethoprim (±sulfamethoxazole), and norfloxacin, with intermittent prophylaxis (e.g., postcoital) being as effective as continuous strategies [87]. The AWMF guideline recommends 3-6 months of continuous antibiotic prophylaxis for patients with frequent recurrences when behavioral modifications and non-antibiotic measures fail. The EAU guideline notes no consensus on optimal duration for continuous antimicrobial prophylaxis, with most studies using 3-12 months until resistance develops. Antimicrobials can be used as long-term continuous low-dose prophylaxis or post-coital prophylaxis, with no significant difference in effectiveness between methods, and no statistically significant differences among various antibiotic regimens (Table 6).

We believe antibiotics are the most effective method for preventing UTI recurrence and should be considered when behavioral modifications and non-antibiotic measures fail. Prophylactic efficacy is limited to the treatment period, and the optimal balance between treatment duration and potential toxicity or adverse effects with long-term use remains unclear. Potential benefits must be weighed against risks including drug toxicity, resistance development, and impact on patient microbiota. Considering evolving antimicrobial spectra and increasing evidence, individualized treatment should account for local uropathogen susceptibility patterns, potential adverse events, resistance development, and patient preferences.

3. Discussion and Conclusion

This article summarizes diagnostic, therapeutic, and preventive strategies from multiple international rUTI guidelines, which demonstrate high consistency in rUTI definitions and evaluation standards. Most guidelines recommend similar antibiotics for acute episodes, including nitrofurantoin, fosfomycin, and TMP-SMX. Evidence-based preventive measures include estrogen replacement, continuous low-dose antibiotic therapy, immunoactive prophylaxis, and methenamine hippurate. Based on these summaries, we have compiled a management flowchart for female rUTI (Figure 2 [Figure 2: see original paper]) for reference by domestic clinicians.

Current guidelines primarily target healthy, non-pregnant women with uncomplicated cystitis. Future guideline versions should consider broader populations, particularly rUTI patients with complicating factors such as diabetes and kidney disease, to optimize assessment and management.

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References: [1] ZENG Z L, ZHAN J, ZHANG K M, et al. Global, regional, and national burden of urinary tract infections from 1990 to 2019: an analysis of the global burden of disease study 2019[J]. World J Urol, 2022, 40(3): 755-763. DOI: 10.1007/s00345-021-03850-9. [2] ZARE M, VEHRESCHILD M J G T, WAGENLEHNER F. Management of uncomplicated recurrent urinary tract infections[J]. BJU Int, 2022, 129(6): 668-678. DOI: 10.1111/bju.15630. [3] NABER K G, TIRÁN-SAUCEDO J, WAGENLEHNER F M E, et al. Psychosocial burden of recurrent uncomplicated urinary tract infections[J]. GMS Infect Dis, 2022, 10: Doc01. DOI: 10.3205/id000078. [4] FLOWER A, HARMAN K, WILLCOX M, et al. The RUTI trial: a feasibility study exploring Chinese herbal medicine for the treatment of recurrent urinary tract infections[J]. J Ethnopharmacol, 2019, 243: 111935. DOI: 10.1016/j.jep.2019.111935. [5] FLOWER A, WANG L Q, LEWITH G, et al. Chinese herbal medicine for treating recurrent urinary tract infections in women[J]. Cochrane Database Syst Rev, 2015, 2015(6): CD010446. DOI: 10.1002/14651858.CD010446.pub2. [6] WANG R, LASALA C. Role of antibiotic resistance in urinary tract infection management: a cost-effectiveness analysis[J]. Am J Obstet Gynecol, 2021, 225(5): 550.e1-550.e10. DOI: 10.1016/j.ajog.2021.08.014. [7] 黄健. 中国泌尿外科和男科疾病诊断治疗指南: 2019 版 [M]. 北京: 科学出版社, 2020. [8] 中国女性尿路感染诊疗专家共识 [J]. 中华医学杂志, 2017, 97(36): 6. [9] KRANZ J, BARTOLETTI R, BRUYÈRE F, et al. European association of urology

guidelines on urological infections: summary of the 2024 guidelines[J]. Eur Urol, 2024, 86(1): 27-41. DOI: 10.1016/j.eururo.2024.03.035. [10] ANGER J T, BIXLER B R, HOLMES R S, et al. Updates to recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline[J]. J Urol, 2022, 208(3): 536-541. DOI: 10.1097/JU.0000000000002860. [11] BETSCHART C, ALBRICH W C, BRANDNER S, et al. Guideline of the Swiss Society of Gynaecology and Obstetrics (SSGO) on acute and recurrent urinary tract infections in women, including pregnancy[J]. Swiss Med Wkly, 2020, 150: w20236. DOI: 10.4414/smw.2020.20236. [12] DE CUETO M, ALIAGA L, ALÓS J I, et al. Executive summary of the diagnosis and treatment of urinary tract infection: Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC)[J]. Enferm Infecc Microbiol Clin, 2017, 35(5): 314-320. DOI: 10.1016/j.eimc.2016.11.005. [13] KRANZ J, SCHMIDT S, LEBERT C, et al. The 2017 update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and management of uncomplicated urinary tract infections in adult patients: part 1[J]. Urol Int, 2018, 100(3): 263-270. DOI: 10.1159/000486138. [14] KODNER C M, THOMAS GUPTON E K. Recurrent urinary tract infections in women: diagnosis and management[J]. Am Fam Physician, 2010, 82(6): 638-643. [15] KWOK M, MCGEORGE S, MAYER-COVERDALE J, et al. Guideline of guidelines: management of recurrent urinary tract infections in women[J]. BJU Int, 2022, 130(Suppl 3): 11-22. DOI: 10.1111/bju.15756. [16] SANTONI N, NG A, SKEWS R, et al. Recurrent urinary tract infections in women: what is the evidence for investigating with flexible cystoscopy, imaging and urodynamics?[J]. Urol Int, 2018, 101(4): 373-381. DOI: 10.1159/000490918. [17] SAUL H, DEENEY B, CASSIDY S, et al. Methenamine is as effective as antibiotics at preventing urinary tract infections[J]. BMJ, 2023, 380: 72. DOI: 10.1136/bmj.p72. [18] ARLANDIS S, BØ K, COBUSSEN-BOEKHORST H, et al. European association of urology guidelines on the management of female non-neurogenic lower urinary tract symptoms. part 2: underactive bladder, bladder outlet obstruction, and nocturia[J]. Eur Urol, 2022, 82(1): 60-70. DOI: 10.1016/j.eururo.2022.01.044. [19] ANGER J, LEE U, ACKERMAN A L, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline[J]. J Urol, 2019, 202(2): 282-289. DOI: 10.1097/JU.0000000000000296. [20] 沈平虎. 绝经生殖泌尿综合征临床诊疗专家共识 [J]. 中华妇产科杂志, 2020, 55(10): 659-666. DOI: 10.3760/cma.j.cn112141-20200610-00494. [21] KRANZ J, SCHMIDT S, LEBERT C, et al. The 2017 update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and management of uncomplicated urinary tract infections in adult patients. part II: therapy and prevention[J]. Urol Int, 2018, 100(3): 271-278. DOI: 10.1159/000487645. [22] NELSON Z, ASLAN A T, BEAHM N P, et al. Guidelines for the prevention, diagnosis, and management of urinary tract infections in pediatrics and adults: a WikiGuidelines Group consensus statement[J]. JAMA Netw Open, 2024, 7(11): e2444495. DOI: 10.1001/jamanetworkopen.2024.44495. [23] TILLOTSON G S. FDA and the safe and appropriate antibiotic use of fluoroquinolones[J]. Lancet Infect Dis, 2016, 16(3): e11-12. DOI: 10.1016/S1473-3099(16)00051-7. [24]

HADIDI M F, ALHAMAMI N, ALHAKAMI M, et al. Antibiotics efficacy in clinical and microbiological cure of uncomplicated urinary tract infection: a systematic review and network meta-analysis[J]. World J Urol, 2024, 42(1): 221. DOI: 10.1007/s00345-024-04922-5. [25] GUPTA K, GRIGORYAN L, TRAUTNER B. Urinary tract infection[J]. Ann Intern Med, 2017, 167(7): ITC49-ITC64. DOI: 10.7326/AITC201710030. [26] FLORES-MIRELES A L, WALKER J N, CAPARON M, et al. Urinary tract infections: epidemiology, mechanisms of infection and treatment options[J]. Nat Rev Microbiol, 2015, 13(5): 269-284. DOI: 10.1038/nrmicro3432. [27] HANNAN T J, ROBERTS P L, RIEHL T E, et al. Inhibition of cyclooxygenase-2 prevents chronic and recurrent cystitis[J]. EBioMedicine, 2014, 2(1): 66-73. DOI: 10.1016/j.ebiom.2014.10.011. [28] WHEELER M A, HAUSLADEN D A, YOON J H, et al. Prostaglandin E2 production and cyclooxygenase-2 induction in human urinary tract infections and bladder cancer[J]. J Urol, 2002, 168(4 Pt 1): 1568-1573. DOI: 10.1016/S0022-5347(05)64510-3. [29] GÁGYOR I, BLEIDORN J, KOCHEN M M, et al. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial[J]. BMJ, 2015, 351: h6544. DOI: 10.1136/bmj.h6544. [30] VIK I, BOLLESTAD M, GRUDE N, et al. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women-a double-blind, randomized non-inferiority trial[J]. PLoS Med, 2018, 15(5): e1002569. DOI: 10.1371/journal.pmed.1002569. [31] KRONENBERG A, BÜTIKOFER L, ODUTAYO A, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial[J]. BMJ, 2017, 359: j4784. DOI: 10.1136/bmj.j4784. [32] SCHAEFFER A J, STUPPY B A. Efficacy and safety of self-start therapy in women with recurrent urinary tract infections[J]. J Urol, 1999, 161(1): 207-211. [33] Urinary tract infection (recurrent): antimicrobial prescribing[EB/OL]. [2024-12-14]. https://www.nice.org.uk/guidance/ng112. [34] HOOTON T M, VECCHIO M, IROZ A, et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: a randomized clinical trial[J]. JAMA Intern Med, 2018, 178(11): 1509-1515. DOI: 10.1001/jamainternmed.2018.4204. [35] BOSLEY S, KRUEGER C G, BIRMINGHAM A, et al. Improved in vitro hemagglutination assays utilizing P-type and type 1 uropathogenic Escherichia coli to evaluate bacterial anti-adhesion activity of cranberry products[J]. J Diet Suppl, 2024, 21(3): 327-343. DOI: 10.1080/19390211.2023.2276962. [36] HOWELL A B, REED J D, KRUEGER C G, et al. A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity[J]. Phytochemistry, 2005, 66(18): 2281-2291. DOI: 10.1016/j.phytochem.2005.05.022. [37] MORO C, PHELPS C, VEER V, et al. Cranberry juice, cranberry tablets, or liquid therapies for urinary tract infection: a systematic review and network meta-analysis[J]. Eur Urol Focus, 2024, 10(6): 947-957. DOI: 10.1016/j.euf.2024.07.002. [38] DAVIS J A, FREEZE H H. Studies of mannose metabolism and effects of long-term mannose ingestion in the mouse[J]. Biochim Biophys Acta, 2001, 1528(2/3): 116-126. DOI: 10.1016/s0304-4165(01)00183-0. [39] FRONZES R, REMAUT H, WAKSMAN G. Architectures and biogenesis of non-flagellar protein

appendages in Gram-negative bacteria[J]. EMBO J, 2008, 27(17): 2271-2280. DOI: 10.1038/emboj.2008.155. [40] MICHAELS E K, CHMIEL J S, PLOTKIN B J, et al. Effect of D-mannose and D-glucose on Escherichia coli bacteriuria in rats[J]. Urol Res, 1983, 11(2): 97-102. DOI: 10.1007/BF00256954. [41] MYDOCK-MCGRANE L K, CUSUMANO Z T, JANETKA J W. Mannose-derived FimH antagonists: a promising anti-virulence therapeutic strategy for urinary tract infections and Crohn' s disease[J]. Expert Opin Ther Pat, 2016, 26(2): 175-197. DOI: 10.1517/13543776.2016.1131266. [42] HAYWARD G, MORT S, HAY A D, et al. D-mannose for prevention of recurrent urinary tract infection among women: a randomized clinical trial[J]. JAMA Intern Med, 2024, 184(6): 619-628. DOI: 10.1001/jamainternmed.2024.0264. [43] KASHOURIS E G. ALTAR trial of antibiotic alternative in recurrent urinary infection is a step towards a more collective conversation[J]. BMJ, 2022, 377: o914. DOI: 10.1136/bmj.o914. [44] OSSET J, BARTOLOMÉ R M, GARCÍA E, et al. Assessment of the capacity of Lactobacillus to inhibit the growth of uropathogens and block their adhesion to vaginal epithelial cells[J]. J Infect Dis, 2001, 183(3): 485-491. DOI: 10.1086/318070. [45] MASTROMARINO P, BRIGIDI P, MACCHIA S, et al. Characterization and selection of vaginal Lactobacillus strains for the preparation of vaginal tablets[J]. J Appl Microbiol, 2002, 93(5): 884-893. DOI: 10.1046/j.1365-2672.2002.01759.x. [46] ATASSI F, SERVIN A L. Individual and co-operative roles of lactic acid and hydrogen peroxide in the killing activity of enteric strain Lactobacillus johnsonii NCC933 and vaginal strain Lactobacillus gasseri KS120.1 against enteric, uropathogenic and vaginosis-associated pathogens[J]. FEMS Microbiol Lett, 2010, 304(1): 29-38. DOI: 10.1111/j.1574-6968.2009.01887.x. [47] ZÁRATE G, NADER-MACIAS M E. Influence of probiotic vaginal lactobacilli on in vitro adhesion of urogenital pathogens to vaginal epithelial cells[J]. Lett Appl Microbiol, 2006, 43(2): 174-180. DOI: 10.1111/j.1472-765X.2006.01934.x. [48] GUPTA K, STAPLETON A E, HOOTON T M, et al. Inverse association of H2O2-producing lactobacilli and vaginal Escherichia coli colonization in women with recurrent urinary tract infections[J]. J Infect Dis, 1998, 178(2): 446-450. DOI: 10.1086/515635. [49] NELWAN E J, HERDIMAN A, KALAIJ A G I, et al. Role of probiotic as adjuvant in treating various infections: a systematic review and meta-analysis[J]. BMC Infect Dis, 2024, 24(1): 505. DOI: 10.1186/s12879-024-09259-3. [50] BEEREPOOT M J, GEERLINGS S E, VAN HAARST E P, et al. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials[J]. J Urol, 2013, 190(6): 1981-1989. DOI: 10.1016/j.juro.2013.04.142. [51] CANALES J, RADA G. Are probiotics effective in preventing urinary tract infection?[J]. Medwave, 2018, 18(2): e7186. DOI: 10.5867/medwave.2018.02.7185. [52] GRIN P M, KOWALEWSKA P M, ALHAZZAN W, et al. Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis[J]. Can J Urol, 2013, 20(1): 1-7. [53] NG Q X, PETERS C, VENKATANARAYANAN N, et al. Use of Lactobacillus spp. to prevent recurrent urinary tract infections in females[J]. Med Hypotheses, 2018, 114: 49-54. DOI: 10.1016/j.mehy.2018.03.001. [54] LÜTHJE P, HIRSCHBERG A L,

BRAUNER A. Estrogenic action on innate defense mechanisms in the urinary tract[J]. Maturitas, 2014, 77(1): 32-36. DOI: 10.1016/j.maturitas.2013.10.018. [55] RAZ R, STAMM W E. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections[J]. N Engl J Med, 1993, 329(11): 753-756. DOI: 10.1056/NEJM199309093291102. [56] CHRISTMAS M M, IYER S, DAISY C, et al. Menopause hormone therapy and urinary symptoms: a systematic review[J]. Menopause, 2023, 30(6): 672-685. DOI: 10.1097/GME.0000000000002187. [57] MARSHBURN P B, CARR B R. Hormone replacement therapy. Protection against the consequences of menopause[J]. Postgrad Med, 1992, 92(4): 145-148, 151-152, 157-159. DOI: 10.1080/00325481.1992.11701471. [58] CHEN Y Y, SU T H, LAU H H. Estrogen for the prevention of recurrent urinary tract infections in postmenopausal women: a meta-analysis of randomized controlled trials[J]. Int Urogynecol J, 2021, 32(1): 17-25. DOI: 10.1007/s00192-020-04397-z. [59] ANTONIOU V, SOMANI B K. Topical and oral oestrogen for recurrent urinary tract infection-evidence-based review of literature, treatment recommendations, and correlation with the European association of urology guidelines on urological infections[J]. Eur Urol Focus, 2022, 8(6): 1768-1774. DOI: 10.1016/j.euf.2022.05.006. [60] SCHMIDHAMMER S, RAMONER R, HÖLTL L, et al. An Escherichia coli-based oral vaccine against urinary tract infections potently activates human dendritic cells[J]. Urology, 2002, 60(3): 521-526. DOI: 10.1016/s0090-4295(02)01767-3. [61] HA U S, CHO Y H. Immunostimulation with Escherichia coli extract: prevention of recurrent urinary tract infections[J]. Int J Antimicrob Agents, 2008, 31(Suppl 1): S63-S67. DOI: 10.1016/j.ijantimicag.2007.07.018. [62] VAN PHAM T, KREIS B, CORRADIN-BETZ S, et al. Metabolic and functional stimulation of lymphocytes and macrophages by an Escherichia coli extract (OM-89): in vitro studies[J]. J Biol Response Mod, 1990, 9(2): 231-240. [63] MAK Q, GREIG J, DASGUPTA P, et al. Bacterial vaccines for the management of recurrent urinary tract infections: a systematic review and meta-analysis[J]. Eur Urol Focus, 2024, 10(5): 761-769. DOI: 10.1016/j.euf.2024.04.002. [64] BRODIE A, EL-TAJI O, JOUR I, et al. A retrospective study of immunotherapy treatment with uro-vaxom (OM-89®) for the prophylaxis of recurrent urinary tract infections[J]. Curr Urol, 2020, 14(3): 130-134. DOI: 10.1159/000499248. [65] KRAAN H, VRIELING H, CZERKINSKY C, et al. Buccal and sublingual vaccine delivery[J]. J Control Release, 2014, 190: 580-592. DOI: 10.1016/j.jconrel.2014.05.060. [66] CZERKINSKY C, CUBURU N, KWEON M N, et al. Sublingual vaccination[J]. Hum Vaccin, 2011, 7(1): 110-114. DOI: 10.4161/hv.7.1.13739. [67] CURTIS NICKEL J, SAZ-LEAL P, CHRISTOPHER DOIRON R. Could sublingual vaccination be a viable option for the prevention of recurrent urinary tract infection in Canada? A systematic review of the current literature and plans for the future[J]. Can Urol Assoc J, 2020, 14(8): 281-287. DOI: 10.5489/cuaj.6690. [68] LORENZO-GÓMEZ M F, FOLEY S, CURTIS NICKEL J, et al. Sublingual MV140 for prevention of recurrent urinary tract infections[J]. NEJM Evid, 2022, 1(4): EVIDoa2100018. DOI: 10.1056/EVIDoa2100018. [69]

NESTLER S, PESCHEL C, HORSTMANN A H, et al. Prospective multicentre randomized double-blind placebo-controlled parallel group study on the efficacy and tolerability of StroVac® in patients with recurrent symptomatic uncomplicated bacterial urinary tract infections[J]. Int Urol Nephrol, 2023, 55(1): 9-16. DOI: 10.1007/s11255-022-03379-y. [70] EGGERS A, BALLÜER M, MOHAMED B A, et al. A suspension of inactivated bacteria used for vaccination against recurrent urinary tract infections increases the phagocytic activity of murine macrophages[J]. Front Immunol, 2023, 14: 1180785. DOI: 10.3389/fimmu.2023.1180785. [71] PARSONS C L, BOYCHUK D, JONES S, et al. Bladder surface glycosaminoglycans: an epithelial permeability barrier[J]. J Urol, 1990, 143(1): 139-142. DOI: 10.1016/s0022-5347(17)39897-x. [72] CICIONE A, CANTIELLO F, UCCIERO G, et al. Restoring the glycosaminoglycans layer in recurrent cystitis: experimental and clinical foundations[J]. Int J Urol, 2014, 21(8): 763-768. DOI: 10.1111/iju.12430. [73] HAUSER P J, BUETHE D A, CALIFANO J, et al. Restoring barrier function to acid damaged bladder by intravesical chondroitin sulfate[J]. J Urol, 2009, 182(5): 2477-2482. DOI: 10.1016/j.juro.2009.07.013. [74] REDDY M, ZIMMERN P E. Efficacy of antimicrobial intravesical treatment for uncomplicated recurrent urinary tract infections: a systematic review[J]. Int Urogynecol J, 2022, 33(5): 1125-1143. DOI: 10.1007/s00192-021-05042-z. [75] DAMIANO R, QUARTO G, BAVA I, et al. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial[J]. Eur Urol, 2011, 59(4): 645-651. DOI: 10.1016/j.eururo.2010.12.039. [76] OCHOA D C, HEALY R. Intravesical agents for prevention of recurrent urinary tract infections[J]. Eur Urol Focus, 2024, 10(5): 726-730. DOI: 10.1016/j.euf.2024.08.001. [77] NALLIAH S, FONG J S H, YI THOR A Y, et al. The use of chemotherapeutic agents as prophylaxis for recurrent urinary tract infection in healthy nonpregnant women: a network meta-analysis[J]. Indian J Urol, 2019, 35(2): 147-155. DOI: 10.4103/iju.IJU_{{{378}}_{{18}}}. [78] AHMED H, DAVIES F, FRANCIS N, et al. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials[J]. BMJ Open, 2017, 7(5): e015233. DOI: 10.1136/bmjopen-2016-015233. [79] PRICE J R, GURAN L A, GREGORY W T, et al. Nitrofurantoin vs other prophylactic agents in reducing recurrent urinary tract infections in adult women: a systematic review and meta-analysis[J]. Am J Obstet Gynecol, 2016, 215(5): 548-560. DOI: 10.1016/j.ajog.2016.07.040. [80] ALBERT X, HUERTAS I, PEREIRÓ I I, et al. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women[J]. Cochrane Database Syst Rev, 2004, 2004(3): CD001209. DOI: 10.1002/14651858.CD001209.pub2. [81] EELLS S J, BHARADWA K, MCKINNELL J A, et al. Recurrent urinary tract infections among women: comparative effectiveness of 5 prevention and management strategies using a Markov chain Monte Carlo model[J]. Clin Infect Dis, 2014, 58(2): 147-160. DOI: 10.1093/cid/cit646. [82] EPP A, LAROCHELLE A. No. 250-recurrent urinary tract infection[J]. J Obstet Gynaecol Can, 2017, 39(10): e422-431. DOI: 10.1016/j.jogc.2017.08.017. [83] LICHTENBERGER

P, HOOTON T M. Antimicrobial prophylaxis in women with recurrent urinary tract infections[J]. Int J Antimicrob Agents, 2011, 38 Suppl: 36-41. DOI: 10.1016/j.ijantimicag.2011.09.005. [84] SEN A Y. Recurrent cystitis in non-pregnant women[J]. BMJ Clin Evid, 2008, 2008: 0801. [85] CHEW L D, FIHN S D. Recurrent cystitis in nonpregnant women[J]. West J Med, 1999, 170(5): 274-277. [86] FISHER H, OLUBOYEDE Y, CHADWICK T, et al. Continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (AnTIC): a randomised, open-label trial[J]. Lancet Infect Dis, 2018, 18(9): 957-968. DOI: 10.1016/S1473-3099(18)30279-2. [87] JENT P, BERGER J, KUHN A, et al. Antibiotics for preventing recurrent urinary tract infection: systematic review and meta-analysis[J]. Open Forum Infect Dis, 2022, 9(7): ofac327. DOI: 10.1093/ofid/ofac327.

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