

## CLINICAL PRACTICE

# Acute Uncomplicated Urinary Tract Infection in Women

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 28-year-old woman telephones her physician to report dysuria and urinary urgency during the preceding three days. She has had several previous urinary tract infections, including three during the past year. She is otherwise healthy, takes no medications, and is sexually active, using spermicide-coated condoms for contraception. She says she does not have fever, chills, vaginal discharge, or flank pain. How should she be evaluated and treated?**

## THE CLINICAL PROBLEM

During any given year, 11 percent of women report having had a urinary tract infection, and more than half of all women have at least one such infection during their lifetime.<sup>1</sup> Each year in the United States, acute cystitis is responsible for 3.6 million office visits by women 18 to 75 years old, accounting for direct costs of \$1.6 billion.<sup>2,3</sup>

Most acute lower urinary tract infections (also termed acute bacterial cystitis) are uncomplicated — that is, they are not associated with signs or symptoms of upper urinary tract infection (fever, chills, or flank pain) or other characteristics suggesting a high risk of upper urinary tract or complicated infection (e.g., diabetes, pregnancy, immunosuppression, previous pyelonephritis, symptoms lasting >14 days, or structural abnormalities of the urinary tract). After an initial infection, most women have sporadic recurrences, and a quarter to half have another infection within one year. Three to 5 percent have recurrent urinary tract infections — that is, symptomatic infections that follow the clinical resolution of a previous episode, generally (but not necessarily) after treatment.<sup>4</sup>

*Escherichia coli* causes 75 to 90 percent of episodes of acute uncomplicated cystitis, and *Staphylococcus saprophyticus* accounts for 5 to 15 percent, mainly in younger women.<sup>5</sup> Enterococci and aerobic gram-negative rods other than *E. coli*, such as *Klebsiella* species and *Proteus mirabilis*, are isolated in the remainder of the cases.

## STRATEGIES AND EVIDENCE

### CLINICAL HISTORY

The probability of cystitis in a woman with dysuria, urinary frequency, or gross hematuria is about 50 percent in primary care settings.<sup>6</sup> Symptoms suggesting vaginitis or cervicitis, such as vaginal irritation or discharge, reduce the likelihood of a diagnosis of cystitis by about 20 percent. Specific combinations of symptoms (e.g., dysuria and frequency without vaginal discharge or irritation) raise the probability of cystitis to more than 90 percent. When a woman who has previously had cystitis has symptoms suggesting a recurrence, there is an 84 to 92 percent chance that an infection is present.<sup>7,8</sup>

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**RISK FACTORS**

The most important risk factors for acute cystitis in young women are a history of previous episodes of cystitis and frequent or recent sexual activity.<sup>9</sup> Celibate women rarely have cystitis.<sup>10</sup> The relative odds of acute cystitis during the 48 hours after sexual intercourse increase by a factor as great as 60.<sup>11,12</sup> The use of spermicidal agents elevates the odds of infection by *E. coli* or by *S. saprophyticus* by a factor of two to three, irrespective of whether the exposure occurs with the use of a diaphragm or a spermicide-coated condom.<sup>13-16</sup> Women with frequent recurrences are more likely to have a maternal history of cystitis and to have had cystitis at an early age.<sup>9</sup> *E. coli* that encode the type 1 pilus, an organelle containing the adhesin FimH, which recognizes a wide range of cell types, are commonly associated with cystitis as well as sepsis and meningitis.<sup>17</sup>

Among elderly women living in institutional settings, the risk of urinary infection increases with age and debility, especially in those with conditions associated with impaired voiding or poor perineal hygiene (e.g., neurologic disease or dementia).<sup>18-20</sup> Estrogen deficiency may also contribute. Among generally healthy postmenopausal women, sexual activity is a less important predictor of cystitis than it is in younger women, and women with diabetes that requires pharmacologic treatment have approximately twice as high a risk of cystitis as nondiabetic women.<sup>21</sup> Recurrent cystitis in this age group is more likely in women who have cystoceles or urinary incontinence or who have previously undergone genitourinary surgery than in other women.<sup>22</sup>

**DIAGNOSTIC TESTS**

The presence of pyuria on urinalysis has high sensitivity (95 percent) but a relatively low specificity (71 percent) for infection. The presence of visible bacteria on microscopical examination is less sensitive but more specific (40 to 70 percent and 85 to 95 percent, respectively, depending on number of bacteria observed). Urinary dipstick testing has largely supplanted microscopy and urine-culture analysis, because the dipstick method is cheaper, faster, and more convenient. Dipsticks are most accurate when the presence of either nitrite or leukocyte esterase is considered a positive result, yielding a sensitivity of 75 percent and a specificity of 82 percent.<sup>23</sup> Defined in this fashion, a positive dipstick test indicates that the likelihood of infection is 25 percent higher than the pretest probability,

and a negative result indicates that it is 25 percent lower.

Most patients with consistent symptoms and a positive dipstick test can be treated without the need to obtain a urine culture, unless any of the factors associated with an upper tract or complicated infection is present. A negative result on a dipstick test cannot, however, reliably rule out an infection when the pretest likelihood is high, and in such instances it is advisable to obtain a culture. Cultures are also warranted to identify unusual or resistant organisms in women whose symptoms either do not abate or recur within two to four weeks after the completion of treatment.

The accuracy of the findings on a culture of a midstream, "clean-catch" specimen of urine depends on how a positive culture is defined. When the traditional criterion, 100,000 bacteria per milliliter, is applied to a voided urine sample, the specificity is high, but the sensitivity is only about 50 percent. Lowering the threshold to 1000 bacteria per milliliter in the cases of young women with symptoms of cystitis raises the sensitivity considerably, with minimal reduction in specificity.<sup>24</sup>

In managed-care settings, treating acute, uncomplicated cystitis by telephone consultation with the patient appears to be safe and effective.<sup>25-27</sup> Published protocols have included only women at low risk who have not recently had another urinary tract infection, who do not have symptoms suggesting vaginitis or cervicitis, and, in some institutions, who are less than 55 years old.<sup>25</sup> Women who do not meet these criteria should usually be seen and examined.

**TREATMENT**

A three-day course of trimethoprim-sulfamethoxazole results in bacteriologic cure (i.e., eradication of pathogens from the urine) within seven days after the start of treatment in approximately 94 percent of women (Table 1).<sup>28</sup> Longer courses (7 to 10 days) are not more effective in eradicating infection or preventing recurrences and are associated with a higher rate of adverse effects (30 percent, as compared with 18 percent). Single-dose treatment is somewhat less efficacious than the three-day course, eradicating infection in about 87 percent of patients, but it is associated with a lower rate of adverse effects (11 percent, as compared with 18 percent).<sup>28</sup> The efficacy of trimethoprim is similar whether it is used alone or in combination with sul-

famethoxazole, and it can be prescribed to patients who are allergic to sulfa. However, trimethoprim itself can cause hypersensitivity and rashes that are erroneously ascribed to sulfa.<sup>29</sup>

In some locales, such as the southeastern and western United States, including southern California, resistance to trimethoprim-sulfamethoxazole has become widespread and is detected in up to 18 percent of the pathogens cultured from the urine of women with acute cystitis,<sup>30,31</sup> most commonly those who have received this agent within the preceding six months.<sup>32,33</sup> Regional or local patterns of resistance<sup>34</sup> are tabulated by most large microbiology laboratories. Some authorities now advocate the use of trimethoprim-sulfamethoxazole only if the patient has no known allergy, if she has not recently received antibiotics, and if the local prevalence of resistance in urinary isolates is below 15 to 20 percent. However, because at least 50 percent of women infected with a resistant organism are successfully treated with trimethoprim-sulfamethoxazole, overall microbiologic and clinical cure rates of 80 to 85 percent can still be expected, even when the prevalence of resistance approaches 30 percent.<sup>35</sup>

The efficacy of ofloxacin equals or exceeds that of trimethoprim-sulfamethoxazole, with recurrence rates of 8 to 9 percent six weeks after the completion of therapy.<sup>36,37</sup> Other fluoroquinolones are presumed to have similar efficacy, but none of the drugs in this class should be regarded as a first-line agent because of their much higher cost and because of concern about promoting bacterial resistance. When trimethoprim-sulfamethoxazole is contraindicated, a three-day course of ciprofloxacin, levofloxacin, norfloxacin, lomefloxacin, or gatifloxacin is a reasonable alternative. Fluoroquinolones are active against *S. saprophyticus* and most typical gram-negative uropathogens, but against only 60 to 70 percent of enterococci. Moxifloxacin attains inadequate urinary concentrations and should not be used in this setting.

Although fewer than 5 percent of isolates are resistant to nitrofurantoin, this drug is considerably less active than trimethoprim-sulfamethoxazole or the fluoroquinolones against aerobic gram-negative rods other than *E. coli*, and it is inactive against proteus and pseudomonas species. Furthermore, it is usually prescribed for seven days and frequently causes gastrointestinal upset. Whereas the macrocrystalline formulation must be taken every six hours, the monohydrate macrocrystal is taken just

twice daily and causes somewhat fewer gastrointestinal symptoms. Nitrofurantoin may assume a more important role than it currently has if resistance to fluoroquinolones continues to spread or if shorter courses of nitrofurantoin are proved to be efficacious.

Fosfomycin tromethamine is another option, taken as a single dose of powder from a sachet. However, because it is less effective than trimethoprim-sulfamethoxazole or the fluoroquinolones, not reliably effective against *S. saprophyticus*, and expensive, it should be considered only when more effective agents cannot be prescribed.<sup>28</sup> The use of beta-lactams (e.g., ampicillin and amoxicillin) should be avoided because of frequent bacterial resistance to these agents and low cure rates. Amoxicillin-clavulanate may be somewhat more active but generally is not recommended because of its high cost and frequent adverse gastrointestinal effects and because data on clinical efficacy are limited.

More than 90 percent of women have relief of acute urinary symptoms within 72 hours after the initiation of antimicrobial therapy.<sup>38</sup> For some women with severe dysuria, use of phenazopyridine (Pyridium [Parke-Davis] or Uristat [Ortho-McNeil]) for one or two days may reduce symptoms, although data from controlled trials are lacking. This compound is now available on an over-the-counter basis, and there is concern that some of the women taking it for dysuria do not seek medical care.<sup>39</sup> Adverse effects include gastrointestinal upset, headaches, rash, hemolytic reactions (in patients with glucose-6-phosphate dehydrogenase deficiency), and (rarely) nephrotoxicity.

#### UNCOMPLICATED ACUTE PYELONEPHRITIS

Some otherwise healthy, nonpregnant women who present with signs or symptoms of acute pyelonephritis (including fever, chills, and flank pain) can be safely treated as outpatients if they do not have factors associated with an upper tract or complicated infection or signs of systemic toxicity, are able to take oral medications, and can be closely followed.<sup>40</sup> For such patients, a 14-day course of a fluoroquinolone, or of trimethoprim-sulfamethoxazole if the organism is susceptible to it, is recommended.<sup>28</sup> Oral amoxicillin or amoxicillin-clavulanate is an alternative for infections caused by gram-positive organisms. Women with acute pyelonephritis who do not meet these criteria should be treated in the hospital with parenteral antimicrobial agents, at least initially.

**Table 1.** Recommended Regimens for the Treatment of Acute Uncomplicated Urinary Tract Infection and for Prophylaxis against Recurrent Urinary Tract Infection.\*

Type of Urinary Tract Infection and Treatment	Antimicrobial Agent	Dosage	Approximate Retail Cost† <i>dollars</i>	FDA Pregnancy Category‡	Adverse Effects
Acute uncomplicated	Trimethoprim–sulfamethoxazole (DS-160/800 mg)	1 tablet twice daily for 3 days	1.83	C	Common: anorexia, nausea, vomiting, rash, urticaria; rare: blood dyscrasias, hypersensitivity or photosensitivity, hepatic necrosis
	Trimethoprim	100 mg twice daily for 3 days	4.33	C	Common: diarrhea, rash; rare: glossitis, taste changes, hypersensitivity, blood dyscrasias
	Norfloxacin	400 mg twice daily for 3 days	25.21	C	Common: dizziness, restlessness, headache, diarrhea, nausea, rash, vaginitis; rare: convulsions, psychosis, severe hypersensitivity, tendon rupture
	Ciprofloxacin	250 mg twice daily for 3 days	53.56	C	As listed above for norfloxacin
	Levofloxacin	250 mg every day for 3 days	43.92	C	As listed above for norfloxacin
	Gatifloxacin	400 mg every day for 3 days or a single 400-mg dose	21.61 or 7.20	C	As listed above for norfloxacin
	Lomefloxacin	400 mg twice daily for 3 days	35.96	C	As listed above for norfloxacin
	Nitrofurantoin macrocrystals	50 or 100 mg four times daily for 7 days	20.29 or 35.22	B	Common: anorexia, nausea, vomiting, headache; rare: pulmonary hypersensitivity, hepatotoxicity, hemolytic anemia, peripheral neuropathy
	Nitrofurantoin monohydrate macrocrystals	100 mg twice daily for 7 days	29.96	B	As listed above for nitrofurantoin macrocrystals (adverse gastrointestinal effects less common)
	Fosfomycin tromethamine	Single 3-g dose (powder)	33.97	B	Common: nausea, vomiting, diarrhea, vaginitis; rare: rash, hypersensitivity
Recurrent	Continuous prophylaxis (initiated after eradication of acute infection)				
	Trimethoprim–sulfamethoxazole (SS-80/400 mg)	Half tablet every night or three times weekly at night for 6 mo	27.50 or 11.00	C	As listed above for trimethoprim–sulfamethoxazole
	Trimethoprim	100 mg every night for 6 mo	102.73	C	As listed above for trimethoprim
	Nitrofurantoin macrocrystals	50 or 100 mg every night for 6 mo	121.74 or 211.32	B	As listed above for nitrofurantoin macrocrystals, plus dyspnea due to interstitial pulmonary fibrosis

Table 1. (Continued.)

Type of Urinary Tract Infection and Treatment	Antimicrobial Agent	Dosage	Approximate Retail Cost† <i>dollars</i>	FDA Pregnancy Category‡	Adverse Effects
	Norfloxacin	200 mg every night for 6 mo	352.92	C	As listed above for norfloxacin
Postcoital regimen	Trimethoprim–sulfamethoxazole (SS-80/400 mg)	Half tablet or one tablet	0.15 or 0.31 per dose	C	As listed above for trimethoprim–sulfamethoxazole
	Nitrofurantoin macrocrystals	Single 50- or 100-mg dose	1.06 or 1.75 per dose	B	As listed above for nitrofurantoin macrocrystals
	Ciprofloxacin	Single 250-mg dose	8.93 per dose	C	As listed above for norfloxacin
	Levofloxacin	Single 250-mg dose	7.32 per dose	C	As listed above for norfloxacin
	Gatifloxacin	Single 400-mg dose	7.20 per dose	C	As listed above for norfloxacin
Intermittent self-treatment (begun at onset of symptoms)	Trimethoprim–sulfamethoxazole (DS-160/800 mg)	1 tablet twice daily for 3 days	1.83	C	As listed above for trimethoprim–sulfamethoxazole
	Trimethoprim	100 mg twice daily for 3 days	3.42	C	As listed above for trimethoprim
	Norfloxacin	400 mg twice daily for 3 days	23.45	C	As listed above for norfloxacin
	Ciprofloxacin	250 mg twice daily for 3 days	53.56	C	As listed above for norfloxacin
	Levofloxacin	250 mg every day for 3 days	43.92	C	As listed above for norfloxacin
	Gatifloxacin	400 mg every day for 3 days or single 400-mg dose	21.60 or 7.20	C	As listed above for norfloxacin
	Lomefloxacin	400 mg twice daily for 3 days	35.96	C	As listed above for norfloxacin

\* Drugs are listed in descending order of general preference. DS denotes double-strength, and SS single-strength.

† The dollar amounts indicate the cost of the entire course of treatment (unless noted otherwise) and are based on the most economical purchase price at a Web-based retail pharmacy as of April 25, 2003.

‡ For drugs in Food and Drug Administration (FDA) pregnancy category B, studies in animals have not shown that the drug poses a risk to the fetus and no controlled studies in humans have been conducted, or studies in animals have shown an adverse effect on the fetus but well-controlled studies in pregnant women have not shown that there is a risk to the fetus. For drugs in category C, studies in animals have shown that the drug exerts teratogenic or embryocidal effects but no controlled studies in women have been conducted, or no studies in either animals or humans have been conducted.

#### FOLLOW-UP AND EVALUATION

Routine follow-up, including urine culture, is generally unnecessary after treatment for cystitis, even among women with sporadic recurrences, unless symptoms do not abate. There is no reason to pursue imaging studies (e.g., ultrasound, computed tomography, or pyelography) or cystoscopy in most cases, since these studies rarely reveal a correctable abnormality in the absence of other indications, such as persistent hematuria.<sup>41</sup>

#### RECURRENT INFECTIONS

Women who have recurrent infections and are exposed to vaginal spermicides, from either condoms or diaphragms, should consider alternative methods of contraception or protection from sexually transmitted diseases. Continuous and postcoital prophylaxis with low-dose antimicrobial agents and intermittent self-treatment are effective in preventing recurrent cystitis.<sup>42</sup> Prophylaxis should not be initiated until the eradication of active infection is

confirmed by a negative urine culture at least one to two weeks after treatment is discontinued.

Continuous prophylaxis, typically with medication taken once daily at bedtime, is an option for women who have had two or more symptomatic infections during one 6-month period or three or more such infections over a 12-month period.<sup>4</sup> Randomized, placebo-controlled trials have documented that continuous prophylaxis with nitrofurantoin, trimethoprim (with or without sulfamethoxazole), ciprofloxacin, or norfloxacin diminishes recurrences by 95 percent (from 2 to 3 episodes per patient-year to 0.1 to 0.2 episode per patient-year) and may prevent pyelonephritis.<sup>4</sup> Because trials comparing specific agents have lacked sufficient statistical power, one agent cannot be recommended over another.<sup>42</sup> Prophylaxis is usually initiated on a trial basis for six months but has been safely and effectively continued for two to five years without the emergence of resistant organisms.<sup>43</sup> The rates of adverse effects associated with the various agents range from 7 to 40 percent for trimethoprim-containing regimens, 0 to 40 percent for nitrofurantoin, 7 to 21 percent for norfloxacin, and 13 percent for ciprofloxacin.<sup>42</sup> The most common adverse effects are gastrointestinal symptoms, rash, and yeast vaginitis (Table 1).

Postcoital prophylaxis may be attractive to women who describe a clear relation between sexual intercourse and subsequent cystitis. The reduction in the frequency of recurrences when nitrofurantoin, trimethoprim-sulfamethoxazole, or a fluoroquinolone is used after intercourse has approximated that obtained with continuous prophylaxis, although data from head-to-head trials are not available.<sup>44</sup>

Another strategy is intermittent self-treatment, rather than prophylaxis. Many women can accurately diagnose recurrent cystitis themselves and can be instructed to begin a three-day course of an antibiotic agent at the onset of symptoms. The frequency of antibiotic use with this approach is similar to that with postcoital prophylaxis, and many women find it preferable.<sup>8</sup> Women should be instructed to seek medical attention if symptoms do not resolve within 48 to 72 hours after the completion of the course.

Long advocated to prevent cystitis, cranberry juice contains proanthocyanidins that appear to inhibit the attachment of pathogens to uroepithelium.<sup>45</sup> Randomized trials suggest that 200 to 750 ml daily of cranberry (or lingonberry) juice or cran-

berry-concentrate tablets reduces the risk of symptomatic, recurrent infection by 12 to 20 percent.<sup>46-48</sup> The amount of actual cranberry in products marketed as cranberry juice ranges from 5 to 100 percent.<sup>49</sup> The actual cranberry content of tablets and capsules varies, and their equivalence to juice products is uncertain.<sup>50</sup>

Several studies indicate that postcoital voiding does not prevent cystitis.<sup>9,12</sup> There is also no evidence that poor urinary hygiene predisposes women to recurrent infections, and there is no rationale for giving women specific instructions regarding the frequency of urination, the timing of voiding, wiping patterns, douching, the use of hot tubs, or the wearing of pantyhose.

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#### AREAS OF UNCERTAINTY

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##### **ARE THERE RELIABLE PREDICTORS OF THE FAILURE OF TREATMENT FOR ACUTE CYSTITIS?**

Ten to 20 percent of women who have a urinary tract infection have another within a few months; reliable predictors of recurrence are lacking. Although some instances of recurrence result from the failure to eradicate the original infection, most are due to reinfection by the same strain, which persists within the vaginal or fecal flora, or infection by a new strain. Ongoing research into host-bacterium interactions and the possible intracellular persistence of bacteria may yield new therapies.

##### **WHAT IS THE OPTIMAL THERAPY FOR ACUTE UNCOMPLICATED CYSTITIS?**

Studies are needed to assess the efficacy of shorter courses of nitrofurantoin (i.e., 3 to 5 days, rather than 7 to 10 days) and to assess the cost effectiveness of this agent or fluoroquinolones in short courses as compared with trimethoprim-sulfamethoxazole. In such studies, the potential for promoting increased resistance to fluoroquinolones should be taken into account. A concern is that patterns of antimicrobial resistance are becoming difficult to track because empirical therapy without analysis of urine cultures is common practice.

##### **IS EXOGENOUS ESTROGEN EFFECTIVE IN PREVENTING RECURRENT URINARY TRACT INFECTIONS IN POSTMENOPAUSAL WOMEN?**

It has been hypothesized that exogenous estrogen can prevent recurrent cystitis by reversing genitourinary mucosal atrophy and restoring a more normal

milieu in the vagina. In a double-blind trial, 36 postmenopausal women using topical estriol cream had significantly fewer documented urinary tract infections than 24 women assigned to placebo (an average of 0.5 vs. 5.9 infections per patient-year).<sup>51</sup> In a randomized, open-label study, the use of an estrogen-impregnated ring was also associated with a significant reduction in recurrent infections.<sup>52</sup> Further studies with larger sample sizes are needed. Although small studies have suggested a benefit associated with oral estrogen replacement, recent randomized trials have failed to show a favorable effect in preventing cystitis, and there is currently no rationale for prescribing oral estrogens to prevent recurrent cystitis.<sup>53-55</sup>

#### GUIDELINES

The Infectious Diseases Society of America has issued guidelines on the management of acute cystitis.<sup>28</sup> A three-day course of trimethoprim-sulfamethoxazole is recommended as initial therapy, except in communities with rates of resistance exceeding 10 to 20 percent, in which case empirical treatment with a fluoroquinolone is an option.

#### CONCLUSIONS AND RECOMMENDATIONS

Because cystitis is common but, in most women, relatively benign, therapy should be safe, convenient, and inexpensive. In most settings, uncomplicated acute cystitis can be safely treated on the basis of the clinical history with a three-day course of trimethoprim-sulfamethoxazole, and I would prescribe such a regimen in the case described in the vignette. However, this recommendation is subject to modification if fluoroquinolones are subsequently shown to offer superior results in geographic locations where resistance to trimethoprim-sulfamethoxazole is common. Women who have frequent recurrences, such as the patient in the vignette, should be advised to avoid exposure to vaginal spermicides and should be offered prophylaxis or methods of self-treatment. Imaging studies should be reserved for women with complicated infections.

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