CLINICAL PRACTICE

Uncomplicated Urinary Tract Infection

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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 30-year-old woman calls you to report a 2-day history of worsening dysuria and urinary urgency and frequency. She reports having no fever, chills, back pain, or vaginal irritation or discharge. One month ago, you treated her with a 3-day course of trimethoprim–sulfamethoxazole for presumptive cystitis, and her symptoms resolved. She is otherwise healthy, but this is her third episode in the past year. How should her case be managed?

THE CLINICAL PROBLEM

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INCIDENCE

Urinary tract infection is the most common bacterial infection encountered in the ambulatory care setting in the United States, accounting for 8.6 million visits (84% by women) in 2007.[1] The self-reported annual incidence of urinary tract infection in women is 12%, and by the age of 32 years, half of all women report having had at least 1 urinary tract infection.[2] The incidence of cystitis (bladder infection) was 0.70 episodes per person-year in a study of college women starting a new contraceptive method[3] and 0.07 episodes per person-year in a population-based study of postmenopausal women.[4] Among young, healthy women with cystitis, the infection recurs in 25% of women within 6 months after the first urinary tract infection,[5] and the recurrence rate increases with more than 1 prior urinary tract infection.[6,7] Acute uncomplicated pyelonephritis is much less common than cystitis (estimated ratio, 1 case of pyelonephritis to 28 cases of cystitis),[7] with a peak annual incidence of 25 cases per 10,000 women 15 to 34 years of age.[8]

CLASSIFICATION

Episodes of acute cystitis and pyelonephritis occurring in healthy premenopausal, nonpregnant women with no history suggestive of an abnormal urinary tract are generally classified as uncomplicated, whereas all others are classified as complicated. This distinction has been used to guide the choice and duration of antimicrobial treatment, with broader-spectrum agents and longer courses of treatment often recommended for persons with complicated urinary tract infections. However, this classification scheme does not account for the diversity of complicated urinary tract infection syndromes and misclassifies as complicated many urinary tract infections that can be managed with short-course treatment regimens (Table 1). A classification scheme that stratifies patients with urinary tract infection into multiple, homogeneous categories has been proposed by European experts, but it is not routinely used in practice.[9]

PATHOGENESIS

Symptomatic urinary tract infection in a healthy woman is a complex event. It is initiated when potential urinary pathogens from the bowel, or in some cases from the va-

gina (as a result of direct inoculation during sexual activity), colonize the periurethral mucosa and ascend through the urethra to the bladder and in some cases through the ureter to the kidney. (The circumstances under which this occurs remain unclear; pyelonephritis is rare in women with untreated cystitis and in men and women with untreated asymptomatic bacteriuria.) Uropathogenic *Escherichia coli*, the predominant pathogens in uncomplicated urinary tract infection, are a specific subset of extraintestinal pathogenic *E. coli* that have the potential for enhanced virulence. Virulence and fitness factors include fimbriae, flagella, diverse adhesins, siderophores, toxins, polysaccharide coatings, and other properties that assist the bacteria in avoiding or subverting host defenses, injuring or invading host cells and tissues, and stimulating a noxious inflammatory response.[10,11] However, the triggers for development of urinary symptoms are not entirely clear.

The vast majority of episodes of recurrent cystitis in healthy women, up to two thirds of which are recurrences involving the same strain of bacteria that caused the initial infection, are thought to be reinfections.[12] Uropathogenic strains can persist in the fecal flora for years after elimination from the urinary tract and can cause recurrent urinary tract infections. Laboratory studies in a mouse model show that inoculated *E. coli* invade the epithelium, resist clearance with antimicrobial agents, and develop quiescent epithelial reservoirs that can result in recurrent bacteriuria.[13] Evidence that this phenomenon occurs in humans is sparse, but intracellular biofilm-like collections of bacteria, similar to those seen in the mouse model, have been identified in exfoliated cells in the urine of women with cystitis.[14]

RISK FACTORS

Risk factors for uncomplicated sporadic and recurrent cases of cystitis and pyelonephritis include sexual intercourse, use of spermicides, previous urinary tract infection, a new sex partner (within the past year), and a history of urinary tract infection in a first-degree female relative.[3,15-17] Case–control studies have shown no significant associations between recurrent urinary tract infection and precoital or postcoital voiding patterns, daily beverage consumption, frequency of urination, delayed voiding habits, wiping patterns, tampon use, douching, use of hot tubs, type of underwear, or body-mass index,[16] but at least some of these null findings might reflect a misclassification of behaviors (particularly if behavioral changes were made after the diagnosis of recurrent urinary tract infection). A genetic predisposition to recurrent urinary tract infection is suggested by the strong association between a history of urinary tract infection in one or more first-degree female relatives and an increased risk of recurrent cystitis and pyelonephritis[17]; marked familial clustering of cases of acute pyelonephritis among the relatives of pyelonephri-

Table 1. Features of Uncomplicated versus Complicated Cystitis and Pyelonephritis.

Variable	Uncomplicated	Complicated*
Typical patient	Otherwise healthy, ambulatory women with no history suggestive of anatomical or functional abnormality of the urinary tract	Men, women, or children with functional, metabolic, or anatomical conditions that may increase the risk of treatment failure or serious outcomes (e.g., obstruction, stone, pregnancy, male sex, diabetes, neurogenic bladder, renal insufficiency, immunosuppression)
Clinical spectrum	Mild cystitis to severe pyelonephritis	Mild cystitis to life-threatening urosepsis
Diagnosis	Infection suspected on the basis of typical symptoms; urinalysis and urine culture not routinely needed for suspected cystitis but recommended for pyelonephritis	Typical symptoms or symptoms that are atypical and subtle (e.g., owing to catheterization, impaired sensation, or altered mental status); urinalysis and urine culture indicated
Antimicrobial resistance	Common but generally predictable (antimicrobial resistance alone does not warrant the designation complicated UTI)	Multidrug resistance common and less predictable; fluoroquinolone resistance not uncommon
Empirical antimicrobial treatment	For cystitis: first-line short-course antimicrobial regimen; for pyelonephritis: first-line oral or intravenous antimicrobial regimen for 5 to 14 days, depending on severity and need for hospitalization	For cystitis: 7-day or longer course of fluoroquinolone preferred†; for pyelonephritis: broad-spectrum antimicrobial agent (e.g., piperacillin–tazobactam or carbapenem, plus vancomycin with either of these agents if MRSA suspected); limited data on duration, but 14-to-21-day duration recommended in general
Response to treatment	Predictable with appropriate agent for recommended treatment duration; persistent symptoms or early recurrence suggests presence of a complicating factor	Less predictable regardless of antimicrobial susceptibility; may require instrumentation for cure

* Complicated urinary tract infections (UTIs) are heterogeneous in that the risks of infection and of treatment failure vary. Current classification schemes are overly simplistic, especially for patients with complicated infections, but the value of more complex classification schemes[9] has not yet been shown. MRSA denotes methicillin-resistant *Staphylococcus aureus*.

† Short-course regimens are likely to be effective for mild-to-moderate cystitis in healthy, ambulatory, compliant women who are elderly, have catheter-associated UTIs, are pregnant, or have mild diabetes.

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tis-prone children, associated with significantly lower expression of CXCR1, an interleukin-8 receptor[18]; and overrepresentation of the blood-group antigen nonsecretor phenotype and P1 phenotype among girls and women with recurrent urinary tract infection.[12]

MICROBIOLOGY

In women, *E. coli* causes 75 to 95% of episodes of uncomplicated cystitis and pyelonephritis; the remaining cases are caused by other Enterobacteriaceae, such as *Klebsiella pneumoniae*, and grampositive bacteria such as *Staphylococcus saprophyticus*, *Enterococcus faecalis*, and *Streptococcus agalactiae* (group B streptococcus). However, the latter two organisms, when isolated from voided urine from women with symptoms of uncomplicated cystitis, often represent contamination of the voided specimen.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Cystitis is usually manifested as dysuria with or without frequency, urgency, suprapubic pain, or hematuria. Clinical manifestations suggestive of pyelonephritis include fever (temperature >38°C), chills, flank pain, costovertebral-angle tenderness, and nausea or vomiting, with or without symptoms of cystitis. Dysuria is also common with urethritis or vaginitis, but cystitis is more likely when symptoms include frequency, urgency, or hematuria; when the onset of symptoms is sudden or severe; and when vaginal irritation and discharge are not present.[19,20] The probability of cystitis is greater than 50% in women with any symptoms of urinary tract infection and greater than 90% in women who have dysuria and frequency without vaginal discharge or irritation.[20] The only finding on physical examination that increases the probability of urinary tract infection is costovertebral-angle tenderness (indicating pyelonephritis).[20]

Assessment for pyuria and bacteriuria is often performed with the use of commercially available dipsticks that test for leukocyte esterase, an enzyme released by leukocytes, and for nitrites, since some bacteria reduce urinary nitrates to nitrites. The dipstick test is most accurate for predicting UTI when the presence of either leukocyte ester-

ase or nitrite is considered a positive result, with a sensitivity of 75% and a specificity of 82%.[20,21] However, results of the dipstick test provide little useful information when the history is strongly suggestive of urinary tract infection, since even negative results for both tests do not reliably rule out the infection in such cases.[20]

A urine culture is performed to confirm the presence of bacteriuria and the antimicrobial susceptibility of the infecting uropathogen. This test is indicated in all women with suspected pyelonephritis but is not necessary for the diagnosis of cystitis, given the reliability of the patient's history in establishing the diagnosis and the delayed availability of culture results.[20,22] Moreover, studies comparing voided urine specimens and bladder-aspirate specimens in women with cystitis have shown that the traditional criterion for a positive culture of voided urine (10^5 colony-forming units per milliliter) is insensitive for bladder infection, and 30 to 50% of women with cystitis have colony counts of 10^2 to 10^4 colony-forming units per milliliter in voided urine.[23] Since most clinical laboratories do not quantify bacteria below a threshold of 10^4 colony-forming units per milliliter in voided urine specimens, a culture report of "no growth" in a woman with urinary symptoms should be interpreted with caution.

Given the accuracy of a diagnosis that is based on the patient's symptoms, in selected women with symptoms of cystitis, the infection can be successfully managed without in-person assessment.[20,24] However, in women who have symptoms of cystitis along with vaginal discharge or irritation, it is reasonable to delay antimicrobial treatment until vaginal examination has been performed and the results of a urine culture are available.[20]

MANAGEMENT

Acute uncomplicated cystitis is a benign condition, with early resolution of symptoms observed in 25 to 42% of women — and only rare cases of progression to pyelonephritis — in the placebo groups in randomized, controlled trials.[25,26] However, cystitis is associated with considerable morbidity,[27] and antimicrobial drugs are routinely prescribed, the primary goal being the rapid resolution of symptoms.[28] The choice of regimen has become more complicated as antimicrobial resistance among the uropathogenic strains of *E. coli* has increased worldwide. Recent large, international studies of the in vitro susceptibility of *E. coli* strains that cause uncomplicated urinary tract infection[28] have revealed rates of resistance to amoxicillin of 20% or higher in all regions and similar rates of resistance to trimethoprim–sulfamethoxazole in many regions. Rates of resistance to fluoroquinolones, oral cephalosporins, and amoxicillin–clavulanate are generally lower than 10%, but resistance to the fluoroquinolones is increasing; the lowest rates of resistance are to nitrofurantoin, fosfomycin, and mecillinam (for which pivmecillinam is the prodrug). (Mecillinam and pivmecillinam are not available in the United States.) Uncomplicated urinary tract infections caused by extended-spectrum beta-lactamase–producing (beta-lactam–resistant) strains of *E. coli* are increasingly being reported worldwide.[29,30] Most of these strains are also resistant to the fluoroquinolones and trimethoprim–sulfamethoxazole, but limited data show that fosfomycin, nitrofurantoin, and to a lesser extent, amoxicillin–clavulanate have in vitro and clinical activity.[29,31]

The recently updated guidelines of the Infectious Diseases Society of America (IDSA)[28] emphasize the importance of considering ecologic adverse effects of antimicrobial agents (i.e., selection for colonization or infection with multidrug-resistant organisms — so-called "collateral damage") when one is selecting a treatment regimen. Thresholds are suggested for the prevalence of resistance in a community above which a drug is not recommended (20% for trimethoprim–sulfamethoxazole and 10% for fluoroquinolones); however, clinicians rarely have access to such information. Local resistance rates reported in hospital antibiograms often reflect cultures obtained from inpatients or those with complicated or recurrent infections and probably overestimate the rates of resistance among patients with uncomplicated urinary tract infections.

Cystitis

Recommended empirical treatment regimens for acute uncomplicated cystitis are shown in Table 2. Short-course regimens (ranging from a single dose to a 5-day regimen, depending on the antimicrobial agent) are recommended as first-line treatment, since they are as effective as longer regimens in achieving symptomatic cure and have fewer adverse effects.[28,32,33] Given the benign nature of uncomplicated cystitis along with its high frequency, the guidelines give equal weight to the risk of ecologic adverse effects and drug effectiveness in the recommendations. Nitrofurantoin is well tolerated and has good efficacy when the monohy-

Table 2. Empirical Treatment of Acute Uncomplicated Cystitis.*

Antimicrobial Regimen	Efficacy	Comments
First-line therapy		
Nitrofurantoin monohydrate macrocrystals, 100 mg twice daily for 5 days (with meals)†	Clinical efficacy of 5-to-7-day regimen: 93% (84 to 95%); a 3-day regimen appears to be less effective than longer regimens; minimal in vitro resistance to *E. coli*	Minimal ecologic adverse effects; avoid if pyelonephritis is suspected; common side effects include nausea, headache, and flatulence
TMP-SMX, 160 mg and 800 mg twice daily for 3 days‡	Clinical efficacy of 3-day TMP-SMX regimen: 93% (90 to 100%); similar efficacy with trimethoprim alone, 100 mg twice daily for 3 days‡; avoid if resistance rate is greater than 20% or if exposure occurred within prior 3 to 6 mo	Probably fewer ecologic adverse effects than seen with fluoroquinolones; common side effects include nausea, vomiting, anorexia, rash, urticaria, hematologic complications, and photosensitivity
Fosfomycin trometamol (Monurol), 3-g sachet in a single dose†	Clinical efficacy: 91% based on a single, random-ized trial,[28] but fosfomycin appears to be less effective than TMP-SMX or fluoroquino-lones[28,32]; minimal in vitro resistance, but most laboratories do not test for resistance	Minimal ecologic adverse effects; avoid if pyelonephritis is suspected; common side effects include diarrhea, nausea, headache, and vaginitis
Pivmecillinam, 400 mg twice daily for 3 to 7 days	Clinical efficacy of 3-to-7-day regimens: 73% (55 to 82%); minimal in vitro resistance	Minimal ecologic adverse effects; avoid if pyelonephritis is suspected; common side effects include nausea, vomiting, and diar-rhea; not available in United States
Second-line therapy		
Fluoroquinolones: ciprofloxacin, 250 mg twice daily for 3 days‡; levofloxacin, 250 mg or 500 mg once daily for 3 days‡	Clinical efficacy: 90% (85 to 98%); minimal in vitro resistance, but prevalence in United States is rising; high prevalence of in vitro resistance in some regions of the world	Propensity for ecologic adverse effects; when possible, reserve for uses other than cysti-tis; common side effects include nausea, vomiting, diarrhea, headache, drowsiness, and insomnia
Beta-lactams (e.g., amoxicillin–clavulanate, cefdinir, cefaclor, and cefpodoxime–proxetil) for 3 to 7 days†	Clinical efficacy of 3-to-5-day regimens: 89% (79 to 98%); less effective than TMP-SMX or fluoroquinolones[28,32]; few efficacy data on narrow-spectrum cephalosporins (e.g., cephalexin); avoid empirical amoxicillin or ampicillin	Probably fewer ecologic adverse effects than seen with parenteral broad-spectrum cephalosporins; common side effects include diarrhea, nausea, vomiting, rash, and urticaria

* Efficacy rates and ranges and antimicrobial recommendations are based on the Infectious Diseases Society of America guidelines.[28,32] Cure rates should not necessarily be compared across agents, owing to differences among trials and varying local patterns of antimicrobial resis-tance. TMP-SMX denotes trimethoprim–sulfamethoxazole. The costs of these antimicrobial agents vary considerably; in general, TMP-SMX and ciprofloxacin are the least expensive, with nitrofurantoin and levofloxacin being relatively higher in cost and fosfomycin (nongeneric) and the beta-lactam regimens shown here being the most expensive.
† This regimen presents no clear risk to the fetus, on the basis of studies in animals, humans, or both (pregnancy category B).
‡ Studies in animals have shown an adverse effect of this regimen on the fetus (pregnancy category C); use only if the potential benefit justi-fies the potential risk to the fetus.

drate macrocrystalline formulation is given twice daily for 5 days, and it has a low propensity for ecologic adverse effects.[28] Despite concern about the high prevalence of resistance to trimethoprim–sulfamethoxazole, it remains very effective (with an estimated overall clinical cure rate of 85% even in regions where the prevalence of resistance is 30%[34]) and is inexpensive and well tolerated. Fos-fomycin and pivmecillinam are also considered first-line regimens owing to their low propensity for ecologic adverse effects, even though they ap-pear to be clinically inferior to trimethoprim–sulfamethoxazole and fluoroquinolones.[28]

The choice of an antimicrobial agent should be individualized on the basis of the patient's allergy and compliance history, local practice patterns, the prevalence of resistance in the local community (if known), availability, cost, and patient and provider threshold for failure.[28] If a first-line antimicrobial agent is not a good choice on the basis of one or more of these factors, fluoroquinolones or beta-lactams are reasonable alternatives, although it is preferable to minimize their use because of con-cerns about ecologic adverse effects and, with re-spect to beta-lactams, efficacy.[28] Unfortunately, U.S. surveys show that fluoroquinolones are the

Table 3. Outpatient Empirical Treatment of Acute Uncomplicated Pyelonephritis.*

Antimicrobial Regimen†	Efficacy	Comments
Fluoroquinolones: ciprofloxacin, 500 mg given orally twice daily,‡ or 1 g (extended–release) given orally once daily, for 7 days‡; levofloxacin, 750 mg given orally once daily for 5 days‡	Clinical efficacy of ciprofloxacin, 500 mg given orally twice daily for 7 days: 96% (some patients were given an initial dose of intravenous ciprofloxacin)[38]; clinical efficacy of levofloxacin, 750 mg given orally or intravenously once daily for 5 days: 86%; versus ciprofloxacin, 400 mg given intravenously or 500 mg orally twice daily for 10 days: 81% (most subjects in both groups received oral therapy)[39]	Oral fluoroquinolone is empirical drug of choice; propensity for ecologic adverse effects; common side effects include nausea, vomiting, diarrhea, headache, drowsiness, and insomnia
TMP-SMX, 160 mg and 800 mg orally twice daily for 14 days‡	Clinical efficacy: 83% (some patients were given an initial dose of intravenous ceftriaxone); clinical efficacy: 92% if pathogen was susceptible *E. coli* strain vs. 35% if not susceptible[38]; inferior choice for empirical therapy owing to high rates of resistance and corresponding failure rates; highly effective if strain is susceptible; *E. coli* resistance exceeds 20% in many areas of world, including some areas of the United States	Probably fewer ecologic adverse effects than with fluoroquinolones; only the 14-day regimen has been approved by FDA and recommended by IDSA guidelines,[28] but 7-to-10-day regimens are likely to be effective in women when defervescence is rapid; common side effects include nausea, vomiting, anorexia, rash, urticaria, hematologic complications, and photosensitivity
Oral beta-lactams (specific agents not listed in IDSA guidelines)[28] for 10 to 14 days	Data are limited, but efficacy is inferior to that of TMP-SMX and fluoroquinolones[28,32]; use only when other recommended agents cannot be used	Probably fewer ecologic adverse effects than with parenteral broad-spectrum cephalosporins; common side effects include diarrhea, nausea, vomiting, rash, and urticaria

* Efficacy rates and antimicrobial recommendations are based on the Infectious Diseases Society of America (IDSA) guidelines.[28,32] FDA denotes Food and Drug Administration.
† If tolerance or resistance to the oral medication is a concern because the prevalence of resistance in the community exceeds 10% (fluoroquinolone) or is unknown (trimethoprim–sulfamethoxazole [TMP-SMX]), because exposure has occurred in the past 3 to 6 months, or because an oral beta-lactam is used, an initial intravenous dose of ceftriaxone, 1 g, or gentamicin, 5 to 7 mg per kilogram of body weight, should be given. (If tolerance to oral fluoroquinolone is a concern, intravenous ciprofloxacin, 400 mg, can also be given.)
‡ Studies in animals have shown an adverse effect of this regimen on the fetus (pregnancy category C); use only if the potential benefit justifies the potential risk to the fetus.

most commonly used antimicrobials for urinary tract infection in the ambulatory setting.[35] Given increasing antimicrobial resistance and the benign nature of cystitis, antimicrobial-sparing management strategies are of increasing interest (e.g., antiinflammatory drugs or delayed treatment, neither of which is in common clinical use).[30,36,37]

Pyelonephritis
Most episodes of acute uncomplicated pyelonephritis are now treated in the outpatient setting.[8,24] Table 3 lists recommended outpatient empirical treatment regimens.[38,39] (For information about inpatient treatment regimens, see Expanded Table 3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) A urine culture and susceptibility test should be performed to guide treatment. Women should be admitted if pyelonephritis is severe, if there is hemodynamic instability or any complicating factor (e.g., diabetes, renal stone, or pregnancy), if oral medications

are not tolerated, or if there is concern regarding potential nonadherence to treatment.[22] Empirical treatment should have broad-spectrum in vitro activity against likely uropathogens and be started quickly to minimize progression. Fluoroquinolones are the only oral antimicrobials recommended for the outpatient empirical treatment of acute uncomplicated pyelonephritis.[28] When there is concern about antimicrobial resistance or tolerance of oral medications, one or more doses of a broad-spectrum parenteral antimicrobial are recommended until in vitro activity can be assured.

Recurrent Cystitis
Urinary symptoms that persist or recur within a week or two of treatment for uncomplicated cystitis suggest infection with an antimicrobial-resistant strain or, rarely, relapse. In such women, a urine culture should be performed and treatment should be initiated with a broader-spectrum antimicrobial agent, such as a fluoroquinolone. Episodes of

Table 4. Strategies for Nonantimicrobial Prevention of Recurrent Acute Uncomplicated Cystitis.*	
Strategy	**Comments**
Behavioral counseling	
Recommend abstinence or reduction in frequency of intercourse	Sexual intercourse is the strongest risk factor for uncomplicated UTIs; often this behavioral strategy is not feasible
If spermicides are used, recommend changing to another method for contraception or prevention of infection	Spermicide use, including use of spermicide-coated condoms, is a strong risk factor, especially if used with a diaphragm; spermicides alter the vaginal flora and favor the colonization of uropathogens
Recommend that patient urinate soon after intercourse, drink fluids liberally, not routinely delay urination, wipe front to back after defecation, avoid tight-fitting underwear, avoid douching	In case–control studies, none of these strategies have been shown to be associated with a reduced risk of recurrent UTIs, and none have been studied prospectively; however, it is reasonable to suggest them to the patient, since they pose a low risk and might be effective
Biologic mediators	
Cranberry juice, capsules or tablets	Biologic plausibility is based on the inhibition of uropathogen adherence to uroepithelial cells; clinical data supporting a protective effect have been limited by design flaws[40]; a recent randomized, placebo-controlled trial showed no benefit from cranberry juice[41]
Topical estrogen	In some postmenopausal women, topical estrogen normalizes the vaginal flora and reduces the risk of recurrent UTIs[42]; oral estrogens are not effective
Adhesion blockers (D-mannose, available in health-food stores and online, is occasionally used as preventive therapy)	UTIs caused by *E. coli* are initiated by adhesion of the bacteria to mannosylated receptors in the uroepithelium by means of FimH adhesin located on type 1 pili; theoretically, mannosides could block adhesion; however, D-mannose has not been evaluated in clinical trials

* Counseling about the pros and cons of these strategies is appropriate for women who have one or more recurrent UTIs or who have questions about any of the strategies.

cystitis that occur at least 1 month after successful treatment of a urinary tract infection should be treated with a first-line short-course regimen (Table 2). If the recurrence is within 6 months, one should consider a first-line drug other than the one that was used originally, especially if trimethoprim–sulfamethoxazole was used, because of the increased likelihood of resistance.[22]

The goal of long-term management of recurrent cystitis should be to improve the quality of life while minimizing antimicrobial exposure. Table 4 lists nonantimicrobial preventive strategies for women who have recurrent cystitis.[40-42] Although data supporting the effectiveness of these strategies are sparse or nonexistent, they carry a low risk of adverse effects and may be helpful. Antimicrobial prophylaxis (Table 5),[43-45] on the other hand, has been shown to reduce the risk of recurrence by approximately 95%[12,24]; however, such treatment should be limited to women who have had three or more urinary tract infections in the past 12 months or two or more urinary tract infections in the past 6 months (at least one of which was confirmed by

a positive culture) in whom nonantimicrobial strategies have not been effective and who prefer prophylactic antimicrobial therapy. The strategy of self-diagnosis and self-treatment is a useful nonpreventive antimicrobial strategy for many women with recurrent cystitis (Table 5). Antimicrobial management strategies should be assessed periodically to determine whether they continue to be appropriate.

Follow-up after Uncomplicated Cystitis or Pyelonephritis

After treatment for uncomplicated cystitis or pyelonephritis, a urine culture is unnecessary if symptoms have resolved, except in pregnant women (for whom treatment of persistent asymptomatic bacteriuria is recommended).[46] In women with recurrent uncomplicated cystitis or pyelonephritis, routine urologic evaluation (with the use of ultrasonography or computed tomography) has a low diagnostic yield and is not recommended.[12] However, it should be considered in women who have persistent hematuria or multiple early recurrences

Table 5. Strategies for Antimicrobial Management of Recurrent Acute Uncomplicated Cystitis.*

Strategy	Comments
Self-diagnosis and self-treatment	
First-line antimicrobial regimen is prescribed for future use; patient is advised to take it at onset of UTI symptoms	This is not a preventive strategy. Women with previously diagnosed cystitis can accurately self-diagnose subsequent cystitis in more than 85 to 95% of cases and can successfully treat themselves[43]; higher patient satisfaction with this strategy than with traditional visits to provider for UTI symptoms and less antimicrobial exposure than with continuous antimicrobial prophylaxis; should be reserved for motivated women with previous culture-confirmed cystitis who will comply with the treatment regimen; urine culture should be obtained periodically before treatment to confirm presence of UTI and drug susceptibilities
Antimicrobial prophylaxis†	
Postcoital antimicrobial prophylaxis: single dose of antimicrobial agent as soon as feasible after intercourse Nitrofurantoin, 50–100 mg‡ TMP-SMX, 40 mg and 200 mg or 80 mg and 400 mg§ TMP, 100 mg§ Cephalexin, 250 mg‡	In a placebo-controlled trial, the rate of recurrent cystitis with postcoital TMP-SMX, 40 mg and 200 mg, was 0.3 episodes per patient-year, vs. 3.6 with placebo (a 92% reduction)[44]; can be used if UTIs are temporally related to coitus; absence of bacteriuria should first be confirmed by negative results on urine culture; results in less antimicrobial exposure than with continuous prophylaxis; fluoroquinolones (e.g., ciprofloxacin, 125 mg) are highly effective but are not recommended§
Continuous antimicrobial prophylaxis: daily bedtime dose (except fosfomycin; see below) Nitrofurantoin, 50–100 mg‡ TMP-SMX, 40 mg and 200 mg (3 times weekly is also effective)§ TMP, 100 mg§ Cephalexin, 125–250 mg‡ Fosfomycin, 3-g sachet every 10 days‡[45]	Randomized, placebo-controlled trials have shown a reduction in cystitis recurrences of approximately 95%; side effects are common (e.g., rash, yeast vaginitis); absence of bacteriuria should first be confirmed by negative results on urine culture; a 6-month trial is recommended, then treatment is discontinued and the patient observed; about 50% of patients have a reversion to the previous pattern of recurrences of cystitis[24]; if recurrences continue, prophylaxis may be restarted; rare toxic effects of long-term exposure to nitrofurantoin include pulmonary hypersensitivity, chronic hepatitis, and peripheral neuropathy; fluoroquinolones (e.g., ciprofloxacin, 125 mg) are highly effective but not recommended§; antimicrobial resistance in colonizing strains or breakthrough infections are reported in some studies

* The choice of antimicrobial agent should be based on the susceptibility pattern of the organism that caused the patient's recent UTI and the patient's history of drug allergies.[12]
† Patients with breakthrough infections should undergo culture testing to assess the drug susceptibility of the infecting uropathogen.
‡ This regimen presents no clear risk to the fetus, on the basis of studies in animals, humans, or both (pregnancy category B).
§ Studies in animals have shown an adverse effect of this regimen on the fetus (pregnancy category C); use only if the potential benefit justifies the potential risk to the fetus.

of cystitis involving the same strain of bacteria. In women with pyelonephritis who have severe or worsening illness, persistent fever 48 to 72 hours after the initiation of appropriate antimicrobial treatment, or symptoms suggestive of a stone, abscess, or obstruction, urologic evaluation should be performed to rule out these latter abnormalities. It is also reasonable to perform imaging studies in women who have two or more recurrences of pyelonephritis.

AREAS OF UNCERTAINTY

Several areas of uncertainty warrant further investigation, including the ecologic adverse effects[28] and changes in gut microbiota[47] caused by specific antimicrobial agents, the presence of uropathogen reservoirs in the bladder,[13] the safety and effectiveness of antimicrobial-sparing approaches (e.g., antiinflammatory drugs or delayed treatment)[30,36,37] in managing urinary tract infections, and the potential role of probiotics,[48,49] adhesion blockers,[50] and vaccines[51] in preventing urinary tract infections.

GUIDELINES

Recently, the IDSA updated its guidelines for the use of antimicrobial treatment in acute uncomplicated cystitis and pyelonephritis in women.[28] The recommendations in this article are largely consistent with these guidelines. International consensus guidelines for the management of uncomplicated urinary tract infection, which are similar to the IDSA guidelines, have also been published recently.[52]

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette appears to have recurrent cystitis on the basis of her symptoms and history. A 3-day course of trimethoprim–sulfamethoxazole is generally my choice of a first-line empirical regimen for cystitis in women who are not allergic to the medication, given that it is inexpensive and effective and that there are no reliable data in my community to suggest a high prevalence of resistance. In this case, however, I would prescribe a different first-line antimicrobial agent, nitrofurantoin (5-day course), since the patient's recent exposure to trimethoprim–sulfamethoxazole increases the likelihood that the current infecting strain will be resistant to this agent. I would also offer her a urinary analgesic (e.g., phenazopyridine [over-the-counter], three times daily as needed) until her dysuria diminishes, which often occurs within a few hours after the start of antimicrobial therapy.[53] An office visit is not required for management, and there is no need for a follow-up urine culture if her symptoms resolve.

The patient should be counseled concerning nonantimicrobial preventive approaches that may reduce the risk of recurrence (e.g., avoidance of spermicides [as appropriate], urination soon after intercourse, and liberal fluid intake) (Table 4); although data on the efficacy of these measures are mostly lacking, they pose little risk. If the patient continues to have recurrences, self-diagnosis and self-treatment with antimicrobial agents could be considered, since this approach has been shown to be an effective management strategy; other options include postcoital antimicrobial prophylaxis and, as a last resort, continuous antimicrobial prophylaxis.

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