

Recurrent Urinary Tract Infection

This Clinical Practice Guideline has been prepared by the Urogynaecology Committee, reviewed by the Family Physicians Advisory Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Key Words: Recurrent urinary tract infection, prophylaxis, treatment, antibiotic, prevention

Abstract

Objective: To provide an update of the definition, epidemiology, clinical presentation, investigation, treatment, and prevention of recurrent urinary tract infections in women.

Options: Continuous antibiotic prophylaxis, post-coital antibiotic prophylaxis, and acute self-treatment are all efficient alternatives to prevent recurrent urinary tract infection. Vaginal estrogen and cranberry juice can also be effective prophylaxis alternatives.

Evidence: A search of PubMed and The Cochrane Library for articles published in English identified the most relevant literature. Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date restrictions.

Values: This update is the consensus of the Sub-Committee on Urogynaecology of the Society of Obstetricians and Gynaecologists of Canada. Recommendations were made according to the guidelines developed by the Canadian Task Force on Preventive Health Care (Table 1).

Options: Recurrent urinary tract infections need careful investigation and can be efficiently treated and prevented. Different prophylaxis options can be selected according to each patient's characteristics.

Recommendations

1. Urinalysis and midstream urine culture and sensitivity should be performed with the first presentation of symptoms in order to establish a correct diagnosis of recurrent urinary tract infection. (III-L)
2. Patients with persistent hematuria or persistent growth of bacteria aside from *Escherichia coli* should undergo cystoscopy and imaging of the upper urinary tract. (III-L)
3. Sexually active women suffering from recurrent urinary tract infections and using spermicide should be encouraged to consider an alternative form of contraception. (II-2B)
4. Prophylaxis for recurrent urinary tract infection should not be undertaken until a negative culture 1 to 2 weeks after treatment has confirmed eradication of the urinary tract infection. (III-L)
5. Continuous daily antibiotic prophylaxis using cotrimoxazole, nitrofurantoin, cephalexin, trimethoprim, trimethoprim-sulfamethoxazole, or a quinolone during a 6- to 12-month period should be offered to women with ≥ 2 urinary tract infections in 6 months or ≥ 3 urinary tract infections in 12 months. (I-A)
6. Women with recurrent urinary tract infection associated with sexual intercourse should be offered post-coital prophylaxis as an alternative to continuous therapy in order to minimize cost and side effects. (I-A)

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.⁸²

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.⁸²

7. Acute self-treatment should be restricted to compliant and motivated patients in whom recurrent urinary tract infections have been clearly documented. (I-B)
8. Vaginal estrogen should be offered to postmenopausal women who experience recurrent urinary tract infections. (I-A)
9. Patients should be informed that cranberry products are effective in reducing recurrent urinary tract infections. (I-A)
10. Acupuncture may be considered as an alternative in the prevention of recurrent urinary tract infections in women who are unresponsive to or intolerant of antibiotic prophylaxis. (I-B)
11. Probiotics and vaccines cannot be offered as proven therapy for recurrent urinary tract infection. (II-2C)
12. Pregnant women at risk of recurrent urinary tract infection should be offered continuous or post-coital prophylaxis with nitrofurantoin or cephalexin, except during the last 4 weeks of pregnancy. (II-1B)

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DEFINITION AND EPIDEMIOLOGY

Urinary tract infection is one of the most common bacterial infections in women, and 50% to 60% of adult women experience a UTI during their lifetime.^{1,2} It is

estimated that in young women there are 0.5 episodes of acute cystitis per person per year.³ This incidence decreases with age. In postmenopausal women, it is estimated that there are 0.07 episodes of acute cystitis per person per year.⁴

Recurrent UTI is defined as 2 uncomplicated UTIs in 6 months or, more traditionally, as ≥ 3 positive cultures within the preceding 12 months.^{5,6} This is estimated to affect 25% of women with a history of UTI. When there is recurrent infection with the same organism despite adequate therapy, it is considered a relapse. Reinfection is defined as recurrent UTI caused by a different bacterial isolate, or by the previously isolated bacteria after a negative intervening culture or an adequate time period (≥ 2 weeks) between infections.⁷

Reinfection is more common than relapse.⁸ Most recurrences occur within the first 3 months after the primary infection, and there can often be clustering of infections.^{9,10} When the initial infection is caused by *E. coli*, there is a higher risk of reinfection within the first 6 months.¹¹

PRESENTATION

Classic symptoms of acute lower UTI include dysuria, urinary frequency, and suprapubic pain plus or minus hematuria. Differential diagnoses include vaginitis, acute urethritis, interstitial cystitis, and pelvic inflammatory disease. Other organisms that may be involved and mimic acute cystitis include *Chlamydia*, *Neisseria gonorrhoea*, *Candida*,

ABBREVIATIONS

<i>E. coli</i>	<i>Escherichia coli</i>
HPF	high-power field
TMP-SMX	trimethoprim-sulfamethoxazole
UTI	urinary tract infection

bacterial vaginosis, and herpes simplex virus.¹² Classic symptoms seem to be highly predictive of true disease. If dysuria, frequency, and hematuria are present in the absence of vaginal discharge, the probability of a positive culture is 81%.¹² Women with recurrent UTI can self-diagnose on the basis of symptoms very accurately, with an 84% positive culture rate.¹³ Positive predictive factors for recurrent UTIs in women are symptoms after intercourse, a prior history of pyelonephritis, absence of nocturia, and prompt resolution of symptoms (48 hours) after initiation of treatment. The main negative predictors are the presence of nocturia and persistence of symptoms between episodes of treated infection.⁵

PATHOPHYSIOLOGY

The main causative pathogen involved in recurrent UTI in women is *E. coli*, which is responsible for approximately 80% of all episodes of infection. Other significant pathogens include *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, which each cause approximately 4% of all episodes of acute cystitis. *Citrobacter* and Enterococci are less likely causes of UTI in women.¹⁴ Infection with organisms that do not usually cause UTIs may be an indicator of underlying structural abnormalities or renal calculi.⁷

Uropathogenic *E. coli* have virulence factors, such as the type of fimbria, that promote binding to the epithelium of the vagina and urethra and enhance their ability to cause cystitis. Other factors increase resistance to serum bactericidal activity and host defence mechanisms. Animal models suggest that *E. coli* can remain dormant in large bacterial reservoirs within the host and be reactivated to cause infection in the future.¹⁵ In a 2007 study,¹⁶ midstream urine samples from women with acute uncomplicated cystitis also showed evidence of intracellular bacterial communities of uropathogenic *E. coli*. These communities are relatively protected from host immune response mechanisms and antibiotic therapy and may reactivate, causing recurrent UTI.¹⁶

In the classic theory for development of UTI, the uropathogen is part of the fecal flora. It colonizes the vagina and distal urethra. Subsequently, it ascends into the bladder and causes infection. This model is the same for sporadic and for recurrent UTI in women.^{8,17} Reservoirs of uropathogenic bacteria can remain in the gastrointestinal tract and vagina of the susceptible individual. The results of one study suggest that household members, including pets, could act as reservoirs for the recolonization of a person with UTI.¹⁸ Lactobacilli in the vagina are protective, because they prevent initial colonization with uropathogens.¹⁹

RISK FACTORS

Premenopausal Women

In young women who suffer from recurrent UTIs there are behavioural risk factors at play. These include increased frequency of intercourse, use of a spermicide, and new sexual partners.²⁰ Intercourse and spermicide exposure increase the rate of vaginal and periurethral colonization with *E. coli*. When a first UTI is caused by *E. coli*, the risk of a second infection within 6 months is greater than when a first infection is caused by another uropathogen.¹¹ Dysfunctional voiding patterns in which there is increased tone of the external sphincter during micturition can also be associated with recurrent UTI in otherwise urologically normal women.²¹ There are also some non-behavioural risk factors for recurrent UTI in young women. These include a history of UTI before age 15 and a maternal history of UTI. This suggests that there are also anatomic and genetic factors involved.²⁰ Most women with recurrent UTI do not have any functional or anatomic abnormalities of the urinary tract, and extensive radiologic and cystoscopic examination is not indicated.^{8,22}

Postmenopausal Women

In premenopausal women, 90% of the vaginal flora are lactobacilli, which protects against colonization with uropathogens such as *E. coli*. Estrogen loss at menopause results in thinning of the vaginal epithelium and decreased amounts of glycogen. The resulting environment is hostile to lactobacilli, and the numbers decrease. The vaginal pH increases, and there is an increased propensity for colonization with uropathogens.¹⁰ Women who are non-secretors of histocompatibility blood-group antigens are at increased risk of recurrent UTI. This is thought to be a result of attachment of P-fimbriated *E. coli* to glycolipids on vaginal and uroepithelial cells.¹⁰ Non-secretor status is a more significant risk factor in postmenopausal than in premenopausal women.

Postmenopausal women who suffer from incontinence and who have significant pelvic floor prolapse and elevated post-void residual volumes are at increased risk for recurrent UTI.¹⁰

Other significant factors for recurrent UTI in postmenopausal woman are diabetes mellitus and a previous history of UTI.³

INVESTIGATION

All women with recurrent UTI should undergo a physical examination to evaluate urogenital anatomy and estrogenization of vaginal tissues and to detect prolapse. Post-void residual urine volume should be measured. Diabetes screening is indicated in patients with other risk

factors, such as family history and obesity. Most women do not require extensive urologic investigations.^{8,22} However, women who suffer infection with organisms that are not common causes of UTI, such as *Proteus*, *Pseudomonas*, *Enterobacter*, and *Klebsiella* may have structural abnormalities or renal calculi. They would benefit from imaging studies of the upper urinary tract and cystoscopy.⁷ Women who have persistent hematuria after resolution of their infection also require a complete urologic workup.⁸

Although empiric therapy based on symptoms is generally accurate and cost-effective, women who are felt to be in the early stages of a problem with recurrent UTI should have documented cultures.²³ Urine culture not only serves as the gold standard for diagnostic accuracy but also provides specific information about the uropathogen and its antibiotic susceptibilities.⁶ The standard definition of a UTI on culture is > 100 000 colony forming units per HPF. This value has excellent specificity but a sensitivity of only 50%.⁷ In women with symptoms of a UTI > 1000 colony forming units per HPF is considered sufficient to document infection without compromising specificity. The sensitivity to detect infection is 80% and the specificity 90%.⁷ When a “clean-catch” or midstream technique is used to obtain a urine sample, the rates of contamination with vaginal flora are approximately 30%.²⁴ The presence of > 20 epithelial cells per HPF on urinalysis suggests contamination by vaginal secretions.²³

Because bacteria reduce urinary nitrates to nitrites, the use of urine dipstick analysis can be helpful. A positive result usually indicates infection, with a specificity of 92% to 100% and a sensitivity of 19% to 48%.²⁵ A negative result does not rule out infection if the patient is symptomatic. Some bacteria such as *Staphylococcus saprophyticus* lack the enzymes to reduce nitrates. If urine has not been present in the bladder for at least 4 hours, there may not have been sufficient time for the reaction to occur.²⁵

Leukocyte esterase is produced by neutrophils and indicates pyuria, which is associated with UTI. Organisms other than uropathogens can produce leukocyte esterase. Therefore, this is a sensitive (72% to 97%) but not specific (41% to 86%) test for UTI in women. Blood on dipstick can help to confirm infection, but this can be associated with other clinical circumstances and therefore is more sensitive (68% to 92%) than specific (42% to 46%) for UTI.²⁵

TREATMENT OF ACUTE URINARY TRACT INFECTIONS

Ampicillin and sulfonamides generally should not be used for empiric therapy because more than one third of isolates demonstrate in vitro resistance.^{26,27} More than 15% to 20% of *E. coli* strains causing uncomplicated cystitis are now resistant to these agents in several areas of the United States

and other countries.²⁸ The prevalence of resistance to nitrofurantoin among *E. coli* is < 5%, although non-*E. coli* uropathogens are often resistant. Resistance to the fluoroquinolones remains < 5% in most studies of uropathogenic strains.

Three-day regimens are recommended because they are associated with better compliance, lower cost, and lower frequency of adverse reactions than 7- to 10-day regimens.²⁹ Several studies and clinical experience have confirmed the effectiveness of 3-day regimens of trimethoprim, trimethoprim-sulfamethoxazole, or a fluoroquinolone for treatment of acute uncomplicated cystitis, and these agents are generally recommended for empiric therapy.²⁹ In comparison, 3-day regimens with beta-lactams are less effective than ≥ 5 days of therapy.²⁹ Nitrofurantoin is a safe and generally effective agent, but it should be administered for a minimum of 7 days. Single-dose regimens are somewhat less effective than 3- to 7-day regimens, even with fluoroquinolones.^{27,29}

First-line treatment suggested by the Infectious Disease Society of America in 1999 was TMP-SMX in a 3-day regimen.²⁹ Given the increasing prevalence of TMP-SMX resistance among uropathogens, it is important to examine risk factors predicting in vitro resistance. These are diabetes, recent hospitalization, antibiotic use in the past 3 to 6 months (for any reason), and recent TMP-SMX use.³⁰ Fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, fleroxacin) are generally not recommended as first-line treatment because of their greater expense and concerns regarding the promotion of quinolone resistance. However, fluoroquinolones can become a reasonable first-line treatment for women who have or are suspected of having antimicrobial resistance or of being allergic to or not tolerating more conventional therapy, and for women in areas where resistance to TMP-SMX is > 15% to 20%.²⁹ Other reasonable empiric choices for mild cystitis include a 7-day course of nitrofurantoin or a single-dose of fosfomycin.²⁹ In 2007, Gupta et al. demonstrated the equivalent efficacy of a 5-day course of nitrofurantoin and a 3-day course of TMP-SMX.³¹

Recurrent cystitis that occurs during or within the first week following treatment suggests possible relapse and should be managed with a pre-treatment urine culture, antimicrobial susceptibility testing, and treatment with a fluoroquinolone for 7 days.⁸

PREVENTION OF RECURRENT URINARY TRACT INFECTIONS

Lifestyle Modification

Women using spermicide-containing contraception should be offered an alternative form of contraception.^{27,32} Several studies have shown that there is no association between recurrent UTI and pre- and post-coital patterns, frequency

of urination, delayed voiding habits, douching, use of hot tubs, bubble baths, BMI, frequent use of pantyhose or tights, use of tight clothing, type of clothing, bicycle riding, and the volume of fluid consumed.^{32,33} However, behavioural approaches are unlikely to be harmful.³⁴

Antimicrobial Strategy

There are as many options for prevention and management of recurrent UTI as there are studies on the issue (Table 2).^{8,10,33,35–39} A Cochrane review,³⁵ of 19 trials including 1120 patients, showed that antibiotics are better than placebo in reducing the number of clinical and microbiological recurrences in pre- and postmenopausal women with recurrent UTI. Seven trials including 257 patients showed a relative risk of having a clinical UTI of 0.15 (95% CI 0.08 to 0.28) favouring antibiotic over placebo. The number needed to treat to prevent one symptomatic recurrent UTI was 2.2. Antibiotics in this review were fluoroquinolones (norfloxacin, ciprofloxacin, pefloxacin), cephalosporins (cephalexin, cefaclor), trimethoprim, sulfamethoxazole, and nitrofurantoin. No antibiotic was superior. Choice of antibiotic should rely on community patterns of resistance, adverse events, and local costs. Three main management strategies generally considered are continuous antimicrobial prophylaxis, post-coital prophylaxis, and patient-administered self-treatment.³⁶ For patients with ≤ 2 UTIs per year, the acute self-treatment may be useful. Patients with ≥ 3 infections annually should be offered a regimen of continuous, low-dose prophylaxis or post-coital prophylaxis.³⁶

Continuous Prophylaxis

Continuous prophylaxis can be given daily at bedtime. Some authors suggest prophylaxis on alternate nights or 3 nights per week (Table 2). One study showed that weekly prophylaxis was better than monthly prophylaxis.⁴⁰ No studies compared daily and weekly prophylaxis.³⁵ No recommendation can be made about the optimal prophylaxis.

Post-coital Prophylaxis

Another study⁴¹ showed that sexually active women who took post-coital ciprofloxacin had similar outcomes to women who took ciprofloxacin daily. A causal relationship between infections and intercourse can be suspected when the interval is consistently between 24 and 48 hours.⁴² Two studies^{41,43} suggest that for sexually active women with UTI related to sexual intercourse, the post-coital approach could be a better option. The authors of one study⁴¹ noted that a major advantage of post-intercourse prophylaxis was that it produced fewer side effects because women took only one third of the amount of antibiotic used in daily prophylaxis.

Table 2. Antimicrobial prophylaxis regimens for women with recurrent urinary tract infections

Oral regimens	
Continuous prophylaxis	
TMP-SMX	40/200 mg daily
TMP-SMX	40/200 mg 3×/week
TMP	100 mg daily
Nitrofurantoin monohydrate/macrocrystals (Macrobid)	50–100 mg daily
Nitrofurantoin macrocrystal (Macrochantin)	50–100 mg daily
Cephalexin	125–250 mg daily
Cefaclor	250 mg daily
Norfloxacin	200 mg daily
Ciprofloxacin	125 mg daily
Cinoxacin	250–500 mg daily
Post-coital prophylaxis (single dose)	
TMP-SMX	40/200 mg
TMP-SMX	80/400 mg
Nitrofurantoin macrocrystal (Macrochantin)	50–100 mg
Cephalexin	125–250 mg
Cinoxacin	250 mg
Ciprofloxacin	125 mg
Norfloxacin	200 mg
Ofloxacin	100 mg
Acute self-treatment	
TMP-SMX	160/800 mg twice daily × 3 days
Ciprofloxacin	250 mg twice daily × 3 days
Norfloxacin	200 mg twice daily × 3 days

Acute Self-treatment

The self-start therapy is ideal for women who are not suitable candidates for long-term daily prophylaxis or who are unwilling to take it. However, this strategy should be restricted to those women who have clearly documented recurrent infections and who are motivated, compliant with medical instructions, and have a good relationship with a medical provider.⁸ Such women should be reminded to call their provider if the symptoms are not completely resolved within 48 hours. The patient identifies episodes of infection on the basis of symptoms, performs her own culture, and initiates a standard 3-day course of empiric treatment. Antimicrobial agents with minimal side effects are recommended, because this approach could lead to some degree of overtreatment (Table 2).⁴²

The efficacy of antimicrobial agents to prevent recurrent UTIs seems to arise through 2 mechanisms. First, agents

such as TMP-SMX and norfloxacin decrease the rate of recovery of aerobic Gram-negative uropathogens such as *E. coli* from the fecal reservoir.⁴⁴ Nitrofurantoin in contrast, decreases the recurrence rate by intermittently sterilizing the urine and possibly by inhibiting bacterial attachment.^{36,45,46}

Adverse Events

In a 2004 Cochrane Review,³⁵ the rates of adverse events were higher in the antibiotic group than in the placebo group. The relative risk for severe side effects requiring withdrawal of treatment was 1.58 (95% CI 0.47 to 5.28) and for mild side effects the relative risk was 1.78 (95% CI 1.06 to 3.00). The most frequently reported adverse events were nausea and vaginal and oral candidiasis. Nitrofurantoin required the highest number of withdrawals, followed by cephalexin and weekly pefloxacin.³⁵ Several adverse effects have been described with the use of nitrofurantoin, including aplastic anemia, polyneuritis, acute cholestatic and hepatocellular reactions, and pulmonary toxicity.⁴⁷ Chronic pulmonary toxicity is uncommon and may develop after 1 month to 6 years of therapy. Patients who are long-term users of nitrofurantoin should be checked regularly for any complications.

Most authorities advocate an antibiotic prophylaxis duration of 6 to 12 months, although in certain cases this has been extended to 2 to 5 years.⁴⁸ However, as no study has looked at prophylaxis for more than 1 year, no conclusion can be made about the optimal duration.

In the two studies that had a follow-up assessment at up to 6 months after the prophylaxis period,^{44,49} there was no difference in the microbiological recurrences between the antibiotic group and the placebo group. There were no studies that assessed clinical recurrences after prophylaxis. However, it appears that most women revert to the previous pattern of recurrent infections once prophylaxis is stopped.

Estrogen Use in Postmenopausal Women

Evidence from two small RCTs shows that in postmenopausal women with recurrent UTI, vaginal estrogens reduce the number of UTIs.^{50,51} Raz and Stamm reported a significant reduction in UTI among postmenopausal women using 0.5 mg of estriol cream vaginally every night for 2-weeks and then twice a week for 8-months compared with those using a placebo (0.5 vs. 5.9 episodes per patient-year, $P < 0.001$).⁵² Eriksen has shown a similar beneficial prophylactic effect with the use of an estradiol-releasing vaginal ring (Estring, Pharmacia & Upjohn) compared with a placebo vaginal ring.⁵³ After 36 weeks of the study, the cumulative likelihood of remaining free of UTI was 45% in the Estring group compared with approximately 20% in the placebo group ($P < 0.008$).⁵³

The mechanism of action is thought to be the reappearance of vaginal lactobacilli which, unlike placebo, decrease the vaginal pH. This results from maturation and thickening of the vaginal epithelium with increased cellular glycogen, a main substrate for lactobacilli.^{52,53} This process prevents overgrowth and colonization of Enterobacteriaceae in the vagina.⁵⁴ It can take at least 12 weeks for the vaginal ring to be effective in reducing the occurrence of UTIs.⁵³

Studies have provided insufficient evidence for recommending a particular type or form of vaginal estrogen.^{50,51} Creams are cheaper and possibly more efficient but could be more difficult to apply for some women and can produce some adverse effects (e.g., itching, burning, occasional spotting). Estradiol vaginal tablets may have fewer side effects but are more expensive. The vaginal ring is also more expensive and may require a trained professional to place it correctly.⁵¹

A recent Cochrane review⁵¹ did not show a significant difference in the number of women with UTI at the end of treatment period between oral estrogens and placebo. It seems that the route of administration may be more important than the compound itself.⁵⁰ The studies comparing vaginal estrogens to antibiotics were inconclusive because of their heterogeneity.^{51,55,56}

Cranberries

Cranberries (particularly in the form of cranberry juice) have been touted as an effective home remedy for the prevention and treatment of UTIs for several decades. So far, no definite mechanism of action has been established. The main suggestion is that cranberries prevent bacteria (particularly *E. coli*) from adhering to uroepithelial cells.^{57,58} Without adhesion, the bacteria cannot infect the mucosal surface of the urinary tract.

A recent Cochrane review⁵⁹ of 10 studies with a total of 1049 subjects showed some evidence that cranberry juice and derivatives may decrease the number of symptomatic UTIs over a period of 12 months, particularly for women with recurrent UTIs. A meta-analysis of the results of 4 RCTs found that cranberry products significantly reduced the incidence of UTIs (RR 0.66; 95% CI 0.47 to 0.92) compared with placebo or control.^{60–63} Further, there is no clear evidence of the amount and concentration that must be consumed and over what period for the intervention to be most effective. No published trials have been undertaken that compare cranberry with established interventions (e.g., antibacterials) for preventing UTIs.⁵⁹

Other Potential Strategies

Antibiotics are usually effective in treating acute infections and are the primary means of prophylaxis for recurrent UTI patients; however, their value is being lessened by the

emergence of increasing numbers of drug-resistant bacteria. Consequently, it is important that alternative prevention strategies be developed.

Acupuncture

Two small RCTs evaluated the role of acupuncture compared with sham acupuncture or no treatment in the prophylaxis of recurrent UTIs.^{64,65} During a 6-month period, both studies demonstrated that acupuncture could play a significant role in preventing recurrent UTIs. Authors concluded that it seems a worthwhile alternative to antibiotic strategy.

Probiotics

The instillation of *Lactobacillus* into the vagina is believed to stop the ascension of uropathogens into the bladder. Available studies suggest that probiotics can be beneficial, and most authors consider this approach promising, but further research is needed before probiotics can be recommended for prevention of UTI.^{66–70}

Vaccines

An injectable vaccine developed in Switzerland was found to be effective, with no adverse effects observed in pregnant women or their offspring.⁷¹ In order to obviate some adverse reactions of the parenteral vaccine, four mucosal vaccines were developed as a vaginal suppository or an oral tablet, but the vaccine's benefits seemed to decline after the last dose.⁷² The only parenteral vaccine currently under development, FimCH, has proven to be safe in a phase I clinical trial.⁷³ A phase II clinical trial has been completed, but data are not yet available.³⁴

Others

Other potential preventive strategies, which include the use of bacterial interference (*E. coli* 83972)⁷⁴ and topical application of carbohydrates (hyaluronic acid),^{34,75–78} are still under development.

PREGNANCY AND RECURRENT UTIs

For pregnant women with symptomatic or asymptomatic bacteriuria, the risk of a preterm delivery and low birth weight infant is significantly increased.⁷⁹ Hooton and Stamm recommend a follow-up culture for test of cure a week after completion of therapy and monthly follow-up until the completion of the pregnancy.³⁴ Indications for prophylaxis are (1) all women with a pre-pregnancy history of recurrent UTIs, (2) persistent symptomatic or asymptomatic bacteriuria after two antibiotic treatments, and (3) after only one UTI for a woman who has other conditions that potentially increase the risk of urinary complications during the episode of UTI (e.g., diabetes or sickle cell trait). Both continuous and post-coital prophylaxis regimens have been shown to

be effective, and agents of choice are nitrofurantoin (50 mg) and cephalexin (250 mg).^{34,36,80,81}

Recommendations

Recommendations were made according to the guidelines developed by the Canadian Task Force on Preventive Health Care (Table 1).

1. Urinalysis and midstream urine culture and sensitivity should be performed with the first presentation of symptoms in order to establish a correct diagnosis of recurrent urinary tract infection. (III-L)
2. Patients with persistent hematuria or persistent growth of bacteria aside from *Escherichia coli* should undergo cystoscopy and imaging of the upper urinary tract. (III-L)
3. Sexually active women suffering from recurrent urinary tract infections and using spermicide should be encouraged to consider an alternative form of contraception. (II-2B)
4. Prophylaxis for recurrent urinary tract infection should not be undertaken until a negative culture 1 to 2 weeks after treatment has confirmed eradication of the urinary tract infection. (III-L)
5. Continuous daily antibiotic prophylaxis using cotrimoxazole, nitrofurantoin, cephalexin, trimethoprim, trimethoprim-sulfamethoxazole, or a quinolone during a 6- to 12-month period should be offered to women with ≥ 2 urinary tract infections in 6 months or ≥ 3 urinary tract infections in 12 months. (I-A)
6. Women with recurrent urinary tract infection associated with sexual intercourse should be offered post-coital prophylaxis as an alternative to continuous therapy in order to minimize cost and side effects. (I-A)
7. Acute self-treatment should be restricted to compliant and motivated patients in whom recurrent urinary tract infections have been clearly documented. (I-B)
8. Vaginal estrogen should be offered to postmenopausal women who experience recurrent urinary tract infections. (I-A)
9. Patients should be informed that cranberry products are effective in reducing recurrent urinary tract infections. (I-A)
10. Acupuncture may be considered as an alternative in the prevention of recurrent urinary tract infections in women who are unresponsive to or intolerant of antibiotic prophylaxis. (I-B)
11. Probiotics and vaccines cannot be offered as proven therapy for recurrent urinary tract infection. (II-2C)

12. Pregnant women at risk of recurrent urinary tract infection should be offered continuous or post-coital prophylaxis with nitrofurantoin or cephalexin, except during the last 4 weeks of pregnancy. (II-1B)

REFERENCES

- Czaja CA, Hooton TM. Update on acute uncomplicated urinary tract infection in women. *Postgrad Med* 2006;119:39–45.
- Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Self reported incidence of urinary tract infection and associated costs. *Ann Epidemiol* 2000;10:509–15.
- Hooton TM. A prospective study for risk factors for symptomatic urinary tract infection in young women. *N Engl J Med* 1996;335:468.
- Jackson SL, Boyko IJ, Scholes D, Abraham L, Gupta K, Fihn SD. Predictors of urinary tract infection after menopause. *Am J Med* 2004;117:903.
- Gopal M, Northington G, Arya L. Clinical symptoms predictive of recurrent urinary tract infection. *Am J Obstet Gynecol* 2007;197:74.e1–4.
- Foster RT Sr. Uncomplicated urinary tract infections in women. *Obstet Gynecol Clin North Am* 2008;35:235–48.
- American College of Obstetricians and Gynecologists. Treatment of urinary tract infection in non pregnant women. *ACOG Practice Bulletin No. 91*, March 2008. *Obstet Gynecol* 2008;11:785–94.
- Hooton. Recurrent urinary tract infection in women. *Int J Antimicrobial Agents* 2001;17:259–268.
- Kraft JK, Stamey TA. The natural history of symptomatic recurrent bacteriuria in women. *Medicine* 1977;56:55–60.
- Gupta K, Stamm WE. Pathogenesis and management of recurrent urinary tract infections in women. *World J Urol* 1999;17:415–20.
- Foxman B, Gillespie B, Koopman J, Zhang L, Palin K, Tallman P, et al. Risk factors for second urinary tract infection among college women. *Am J Epidemiol* 2000;151:1194–205.
- Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute urinary tract infection? *JAMA* 2002;287:2701–10.
- Gupta K, Hooton TM, Roberts PL, Stamm WE. Patient-initiated treatment of recurrent urinary tract infection in women. *Ann Intern Med* 2001;135:9–16.
- Echols RM, Tosiello RL, Haverstock DC, Tice AD. Demographic, clinical and treatment parameters influencing the outcome of acute cystitis. *Clin Infect Dis* 1999;29:113–9.
- Mulvey MA, Schilling JD, Jultgren SJ. Establishment of a persistent *Escherichia coli* reservoir during the acute phase of a bladder infection. *Infect Immun* 2001;69:4572–9.
- Rosen DA, Hooton TM, Stamm WE, Humphrey PA, Hultgren SJ. Detection of intracellular bacterial communities in human urinary tract infection. *PLOS Med* 2007;4:e329.
- Fihn SD. Acute uncomplicated urinary tract infection in women. *N Engl J Med* 2003;349:259–66.
- Johnson JR, Clabots C. Sharing of virulent *Escherichia coli* clones among household members of a woman with acute cystitis. *Clin Infect Dis* 2006;43:e101–8.
- Gupta K, Stapleton AE, Hooton TM, Roberts PL, Fennell CL, Stamm WE. Inverse association of H202-producing *Lactobacilli* and vaginal *E. coli* colonization in women with recurrent urinary tract infection. *J Infect Dis* 1998;178:446–50.
- Scholes D, Hooton TM, Roberts PL, Stapleton AE, Gupta K, Stamm WE. Risk factors for recurrent urinary tract infection in young women. *J Infect Dis* 2000;182:1177–82.
- Minardi D, Parri G, d'Anzeo G, Fabiani A, El Asmar Z, Muzzonigro G. Perineal ultrasound evaluation of dysfunctional voiding in women with recurrent urinary tract infections. *J Urol* 2008;179:947–51.
- Car J, Sheikh A. Recurrent urinary tract infection in women. *BMJ* 2003;327:1204.
- Car J. Urinary tract infections in women: diagnosis and management in primary care. *BMJ* 2006;332:94–7.
- Lifshitz E, Kramer L. Outpatient urine culture. Does collection technique matter? *Arch Intern Med* 2000;160:2537–40.
- Simerville JA, Maxted WC, Pahlira JJ. Urinalysis: a comprehensive review. *Am Fam Physician* 2005;71:1153–62.
- Drekonja DM, Johnson JR. Urinary tract infections. *Prim Care* 2008;35:345–67.
- Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am* 1997;11:551–81.
- Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis. *J Am Med Assoc* 1999;281: 736–8.
- Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clin Infect Dis* 1999;29:745–58.
- Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. *J Gen Intern Med* 1999;14:606–9.
- Gupta K, Hooton TM, Roberts MS, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med* 2007;167(20):2207–12.
- Franco AV. Recurrent urinary tract infections. *Best Pract Res Clin Obstet Gynaecol* 2005;19:861–73.
- Reid G. Potential preventive strategies and therapies in urinary tract infection. *World J Urol* 1999;17:359–63.
- Hooton TM, Stamm WE. Urinary tract infections and asymptomatic bacteriuria in pregnancy. *UpToDate* 2008; version 16.2 (May 31, 2008).
- Albert X, Huertas I, Pereiró II, San félix J, Gosalbes V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev* 2004;(3):CD001209.
- Stapleton A, Stamm WE. Prevention of urinary tract infection. *Infect Dis Clin North Am* 1997;11:719–33.
- Orenstein R, Wong ES. Urinary tract infections in adults. *Am Fam Physician* 1999;59(5):1225–34,1237.
- Dwyer PL, O'Reilly M. Recurrent urinary tract infection in the female. *Curr Opin Obstet Gynecol* 2002;14:537–43.
- Nicolle LE. Urinary tract infection: traditional pharmacologic therapies. *Am J Med* 2002;113(Suppl 1A):35S-44S.
- Guibert J, Humbert G, Meyrier A, Jardin A, Vallancien G, Piccoli S et al. Antibiovention of recurrent cystitis. A randomized double-blind comparative trial of 2 dosages of pefloxacin. *Presse Med* 1995;24:213–6.
- Melekos MD, Asbach HW, Gerharz E, Zarakovitis IE, Weingaertner K, Naber KG. Post-intercourse versus daily ciprofloxacin prophylaxis for recurrent urinary tract infections in premenopausal women. *J Urol* 1997;157:935–9.
- Engel JD, Schaeffer AJ. Evaluation of and antimicrobial therapy for recurrent urinary tract infections in women. *Urol Clin North Am* 1998;25:685–701.
- Stapleton A, Latham RH, Johnson C, Stamm WE. Postcoital antimicrobial prophylaxis for recurrent urinary tract infection. A randomized, double-blind, placebo-controlled trial. *JAMA* 1990;264:703–6.

44. Stamm WE, Counts GW, Wagner K, Martine D, Gregory D, McKeivitt M, et al. Antimicrobial prophylaxis of recurrent urinary tract infections: a double-blind, placebo-controlled trial. *Ann Intern Med* 1980;92:770–5.
45. Nicolle LE. Prophylaxis: recurrent urinary tract infections in women. *Infection* 1992; 20(Suppl 3):S203–5.
46. Zhanel GG, Nicolle LE. Effects of sub-inhibitory antimicrobial concentration (sub-MICs) on in-vitro bacterial adherence to uroepithelial cells. *J Antimicrob Chemother* 1992;29:617–27.
47. Goemaere NNT, Grijm K, ThW van Hal P, Bakker MA. Nitrofurantoin-induced pulmonary fibrosis: a case-report. *J Med Case Report* 2008;2:169.
48. Nicolle LE, Harding GK, Thomson M, Kennedy J, Urias B, Ronald AR. Efficacy of five year of continuous, low-dose trimethoprim-sulfamethoxazole prophylaxis for urinary tract infection. *J Infect Dis* 1988;157:1239–42.
49. Schaeffer AJ, Jones JM, Flynn SS. Prophylactic efficacy of cinoxacin in recurrent urinary tract infection: biologic effects on the vaginal and fecal flora. *J Urol* 1982;127:1128–31.
50. Cardozo L, Lose G, McClish D, Versi E, de Koning Gans H. A systematic review of estrogens for recurrent urinary tract infections: third report of the hormones and urogenital therapy (HUT) committee. *Int Urogynecol J Pelvic Floor Dysfunct* 2001;12:15–20.
51. Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev* 2008;(2):CD005131.
52. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *New Engl J Med* 1993;329:753–6.
53. Eriksen BC. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol* 1999;180:1072–9.
54. Raz R. Hormone replacement therapy or prophylaxis in postmenopausal women with recurrent urinary tract infection. *J Infect Dis* 2001;183(Suppl 1):S74–6.
55. Raz R, Colodner R, Rohana Y, Battino S, Rottensterich E, Wasser I, et al. Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. *Clin Infect Dis* 2003;36:1362–8.
56. Xu R, Wu Y, Hu Y. Prevention and treatment of recurrent urinary system infection with estrogen cream in postmenopausal women. *Zhonghua Fu Chan Ke Za Zhi* 2001;36:531–3.
57. Schmidt DR, Sobota AE. An examination of the antiadherence activity of cranberry juice on urinary and non-urinary bacterial isolates. *Microbios* 1988;55:173–81.
58. Zafriri D, Ofek I, Adar R, Pocino M, Sharon N. Inhibitory activity of craberry juice on adherence of type 1 and type P fimbriated *Escherichia coli* to eucaryotic cells. *Antimicrob Agents Chemother* 1989;33:92–8.
59. Jepson JP, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2008;(1):CD 001321.
60. Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. *BMJ* 2001;322(7302):1571–3.
61. McMurdo ME, Bissett LY, Price RJ, Phillips G, Crombie IK. Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial. *Age Ageing* 2005;34:256–61.
62. Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol* 2002;9:1558–62.
63. Waites KB, Canupp KC, Armstrong S, DeVivo MJ. Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury. *J Spinal Cord Med* 2004; 27:35–40.
64. Aune A, Alreak T, LiHua H, Baerheim A. Acupuncture in the prophylaxis of recurrent lower urinary tract infection in adult women. *Scand J Prim Health Care* 1998; 16:37–9.
65. Alraek T, Fagerheim U, Baerheim A. Acupuncture treatment in the prevention of uncomplicated recurrent lower urinary tract infections in adult women. *Am J Public Health* 2002;92:1609–11.
66. Reid G, Bruce AW. Probiotics to prevent urinary tract infections: the rational and evidence. *World J Urol* 2006;24:28–32.
67. Reid G, Bruce AW, Taylor M. Instillation of Lactobacillus and stimulation of indigenous organisms to prevent recurrence of urinary tract infections. *Microecol Ther* 1995;23:32–45.
68. Uehara S, Monden K, Nomoto K, Seno Y, Kariyama R, Kumon H. A pilot study evaluating the safety and effectiveness of Lactobacillus vaginal suppositories in patients with recurrent urinary tract infection. *Int J Antimicrob Agents* 2006;28(Suppl 1):S30–4.
69. Baerheim A, Larsen E, Digranes A. Vaginal application of lactobacilli in the prophylaxis of recurrent urinary tract infection in women. *Scand J Prim Health Care* 1994;12:239–43.
70. Falagas ME, Betsi GI, Tokas T, Athanasiou S. Probiotics for prevention of recurrent urinary tract infections in women. *Drugs* 2006;66:1253–61.
71. Grischke EM, Rüttgers H. Treatment of bacterial infections of the female urinary tract by immunization of the patiets. *Urol Int* 1987;42:338–41.
72. Uehling DT, Hopkins WJ, Beierle LM, Kryger JV, Heisey DM. Vaginal mucosal immunization for recurrent urinary tract infection: extended phase II clinical trial. *J Infect Dis* 2001;183 (Suppl 1): S81–3.
73. Hopkins WJ, Uehling DT. Vaccine development for the prevention of urinary tract infections. *Curr Infect Dis Rep* 2002;4:509–13.
74. Sundén F, Håkansson L, Ljunggren E, Wullt B. Bacterial interference—is deliberate colonization with *Escherichia coli* 83972 an alternative treatment for patients with recurrent urinary tract infection? *Int J Antimicrob Agents* 2006;28(Suppl 1):S26–9.
75. Lipovac M, Kurz C, Reithmayr F, Verhoeven HC, Huber JC, Imhof M. Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. *Int J Gynaecol Obstet* 2007;96:192–5.
76. Constantinides C, Manousakas T, Nikolopoulos P, Stanitsas A, Haritopoulos K, Giannopoulos A. Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. *BJU Int* 2004;93:1262–6.
77. Eden CS, Fretr R, Hagberg L, Hull R, Hull S, Leffler H, et al. Inhibition of experimental ascending urinary tract infection by an epithelial cell-surface receptor analogue. *Nature* 1982;298(5874):560–2.
78. Zopf D, Roth S. Oligosaccharides anti-infectives agents. *Lancet* 1996;347(9007):1017–21.
79. Romero R, Oyarzun E, Mazor M, Sirtori M, Hobbins JC, Bracken M. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. *Obstet Gynecol* 1989;73:576–82.
80. Pfau A, Sacks TG. Effective prophylaxis for recurrent urinary tract infections during pregnancy. *Clin Infect Dis* 1992;14:810–4.
81. Ovale A, Levancini M. Urinary tract infections in pregnancy. *Curr Opin Urol* 2001;11:55–9.
82. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. *CMAJ* 2003;169:207–8.