



Mini Review

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Alternative Management of Uncomplicated UTIs in Women



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Abstract

UTIs typically cause women to have a severe urge to urinate, and to do so frequently. It's also often very painful when they do, and many experiences a burning sensation in their bladder or urethra. Two common factors emerged in urine that had a better ability to resist bacterial growth: it had a high pH-one that's more alkaline, in other words-and higher levels of certain metabolites formed by gut microbes. Physicians already know how to raise urinary pH with things like calcium supplements, and alkalinizing agents are already used in the U.K. as over-the-counter UTI treatments. However, early on in an infection, cells produce a protein called siderocalin that blocks bacterial growth, including the growth of *E. coli*. Uncomplicated UTIs usually go away with drugs within two to three weeks, but in some cases, women may take antibiotics for 6 months or longer if their UTIs keep coming back. Most UTIs are caused by the bacteria *Escherichia coli* (*E. coli*), and recent surveillance data shows a significant rise in cases of UTIs caused by *E. coli* that are resistant to the antibiotics most commonly used to treat them. Doctors say "It's uncomfortable but not life-threatening, so women don't go in" [1].

Keywords: *Escherichia coli*; Cystitis; Recurrent UTIs; Bacterial biofilm; Fluid consumption; Essential oil

Abbreviations: RUTIs: Recurrent UTIs; IC/BPS: Interstitial Cystitis/Bladder Pain Syndrome; ASB: Asymptomatic Bacteriuria; DMSO: Dimethylsulfoxide; CHM: Chinese Herbal Medicine; AMPs: Endogenous Antimicrobial Peptides; IC/BPS: Interstitial Cystitis/Bladder Pain Syndrome

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UTIs are among the most common causes of sepsis presenting to hospitals (Figure 1). Typically, this is an infection in a nonpregnant immune competent female patient [2]. Pathogenic bacteria ascend from the perineum, causing UTI. Women have shorter urethras, with its close relationship to the anus, makes it easy for bacteria to ascend in the urinary tract with chances of fecal-perineal-urethral contamination [3-5]. Between 50% and 60% of adult women will have at least one UTI in their life, and close to 10% of postmenopausal women indicate that they had a UTI in the previous year, according to Medina et al. [6]. Recurrent UTIs (RUTIs) are mainly caused by reinfection by the same pathogen mostly caused by frequent sexual intercourse, heterosexual lack of circumcision receptive anal intercourse (without a condom), multiple sexual partners (Each sex partner shares his/her UGT microbiota with the other), use of spermicide and a new sexual partner [7-17]. Many other factors have been thought to predispose women to RUTIs, such as voiding patterns pre- and post-co-

itus, wiping technique, wearing tight undergarments, deferred voiding habits and vaginal douching; nevertheless, there has been no proven association [18]. Obesity was found to be associated with RUTIs in premenopausal women [19]. Several other risk factors are associated with cystitis, a prior UTI, vaginal infection, diabetes, and genetic susceptibility [20]. Pathogens responsible most commonly are *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis* and *Staphylococcus saprophyticus* [7,20-24]. The role of dietary habits in recurrent UTI is also not clear. Increasing fluid consumption is often recommended for patients with UTI [3,15,21-28] but there has been no clear clinical evidence to support this recommendation [29]. After a first episode of a UTI, 27% of women have a confirmed recurrence within the next 6 months [6]. Approximately one-third of women will have had UTI by age 24 and one half by age 32 [17]. Bacterial infections tend to account for 80% of all UTIs, and antibiotics may sometimes prove ineffective. Parvizi et al. [30] stated that UTIs can be associated with

myriad symptoms (e.g., fever, chill, pain, leukocytosis, and pyuria), or present as asymptomatic bacteriuria (ASB). Shih et al. [31]. revealed that UTI is the 3rd leading cause of infection in home care population, leading to 4.4% of overall unplanned hospitalizations in US [31]. Although the estimated mortality rate is generally low but it may rise 25%-30% if complicated with bacteremia or septic shock [2,31-34]. Gaitonde et.al, 2019 estimated that cost of acute RUTI workup ranged from \$390 to \$730 [35]. Urinary tract infections are a common reason for healthcare visits. In the United States, UTIs result in an estimated 7 million office visits, 1 million emergency department visits, and over 100000 hospitalizations with an associated annual cost of \$3.5 billion [20,25,36-41]. Within a year of infection, 27% to 46% of women will have another UTI. A physical examination with acute uncomplicated cystitis is typically normal except in 10% to 20% of women with suprapubic tenderness [42]. According to Nickel et.al, 2019 approximately 3.8 million women and 1.4 million men suffer from Interstitial cystitis/bladder pain syndrome (IC/BPS) in US. Amitriptyline, cimetidine, hydroxyzine, pentosanpolysulfate sodium while intravesical instillations of dimethylsulfoxide (DMSO), heparin or lidocaine are employed when medical therapy is not successful [43]. Symptoms may vary over time, periodically flaring in response to common triggers, such as menstruation, sitting for a long time, stress, exercise, and sexual activity [44]. "Honeymoon cystitis" is a very real medical condition, occurs whenever vaginal intercourse leads to burning sensation during urination [45,46]. Pyuria and/or bacteriuria without any symptoms is not a UTI and may not require treatment. Many cases of uncomplicated UTI will resolve spontaneously, without treatment, but many patients seek treatment for symptoms. Treatment is aimed at preventing spread to the kidneys or developing into upper tract disease/pyelonephritis, which can cause the destruction of the delicate structures in the nephrons and lead to hypertension [47-49]. Symptomatic treatments available OTC from community pharmacies include alkalinizing agents, cranberry products, and analgesia. Although urine alkalization (for example, with potassium or sodium citrate) has traditionally been used to relieve UTI symptoms, there is little evidence to support its use [50]. Shaheen et al. [31] reported that *Vaccinium macrocarpon*, *Tribulus terrestris*, *Trachyspermum copticum*, *Cinnamomum verum* and *Hybanthus easpermus* are some common medicinal plants reported to have therapeutic potential for the management and cure of the UTI [51]. Lagha et al. [52] revealed that Essential oil from *Origanum majorana*, *Thymus zygis* and *Rosmarinus officinalis* showed potential antibacterial activity [52]. Anti-biofilm effect of cranberry juice with natural borne antimicrobials derived from coconut oil (caprylic acid) and oregano essential oil (thymol) could synergistically enhance its eradicating activity against *E. coli* biofilms [53]. Bruyère et al. [54] demonstrated for the first time that cranberry and propolis supplementation significantly reduces the incidence of UTIs during the first 3 months and delays the onset of an episode of cystitis. *Tribulus terrestris* induces its effect in fer-

tility, sexual functions and southerner through the steroidal saponins, particularly the dominant saponins protodioscin [55]. Yap et al. [56] reported that essential oil of *Cinnamomum verum* has the potential to reverse *E. coli* J53 R1 resistance to piperacillin through two pathways; modification in the permeability of the outer membrane or bacterial QS inhibition [56]. Ebani et al. [57] reported that *T. vulgaris* and *O. vulgare* essential oils showed the strongest antimicrobial activity against *E. coli*, *Enterococcus* spp., *C. albicans* and *C. famata* [57]. EU has approved the rosemary extract (E392) as a safe and effective natural antioxidant for food preservation. It has potential anti-inflammatory, antioxidant, antimicrobial, protective, inhibitory and attenuating activities [58]. Flower et.al [59] suggested that Chinese Herbal Medicine (CHM) in conjunction with antibiotics may be beneficial for treating recurrent UTIs. D-mannose can be an effective aid in acute cystitis management and also a successful prophylactic agent in a selected population [60-62]. Duncan et al. [63] reported that it may be useful for UTI prevention instead of prophylactic antibiotics, which was no different than in Nitrofurantoin group [64]. While research has proven this to be effective, there is a risk that long-term antibiotic use will increase the likelihood of bacteria becoming resistant to antibiotics. Trill et al. [64] stated that Urine is now the most commonly received specimen in microbiological laboratories, but more than 20% of isolates are resistant to trimethoprim and cephalosporins and 50% are resistant to amoxicillin [65]. Several fruits, vegetables and supplements contain D-mannose, including: cranberry (*Vaccinium macrocarpon*), apples, oranges, peaches, broccoli, green beans, dandelion extract, hibiscus, rose hips, probiotics [66]. Marshmallow Root (*Althea officinalis*) is the great soother of the kidney system [67]. The leaf extract of *Arctostaphylos uva-ursi* (bearberry) has been approved for use for urinary tract inflammation by the German Federal Institute for Drugs and Medical Devices and is available on prescription in Germany for this indication. It was found safe and effective in combination with ibuprofen for relief of the distressing symptoms of uncomplicated UTI in women [64,68]. Although there have been few studies on the prevention of recurrent UTIs without use of antibiotics within the past years, interest probiotics has increased over the years. Reviews by Akgül et al. [69] concluded that evidence of probiotic application in UTIs is not yet sufficient to recommend use of probiotics. Different vaccines based on the whole cells (killed or live-attenuated vaccines) and antigens (subunits, toxins and conjugated vaccines) have been evaluated against UTIs pathogens by Asadi et al. [70]. Substantial efforts have been expended in development of endogenous antimicrobial peptides (AMPs) as new therapeutic options suitable in the treatment of drug-resistant microbial infections. For example, Wnorowska et al. [71] reported that combination of natural peptide LL-37 with synthetic analogs might be a potential solution to treat UTIs caused by drug-resistant bacteria [71]. Finally, a simple lifestyle modification is suggested with uncomplicated UTI patients like avoiding coffee, alcohol, and soft drinks containing citrus juices or caf-

feine until infection has cleared. They can irritate bladder and tend to aggravate frequent or urgent need to urinate. Applying warm, but not hot, heating pad on abdomen to minimize bladder pressure or discomfort. There's weak but little evidence of relationship between UTI risk with pre- or post-coital voiding, frequency of urination, delayed voiding habits, wiping patterns, douching, use of hot tubs, use of tampons, use of pantyhose or tights and asking male partners to wash under their foreskin (prepuce) if uncircumcised to reduce bacterial load. Whilst without significant evidence to support their practices, the lack of harm associated with many of these suggestions leads to their ongoing recommendation.



Figure 1: Pain and Depression [1]. The sudden, unforeseeable, and distressing nature of painful UTI episodes often causes patient anxiety. The resulting social handicap is known to induce feelings of self-devaluation or culpability, which can lead to clinical symptoms of depression. In a study of patients' quality of life (QoL) and recurrent UTI, Renard et.al 2014 revealed that more than 60% patients exhibited some degree of depression at baseline.

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