

Recurrent UTIs in Women

How to Refine Your Care

Which risk factors are (really) associated with recurrence? Which prophylactic and nonpharmacologic strategies are useful? This guide provides the answers.

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PRACTICE RECOMMENDATIONS

- Avoid routine use of cystoscopy and imaging when evaluating women with recurrent urinary tract infection (UTI). **B**
- Keep in mind that three- to five-day courses of antibiotics (nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin, or beta-lactams) for UTIs are as effective as longer courses and are associated with better compliance and fewer adverse effects. **A**
- Assure patients considering prophylaxis for recurrent UTI that either continuous or postcoital antibiotics are effective. **A**

STRENGTH OF RECOMMENDATION

- A** Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

For the third time in nine months, Joan, 28, presents with complaints of painful, frequent, and urgent urination. Joan is sexually active; her medical history is otherwise unremarkable. In each of the previous two episodes, her urine culture grew *Escherichia coli*, and she was treated with a five-day course of nitrofurantoin. Now, she asks about the need for additional workup and treatment, as well as whether there is a way to prevent further infections.

Urinary tract infections (UTIs) are the most common bacterial infection in women and account for an estimated 5.4 million primary care office visits and 2.3 million emergency department visits annually.^{1,2} For women, the lifetime risk for a UTI is greater than 50%.³ In one study of UTI in a primary care setting, 36% of women younger than 55 and 53% of women older than 55 had a recurrent infection within a year.⁴ Most women with UTI are treated as outpatients, but 16.7% require hospitalization.⁵ In the United States, direct costs for evaluation and treatment of UTI total \$1.6 billion each year.⁵

Accurately characterizing recurrent UTI

Bacteriuria is defined as the presence of 100,000 colony-forming units (ie, viable bacteria) per milliliter of urine collected midstream on two consecutive urinations.⁶ UTIs are symptomatic infections of the urinary tract and may involve the urethra, bladder, ureters, or kidneys.⁷ Infections of the lower tract (bladder and urethra) are commonly referred to as *cystitis*; infections of the upper tract (kidney and ureters) are referred to as *pyelonephritis*.

Most UTIs are uncomplicated and do not progress to more serious infections. However, patients who are pregnant or who have chronic medical conditions (eg, renal insufficiency or use of immunosuppressant

medications), urinary obstruction, or calculi may develop complicated UTIs.⁸

Recurrent UTI is an infection that follows resolution of bacteriuria and symptoms of a prior UTI; the term applies when such an infection occurs within six months of the previous UTI or when three or more UTIs occur within a year.⁷ Recurrent infection can be further characterized as relapse or reinfection. Relapse occurs when the patient has a second UTI caused by the same pathogen within two weeks of the original treatment.⁹ Reinfection is a UTI that occurs more than two weeks after completion of treatment for the original UTI. The pathogen in a reinfection may be the same one that caused the original UTI or it may be a different agent.⁹

It's also important to differentiate between *recurrent* and *resistant* UTI. In resistant UTI, bacteriuria fails to resolve following seven to 14 days of appropriate antibiotic treatment.⁹

FACTORS THAT INCREASE RISK FOR RECURRENT UTI

Premenopausal women

Both modifiable and nonmodifiable factors (see Table 1, page 46) have been associated with increased risk for recurrent UTI in premenopausal women.¹⁰⁻²¹ Among those with specific blood group phenotypes (Lewis non-secretor, in particular), rates of UTI rise secondary to increased adherence of bacteria to epithelial cells in the urinary tract.¹⁰ Other nonmodifiable risk factors include congenital urinary tract anomalies, obstruction of the urinary tract, and a history of UTI.^{11,12} Women whose mothers had UTIs are at higher risk for recurrent UTI than are those whose mothers had no such history.¹³

Modifiable risk factors for recurrent UTI include contraceptive use (spermicides, spermicide-coated condoms, and oral contraceptives) and frequency of intercourse (≥ 4 times/month).¹³ Spermicides alter the normal vaginal flora and lead to increased colonization of *E coli*, which increases the risk for UTI.¹⁴ Women with recurrent UTIs were 1.27 to 1.45 times more likely to use oral contraceptives than those without recurrent UTIs.¹³ Compared with college



women who had not had intercourse, sexually active college women who had engaged in intercourse three times in a week had a 2.6-fold increase in relative risk for UTI.¹⁵ Those who had daily intercourse had a 9-fold increase in relative risk for UTI.¹⁵ This elevated risk is due to trauma to the lower urogenital tract (urethra) and introduction of bacteria into the urethra via mechanical factors.^{16,17}

Postmenopausal women

Atrophic vaginitis, catheterization, declining functional status, cystocele, incomplete emptying, incontinence, and history of premenopausal UTIs are all risk factors for recurrent UTI in postmenopausal women.^{19,20} Decreased estrogen and resulting vaginal atrophy appear to be associated with increased rates of UTI in these women. Additionally, postmenopausal women's vaginas are more likely to be colonized with *E coli* and have fewer lactobacilli than those of premenopausal women, which is thought to predispose them to UTI.²¹ These risk factors are summarized in Table 1.¹⁰⁻²¹

INITIAL EVALUATION OF RECURRENT UTI

Patients with recurrent UTI experience signs and symptoms similar to those with isolated uncomplicated UTI: dysuria, frequency, urgency, and hematuria. Focus your history interview on potential causes of complicated UTI (see Table 2, page 47).¹⁸ Likewise, perform a pelvic exam to evaluate for predisposing anatomic abnormali-

TABLE 1
Risk Factors for Recurrent UTIs in Women

Modifiable	Nonmodifiable
Premenopausal women	
Contraceptive use (eg, spermicides, spermicide-coated condoms, oral contraceptives) Intercourse ≥ 4 times/mo	Congenital urinary tract anomalies History of UTI in the patient or her mother Lewis non-secretor blood type Urinary tract obstruction
Postmenopausal women	
Atrophic vaginitis Cystocele Incontinence	Catheterization Declining functional status History of premenopausal UTI Incomplete emptying
Not proven to be associated with UTI	
BMI Bubble baths Caffeine consumption Chronic disease	Douching Noncotton underwear Postcoital voiding habits Sexually transmitted infections

Abbreviation: UTI, urinary tract infection.
Sources: Sheinfeld J et al. *N Engl J Med*. 1989¹⁰; Foxman B et al. *Am J Epidemiol*. 2000¹¹; Twajj M. *J R Soc Health*. 2000¹²; Scholes D et al. *J Infect Dis*. 2000¹³; Hooton TM et al. *J Infect Dis*. 1991¹⁴; Hooton TM et al. *N Engl J Med*. 1996¹⁵; Hooton TM et al. *JAMA*. 1991¹⁶; Foxman B et al. *Epidemiology*. 1997¹⁷; Dason S et al. *Can Urol Assoc J*. 2011¹⁸; Hooton TM. *J Antimicrob Chemother*. 2000¹⁹; Raz R et al. *Clin Infect Dis*. 2000²⁰; Gupta K et al. *J Infect Dis*. 1998.²¹

ties.²² Finally, obtain a urine culture with antibiotic sensitivities to ensure that previous treatment was appropriate and to rule out microbes associated with infected uroliths.¹⁸ Given the low probability of finding abnormalities on cystoscopy or imaging, neither one is routinely recommended for the evaluation of recurrent UTI.¹⁸

TREATMENT OPTIONS AND PRECAUTIONS

As with isolated UTI, *E coli* is the most common pathogen in recurrent UTI. However, recurrent UTI is more likely than isolated UTI to result from other pathogens (odds ratio [OR], 1.5), such as *Klebsiella*, *Enterococcus*, *Proteus*, and *Citrobacter*.²³ Since a patient’s recurrent UTI most likely arises from the same pathogen that caused the

prior infection, start an antibiotic you know is effective against it.⁸ Additionally, take into account local resistance rates; antibiotic availability, cost, and adverse effects; and a patient’s drug allergies.

Preferred antibiotics. Trimethoprim-sulfamethoxazole (TMP-SMX; 160 mg/800 mg bid for 3 d) has long been the mainstay of treatment for uncomplicated UTI. In recent years, however, resistance to TMP-SMX has increased. While it is still appropriate for many situations as firstline treatment, it is not recommended for empiric treatment if local resistance rates are higher than 20%.²⁴ Nitrofurantoin (100 mg bid for 5 d) has efficacy similar to that of TMP-SMX but without significant bacterial resistance. While fosfomycin (3 g as a single dose) is still recommended as firstline treatment, it is less effective than either TMP-SMX or nitrofurantoin. Table 3 summarizes these antibiotic choices and their efficacies.²⁴

Agents to avoid or use only as a last resort. For patients who are unable to take any of the mentioned drugs, consider β-lactam antibiotics—although they are typically less effective for this indication. While fluoroquinolones are very effective and have low (but rising) resistance rates, they are also associated with serious and potentially permanent adverse effects. As a result, on May 12, 2016, the FDA issued a Drug Safety Communication recommending that fluoroquinolones be used only in patients without other treatment options.^{24,25} Do not use ampicillin or amoxicillin, which lack effectiveness for this indication and are compromised by high levels of bacterial resistance.

Shorter course of treatment? When deciding on the length of treatment for recurrent UTI, remember that shorter antibiotic courses (3-5 d) are associated with similar rates of cure and progression to systemic infections as longer courses (7-10 d). Also, patients adhere better to the shorter treatment regimen and experience fewer adverse effects.^{26,27}

Standing prescription? Studies have shown that women know when they have a UTI. Therefore, for those who experience recurrent UTI, consider giving them a standing prescription for antibiotics that

they can initiate when symptoms arise (see Table 3).²⁴ Patient-initiated treatment yields similar rates of efficacy as clinician-initiated treatment, while avoiding the adverse effects and costs associated with preventive strategies (see text on page 48).²⁸

TIME FOR IMAGING AND REFERRAL?

For patients with a high risk for complicated UTI or a surgically amenable condition, either ultrasound or CT of the abdomen and pelvis with and without contrast is appropriate to evaluate for anatomic anomalies. While CT is the more sensitive imaging study to identify anomalies, ultrasound is less expensive and minimizes radiation exposure and is therefore also appropriate.¹⁸

Consider referring patients to a urologist if they have an underlying condition that may be amenable to surgery, such as bladder outlet obstruction, cystoceles, urinary tract diverticula, fistulae, pelvic floor dysfunction, ureteral stricture, urolithiasis, or vesicoureteral reflux.¹⁸ Additional risk factors for complicated UTI, which warrant referral as outlined by the Canadian Urologic Association, are summarized in Table 2.¹⁸

Two weeks later ... and it's back? Finally, for women who experience recurrent symptoms within two weeks of completing treatment, obtain a urine culture with antibiotic sensitivities to ensure that the infecting organism is not one typically associated with urolithiasis (*Proteus* and *Yersinia*) and that it is susceptible to planned antibiotic therapy.¹⁸ *Proteus* and *Yersinia* are urease-positive bacteria that may cause stone formation in the urinary tract system. Evaluate any patient who has a UTI from either organism for urinary tract stones.

PREVENTION DOS AND DON'TS

Popular myth suggests that recurrent UTIs are more common in patients who do not void after intercourse or those who douche, consume caffeinated beverages, or wear noncotton underwear. Research, however, has failed to show a relationship between any of these factors and recurrent UTIs.^{13,18} Clinicians should therefore stop recommending that patients modify these behav-

TABLE 2
Findings That Warrant Further Evaluation of Recurrent UTI

Asymptomatic microhematuria
Evidence of fistula (eg, fecaluria or pneumaturia)
Gross hematuria following treatment of infection
History of malignancy in the abdomen or pelvis
History of urolithiasis
History of urologic surgery or trauma
Immunocompromised state (eg, diabetes)
Outflow obstruction
Persistent bacteriuria following treatment with antibiotic to which it is sensitive
Recurrent pyelonephritis
Urea-positive bacteria associated with urolithiasis

Abbreviation: UTI, urinary tract infection
Source: Dason S et al. *Can Urol Assoc J*. 2011.¹⁸

TABLE 3
Antibiotics for the Acute Treatment of Recurrent Urinary Tract Infection

Antibiotic	Dose	Frequency	Duration (days)	Cure rate (%)
Trimethoprim-sulfamethoxazole	160 mg/800 mg	Twice daily	3	93
Nitrofurantoin	100 mg	Twice daily	5-7	93
Fosfomycin	3 g	Single dose	1	91
β-lactams*	Varies by drug	Varies by drug	3-5	89
Fluoroquinolones*	Varies by drug	Varies by drug	3	90

*The FDA recommends using only when no other treatment options exist.²⁵

Source: Gupta K et al. *Clin Infect Dis*. 2011.²⁴

iors to decrease recurrent infections.

Antibiotic prophylaxis decreases the rate of recurrent UTI by 95%.²⁹ It has been recommended for women who have had two or more UTIs in the past six months or three or more UTIs in the past year.^{29,30} Effective strategies to prevent recurrent UTI are low-dose continuous antibiotic prophylaxis or postcoital antibiotic prophylaxis.

While a test-of-cure culture is not typi-

TABLE 4
Antibiotics for Preventing
Recurrent Urinary Tract Infection

Antibiotic	Postcoital (within 2 hours)	Continuous
Trimethoprim	N/A	100 mg/d
Trimethoprim-sulfamethoxazole	40 mg/200 mg	40/200 mg/d or 3x/wk
Nitrofurantoin	50-100 mg	50-100 mg/d
Cephalexin	250 mg	125-250 mg/d
Fosfomycin	N/A	3 g every 10 d
Ciprofloxacin*	125 mg	125 mg/d
Norfloxacin*	200 mg	200 mg/d

*The FDA recommends using only when no other treatment options exist.²⁵
 Source: Aydin A et al. *Int Urogynecol J*. 2015.³¹

cally recommended following treatment for uncomplicated UTI, you will want to obtain a confirmatory urine culture one to two weeks before starting low-dose antibiotic prophylaxis. Base your choice of antibiotic on known patient allergies and previous culture results. Agents typically used are trimethoprim, TMP-SMX, or nitrofurantoin (see Table 4), none of which demonstrated superiority in a Cochrane review.³¹⁻³³ Although the same review showed no optimal duration of treatment, six to 24 months of treatment is usually recommended.^{29,33}

A single dose of antibiotic following intercourse may be as effective as daily low-dose prophylaxis for women whose UTIs are related to sexual activity.³⁴ Studies have shown that single doses of TMP-SMX, nitrofurantoin, cephalexin, or a fluoroquinolone (see earlier notes about the FDA warning on fluoroquinolone use) are similarly effective in decreasing the rate of recurrence (see Table 4).^{31,35,36}

Several nonpharmacologic strategies have been suggested for prevention of recurrent UTI. Among them are use of cranberry products, lactobacillus, vaginal estrogen in postmenopausal women, methenamine salts, and D-mannose.

A 2012 Cochrane review of 24 studies found that cranberry products were less effective in preventing recurrent UTIs than previously thought, with no statistically significant difference between women who took them and those who did not.³⁷

Results have been mixed in using lactobacilli or probiotics to prevent recurrent UTIs. One study examining the use of lactobacilli to colonize the vaginal flora found a reduction in the number of recurrent infections in premenopausal women taking intravaginal lactobacillus over 12 months.³⁸ A second study, involving postmenopausal women, found that those who were randomized to take lactobacillus tablets for 12 months had more frequent recurrences of UTIs than women randomized to take daily TMP-SMX.³⁹ However, this last study was designed as a noninferiority trial, and its results do not negate the prior study's findings. Additionally, vaginal estrogen, which is thought to work through colonization of the vagina with lactobacilli, has prevented recurrent UTIs in postmenopausal women.⁴⁰

Ascorbic acid (which is bacteriostatic), methenamine salts (which are hydrolyzed to bactericidal ammonia and formaldehyde), and D-mannose (which inhibits bacterial adherence) have been shown—in limited studies—to decrease recurrence of UTIs.⁴¹⁻⁴³ Further study is necessary to confirm their efficacy in preventing UTIs.

As noted, the only behavioral modifications that have been shown to decrease the risk for recurrent UTI are discontinuing the use of spermicides/spermicide-coated condoms or oral contraceptives, and decreasing the frequency of intercourse.¹³

Joan is started on a three-day course of TMP-SMX. Further questioning reveals that each of her three UTIs followed sexual intercourse. Her clinician discusses the options of self-directed therapy using continuous prophylaxis or postcoital prophylaxis, either of which would be an appropriate evidence-based intervention for her. After engaging in shared decision-making, she is prescribed TMP-SMX to be taken as a single dose following intercourse in the future. **CR**

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