



Review

Preventing urinary tract infections after menopause without antibiotics



Marta Caretto, Andrea Giannini, Eleonora Russo, Tommaso Simoncini*

University of Pisa, Italy

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ABSTRACT

Urinary tract infections (UTIs) are the most common bacterial infections in women, and increase in incidence after the menopause. It is important to uncover underlying abnormalities or modifiable risk factors. Several risk factors for recurrent UTIs have been identified, including the frequency of sexual intercourse, spermicide use and abnormal pelvic anatomy. In postmenopausal women UTIs often accompany the symptoms and signs of the genitourinary syndrome of menopause (GSM). Antimicrobial prophylaxis has been demonstrated to be effective in reducing the risk of recurrent UTIs in women, but this may lead to drug resistance of both the causative microorganisms and the indigenous flora. The increasing prevalence of *Escherichia coli* (the most prevalent uropathogen) that is resistant to antimicrobial agents has stimulated interest in novel non-antibiotic methods for the prevention of UTIs. Evidence shows that topical estrogens normalize vaginal flora and greatly reduce the risk of UTIs. The use of intravaginal estrogens may be reasonable in postmenopausal women not taking oral estrogens. A number of other strategies have been used to prevent recurrent UTIs: probiotics, cranberry juice and D-mannose have been studied. Oral immunostimulants, vaginal vaccines and bladder instillations with hyaluronic acid and chondroitin sulfate are newer strategies proposed to improve urinary symptoms and quality of life. This review provides an overview of UTIs' prophylaxis without antibiotics, focusing on a practical clinical approach to women with UTIs.

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* Corresponding author at: Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Italy.
E-mail address: tommaso.simoncini@med.unipi.it (T. Simoncini).

1. UTIs in ageing women

Urinary tract infections (UTIs) are the most common bacterial infections in women and their incidence rises dramatically in postmenopausal women. Approximately 20%–30% of women with UTIs will have a recurrence. Recurrent UTIs (rUTIs) are defined as at least three episodes of UTIs in twelve months, or at least two episodes in six months. rUTIs can be a relapse or a reinfection. A relapse refers to UTIs caused by the same microorganism after adequate treatment. Reinfections are rUTIs caused by a different microorganism or by a previously isolated microorganism after treatment and a subsequent negative urine culture. The majority of rUTIs is caused by reinfection from extraurinary sources such as the rectum or vagina: uropathogenic *Escherichia coli* (UPEC) is now known to invade urothelial cells and form a quiescent intracellular bacterial reservoir [1].

The first step in the management of rUTIs is to obtain a detailed history, including information about previously UTIs' episodes, menopausal status, recent antibiotic use, and sexual history, including number of partners, spermicide use and use of barrier contraceptives. The second step is a physical examination: complete pelvic examination to analyze vaginal epithelium, urinary incontinence (UI), the presence or absence of pelvic organ prolapse (POP) [2]. Antibiotics, even at low-doses, are effective in the treatment and prophylaxis of UTIs but lead to an increase antibiotic resistance in microorganisms [3].

2. Strategies to prevent and manage UTIs in ageing women

Several strategies have been proposed for preventing rUTIs and the first is a change in behavior. It is reasonable to suggest to women with rUTIs a different contraceptive (avoiding spermicides) or early postcoital voiding and more liberal fluid intake to increase the frequency of micturition [4].

3. Estrogens and UTIs

Menopausal estrogen withdrawal is associated with a decrease in volume of the vaginal muscles and of the muscles of the pelvic floor. This, along with the vascular changes in the pelvic and periurethral districts and with the increases looseness of the pelvic ligaments favors the development of UI and POP [5]. Estrogen stimulates the proliferation of lactobacillus, reduces vaginal pH, and avoids vaginal colonization of Enterobacteriaceae. Pabich et al. have studied the association between UTIs and other peculiarities of ageing women (incontinence, diabetes, the use of HRT), with vaginal microbial flora. Their data suggest that the restoration of vaginal lactobacilli via topical estrogen in postmenopausal women with rUTIs could be associated with a marked reduction in UTIs incidence [6].

Systemic estrogens are rarely a clinical option for older women. However, vaginal estrogens remain a life-long opportunity to treat vulvo-vaginal atrophy (VVA) even at later stages in life, and this is considered a viable option to prevent UTIs, as well. Indeed, a trial performed by Raz and Stamm [7] and a study by Eriksen [8] show that vaginal estrogens significantly reduced the incidence of UTIs and the frequency of urogenital symptoms, such as VVA and UI. However, contradicting results are found in the literature: another study showed that the use of vaginal estrogens is less effective to prevent rUTIs than antibiotic therapy.

In conclusion, in postmenopausal women there is a trend toward fewer UTIs recurrences with vaginal estrogens, which was not seen with oral estrogens. Vaginal estrogens are safe and effective [9], however long-term adherence is an issue with most patients, with high dropout rates. The recent introduction of

Ospemifene, an orally available selective estrogen receptor modulator with the indication of prevention and treatment of VVA, may represent a new option for those patients who are intolerant to long-term use of vaginal estrogens. However, data on its possible effect on UTIs prevention are currently missing [10].

4. Vitamin D and UTIs

Vitamin D could enhance cathelicidin production in the urinary tract and thereby help protecting from microbial invasion. This could make 25-OH D3 an effective and safe way of activating the endogenous antimicrobial response locally at the site of infection [11]. Restoring proper vitamin D levels in postmenopausal women with a history of rUTIs may therefore help the bladder epithelium to prepare a stronger and faster immune response once bacteria enter the bladder.

5. Use of probiotics for the prevention and treatment of UTIs

Vaginal lactobacilli have protective roles: they are able to produce antimicrobial compounds such as lactic acid, hydrogen peroxide; to produce a biosurfactant that inhibits the adhesion of uropathogens to surfaces; and to stimulate non-specific innate immune system. Restoration of vaginal flora with lactobacilli using probiotics is an effective strategy to decrease the frequency of UTIs.

A recent study suggests that the administration of vaginal suppositories containing *L. crispatus* GAI 98332 is safe and effective in preventing rUTIs. Evidence show that *L. rhamnosus* Gr-1 and *L. fermentum*-RC can also colonize the vagina. However, clinical studies that determine the optimal dosage, duration and mode of lactobacilli delivery for establishing vaginal and/or periurethral colonization are still lacking [12].

6. Cranberry in the prevention and treatment of UTIs

Cranberry contains a proanthocyanidin that counteracts bladder colonization by *E. coli* by inhibiting the attachment of bacteria to the uroepithelial mucosa. Anti-inflammatory activity of cranberry extract prevents the development of symptoms but also to lower intercellular bacterial propagation, and thus reduces the frequency of UTIs and the propensity towards chronic infection.

Evidence shows that consumption of cranberry juice significantly reduces clinical UTIs' episodes in women with a history of UTIs in the previous year and antibiotic use for treatment of these events [13]. A more recent Cochrane review reports a non-significant reduction in risk of rUTIs with cranberry treatment and a study by Juthani-Mehta et al. supports the view that cranberry products should not be recommended as a medical intervention for the prevention of rUTIs [14].

In spite of these data, literature as well as expert opinion is still conflicting on the clinical role of cranberry to prevent UTIs. In the wake of conclusive data, cranberry remains a popular and safe approach in the management of UTIs.

7. D-Mannose and UTIs

D-Mannose is a simple sugar, a monosaccharide, closely related to glucose. D-Mannose is rapidly absorbed and then excreted by the urinary tract. The bladder wall is coated with various mannose-late proteins, such as Tamm-Horsfall protein (THP) that interfere directly with the adhesion of bacteria on the mucosa. THP may fasten to *E. coli* with a specific bond, which may be inhibited by exogenous D-mannose. This provides the rationale for use of D-

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