Urinary tract infections (UTIs) are a common and costly medical problem, with costs estimated at more than $1.6 billion in 1995 [1]. While many patients with serious illnesses develop UTIs in the hospital or nursing home as a consequence of bladder dysfunction and/or catheterization, women seem to be especially vulnerable to getting UTIs, even women who are otherwise healthy. Approximately 50% of adult women report having had a UTI in the past [2], and young sexually active women have UTIs at a rate as high as 0.5 episodes per woman-year [3]. In a random telephone survey, nearly 11% of women reported having had at least 1 UTI in the previous 12 months [1].

Because UTI is a common and troublesome condition for ambulatory women, a management strategy that results in consistent and optimal care of women with UTI would be an important contribution. There is universal consensus that UTIs can be managed in the ambulatory setting, but which diagnostic and therapeutic approaches are optimal in terms of clinical outcomes and cost-effectiveness remains uncertain. Questions surrounding the care of ambulatory women with UTI include the following: What contemporary information regarding UTI management is reliable, and how can we assess whether it is applicable to the typical patient? Can we reconcile the challenges of avoiding excess morbidity due to either inadequate workup and treatment or inordinate diagnostic evaluation and prolonged therapy? Will current therapeutic approaches need to be revised due to evolving patterns of microbial resistance and the development of new antibiotics?

This article discusses these and other issues that bear directly on the management of UTI in ambulatory women. Two sets of guidelines published in 1999 present the rationale for the current approach to UTI management [4,5]. Elements of the guidelines are presented here, and potential problems with the guidelines are discussed. UTI is much less common in men than in women, and although the presentation is clinically similar, the diagnostic and therapeutic approaches are different and thus will not be considered in this article. The following 2 cases represent visits to a primary care clinic on a single day.

**CASE STUDY**

**Initial Presentation**

**Patient 1**

A 35-year-old woman presents to an outpatient clinic with a 2-day history of worsening urinary burning and frequency. The patient reports no medical problems other than the urinary symptoms. She is sexually active and is in a monogamous relationship. She has 2 children and is taking birth control pills without problems. She recalls having had a possible UTI while she was in college but remembers only that she “took a bunch of pills all at once” and had no sequelae of UTI. On examination, the patient looks mildly uncomfortable but otherwise is in no distress. She is afebrile and has normal vital signs. The general examination is benign. There is no costovertebral angle tenderness. There is slight discomfort with deep palpation over the pubis, but the bladder is not enlarged. The patient refuses a pelvic examination at this time, saying that she had seen her gynecologist 2 weeks earlier for a routine checkup and was told everything was fine. Urine dipstick testing done in the office is strongly positive (read as 4+ on the dipstick scale) for leukocyte esterase and nitrites but negative for blood, protein, and glucose.

**Patient 2**

A 63-year-old woman presents to the clinic with a 2-day history of dysuria. The patient recently retired from her job because complications of diabetes, including early cataracts and mild painful neuropathy, had made it difficult for her to get back and forth to work. She recently completed a course of antibiotics (cephalosporins) for cellulitis of the left foot. Due to diabetic neuropathy, she was unaware of the infection until she saw that her foot was red and swollen. The foot redness has improved with therapy. The foot redness has improved with therapy. Otherwise, she has been in reasonably good general health and has not required overnight hospitalization. She is not taking any medicines for prevention of osteoporosis; she had been on estrogen...
replacement therapy for 2 years immediately following menopause at age 50 years.

The patient says that her voiding symptoms are moderately severe. She believes that she might have had a fever and some mild sweats, but at the time of the office visit she is afebrile. The remainder of the examination is unremarkable except for mild left costovertebral angle tenderness and diminished sensation in both feet. There is no evidence of ongoing cellulitis. Pelvic examination is normal. A urine specimen is obtained, and the dipstick test is positive for leukocyte esterase and glucose and negative for all other tests, including nitrite.

• What components of the history and physical examination are important in the evaluation of a woman with UTI symptoms?

History and Physical Examination
The usual clinical presentation of UTI consists of voiding symptoms (burning, frequency, urgency) and variable pubic discomfort and is almost always sufficiently suggestive to guide the initial workup. The most frequent presenting complaints in women with UTI involve alterations in the normal voiding experience. Dysuria can be manifested as increased frequency of voiding, increased sense of urgency to void, and difficulty or pain during voiding.

The office workup of both of these patients was appropriate, with a good history, a physical examination focused on the urinary and genital areas, and a limited office laboratory workup. Since the major illnesses in the differential diagnosis of UTI are sexually transmitted diseases and vulvovaginal infections, taking a sexual history and inquiring about genital complaints not associated with urination (itching, discharge, dyspareunia) are important elements of the history, and a pelvic examination may be advisable. Current guidelines [5] recommend distinguishing between patients who have complicating factors that increase the risk of pyelonephritis or infection with resistant organisms (Table) and patients with no complicating factors. The presence of complicating factors may affect subsequent management decisions, including whether to obtain a urine culture, duration of therapy, and the need for follow-up [5]. The clinical approach may vary depending on the weight the physician ascribes to the risk factors present in a given patient.

• What diagnostic tests are used for UTI?

Urinalysis
In terms of noninvasive diagnostic tests that can be done in the office, there are basically 2 simple options: microscopic analysis of the urinary sediment and urine culture. With urine microscopy, the concentration of leukocytes in the urine is determined in a semiquantitative manner (eg, on a scale of 1+ to 4+); this test is done as a routine part of the urinalysis in many hospital laboratories. However, the urine dipstick is almost as reliable as the microscopic analysis in confirming UTI [6] and is quicker and less expensive than microscopy. Both tests are imperfect, but in an emergency room study each test had roughly the same number of false-negative and false-positive results when compared with the results of urine culture [7]. Although other indications for urine microscopy (eg, looking for cellular casts) cannot be replaced by chemical dipstick tests, adding urine microscopy to the urine dipstick test may provide little additional benefit in making the diagnosis of UTI [6].

Every patient should have at minimum a dipstick test of the urine to confirm a diagnosis of UTI. Microscopy is not costly, but it does require some expertise and may not be universally available. In terms of UTI diagnosis, a dipstick is enough to guide therapeutic decisions when it confirms the presence of inflammatory cells (leukocyte esterase) and/or gram-negative bacteria (nitrite). The microscopic evaluation confirms the diagnosis in most cases and may occasionally support the diagnosis of UTI when the dipstick test is negative. While it may be optimal to have the information from both tests, there should not be a delay in treatment based on the lack of availability of a microscopic evaluation.

Urine Culture
When cultures are properly done, they can definitively diagnose UTI. By strict definition, a count of $\geq 10^9$ colony-forming units of microbe per milliliter of cultured urine represents a
UTI [8]. However, urine cultures demand time for processing and growth (at least 18 hours) and further time for identification of the microbe and determination of antimicrobial susceptibility (36 hours). Although there is no harm in obtaining a urine culture, a treatment delay while awaiting the results can increase the morbidity of UTI, and the culture itself increases the cost of diagnosis. The clinical response to treatment is so rapid that a woman with cystitis will usually feel appreciably better with successful antimicrobial therapy before the results from urine culture and sensitivities are complete. Urine cultures are obtained in patients who require hospitalization, who are allergic to first-line antibiotics, who fail therapy due to resistance or drug intolerance, or who have significant risk factors for complicated infection.

- Is further laboratory testing needed in either patient?

Both of these women have in common a short history of dysuria and no prior known urinary pathology. Patient 1 should have the best possible treatment response for her UTI since she has no risk factors or physical findings for upper tract infection or complicated UTI. Poor responses to UTI treatment occur in the setting of resistant organisms, nonadherence to prescribed medications, occult pyelonephritis, or complicated infection, or when UTI is a misdiagnosis of another entity. This patient does not need a urine culture since the success of treatment will likely be known before the results of the culture are available.

Patient 2 also could have a good treatment outcome, but there are some issues that should be considered. First, since UTIs are caused by bacteria that first colonize the lower gastrointestinal tract and the genitals, it is possible to change the organism(s) responsible for UTI by altering the flora of these areas. Her previous course of antibiotics (cephalosporins) has likely changed the potential uropathogens, and may have selected a more antibiotic-resistant flora. Second, the presence of a significant diabetic neuropathy might portend autonomic neuropathy and incomplete bladder emptying. Significant residual bladder urine increases the risk of upper tract infection and treatment failure.

There are 2 ways to use urine culture for Patient 2: obtain a culture before initiating antibiotics (early culture), or obtain a culture only if there is a clinical failure of therapy (late culture). Early culture is appropriate if facilities are available to collect urine for culture in the office and if culture reports are promptly and reliably available to the primary care physician; if culture would be hard to obtain in the event of treatment failure; or if treatment involves less optimal medications. A late culture strategy is appropriate if cultures are difficult to obtain and if compliance with medication and follow-up is likely to be excellent. These strategies have not been formally compared in clinical trials.

In both of these cases as well as in other women, a failure to choose the right treatment will be apparent quite rapidly. In many regions of the country, the susceptibility of uropathogens to standard, first-line antimicrobials (trimethoprim-sulfamethoxazole [TMP/SMX] or a fluoroquinolone) is so high that it is cost-ineffective to check routine cultures. There is even some clinical success in women with organisms that are reported to be resistant to the drug chosen for treatment. Successful treatment in such cases might result from spontaneous cure or from achieving an antimicrobial concentration in the urine high enough to result in cure despite apparent resistance.

- Is it necessary to determine the anatomic location of the infection?

The workup in these patients does not address whether the infection involves the upper tract (ureters, renal pelvis, and kidney) or is confined to the lower tract (cystitis or urethritis), as the presence of dysuria is common to both and both can give positive results with urinary dipstick tests. In the first 2 decades of UTI treatment following the development of quantitative urine cultures and reliably effective antimicrobials in the 1950s, there was a strong emphasis on knowing whether the infection involved the upper tract or was confined to the bladder and urethra. Determining the location of infection in the lower urinary tract or the upper tract is now less emphasized than it used to be. The usual methods to determine the localization of UTI are either invasive (some involve bladder catheterization and/or ureteral catheterization), expensive (computed tomography scans), or technically difficult (antibody-coated bacteria testing). Guidelines from the American College of Radiology do not recommend radiographic localization of infection in uncomplicated UTI [9], even when upper tract infection is suspected. Other methods of determining the upper tract location are cumbersome and seldom used outside the research setting [10]. Overall, the treatment approaches for UTI are so successful that it is rarely necessary to determine the location of a UTI by direct techniques before starting therapy.

Initiation of Antimicrobial Therapy

Patient 1

The physician makes a diagnosis of acute uncomplicated UTI. After checking to make sure the patient has no drug allergies, the physician prescribes a 3-day course of TMP/SMX (160/800 mg orally twice daily). A phone call to the patient 2 days after the completion of therapy reveals that her symptoms have totally resolved.
and that she experienced only mild nausea on antimicrobial therapy.

Patient 2
The physician makes a diagnosis of uncomplicated UTI with the possibility of upper tract involvement. Because of the patient’s recent antibiotic course, the physician requests a urine culture. While awaiting culture results, she begins a course of antibiotics with TMP/SMX 160/800 mg orally twice daily with the intention of giving a 14-day course of treatment. The laboratory report on the culture shows that the patient has an *Escherichia coli* that is resistant to ampicillin and tetracycline but is susceptible to all the other agents tested. The patient seems to respond clinically within 2 days of starting treatment. At the conclusion of her 14-day course of therapy, she reports feeling back to normal, and at the time of a follow-up office visit 2 weeks later, has no symptoms or physical findings of UTI.

- Were both treatment decisions appropriate according to current guidelines?
- What issues must be considered when applying the evidence in clinical practice?

**Recommendations for UTI Treatment**

**Agents and Duration of Therapy**
Recent guidelines published by the Infectious Diseases Society of America (IDSA) [4] and the University of Michigan [5] concur with regard to the general therapeutic approach to UTI in the ambulatory female population. Both sets of guidelines indicate that 3-day courses of treatment with TMP/SMX or a fluoroquinolone are effective but that routine use of single-dose therapy is frequently unsuccessful. Comparative studies of the efficacy of these drugs show no difference in outcome or adverse effects [11]. However, the drugs differ in cost of acquisition (generic TMP/SMX ≤ $2 for the full course of therapy compared to $15 to $20 for fluoroquinolones) [12]. Issues regarding resistance will be discussed later. Each of these patients received therapy well within the range recommended by the guidelines. While other treatments might well have been successful, the approach used in these cases has the highest likelihood of success with minimum risk of side effects and the lowest cost.

Single-dose therapy is not recommended as a first-line approach in treating UTI in women. The failure rate and early recurrence rate for single-dose treatment of UTI is considerably higher than that for short-course (usually 3-day) treatments [13,14]. The IDSA guidelines evaluated the relative efficacy of single-dose versus 3-day or longer therapy and showed clearly better outcome with the 3-day or longer therapy. Study of single-dose therapy using β-lactams, TMP, TMP/SMX, and fluoroquinolones has essentially been halted not only because the clinical outcomes are worse, but also because the total costs (eg, missed work days, repeated visits to health care providers) are magnified by relatively small differences in the recurrence rate [15,16]. The only drug still given in a single dose, fosfomycin, has a long half-life (5.7 hours) and achieves high urinary levels (a single 3-g dose is given as a sachet dissolved in water) [17]. The use of single-dose fosfomycin or longer courses of nitrofurantoin (7 days) is accompanied by a lower cure rate than TMP/SMX or fluoroquinolones [15,18]. Therefore these agents find their greatest use in salvage regimens or when patients have significant drug allergies or intolerance. β-Lactams, including amoxicillin and cefadroxil (except in pregnancy), also are not recommended as first-line therapy. Numerous studies have shown the inferiority of β-lactams for UTI [15,19]. Some patients do respond well to inexpensive β-lactams (eg, amoxicillin), but the overall rates of response and relapse are disappointing compared with other drugs. This is true even if there is not a great amount of β-lactam resistance in the uropathogens.

**Treatment Issues**
Despite the general consensus regarding treatment strategies for UTI, there are issues regarding the evidence that must be recognized. The first pertains to the application of older studies in current practice. As discussed earlier, locating the anatomic level of infection had been an important part of the UTI workup during the first decades of UTI treatment, but this approach is no longer recommended. Because of this shift in approach, some older, well-designed and useful studies [20] that focused on distinctions between upper and lower tract infection and prescribed different strategies based on that distinction might be less helpful in contemporary practice. The enthusiasm for single-dose antibiotic therapy that occurred in the late 1970s and early 1980s showed that many UTIs could be treated in much less time than it took to obtain the results of a urine culture. Thus it was shown that an effort to localize infection might be unwarranted when such short-course therapy became, effectively, a diagnostic test as well as a treatment strategy. Curiously, while it was confirmed that the vast majority of women with lower tract infection would respond to single-dose therapy, even some women with upper tract involvement seemed to respond. Therefore, the notion of easy to treat versus hard to treat became more practically useful than lower tract versus upper tract by the mid 1980s when 3-day courses of treatment began to displace single-dose therapy.

An additional concern regarding the evidence is the constantly changing patterns of resistance of the infectious...
agents that cause UTI [21]. Changes in medication, drug doses, and the strains and resistance patterns of these bacteria make the interpretation of older studies potentially confusing. An example is a large, well-designed study from the 1990s comparing the outcome of treatment with ciprofloxacin, ofloxacin, or TMP/SMX in women with UTI [11]. Although a large number of women were in this study (866 were recruited and 688 were available for analysis), there were no significant differences among the 3 study drugs in terms of outcome or adverse reactions. Of note, patient outcomes were as good as or better than expected (bacteriologic responses between 92% to 97% and clinical responses between 93% and 96%), even though the ciprofloxacin dose used in this study was the lowest recommended dose. Because resistance to the drugs used in this study was quite low, the results may not apply in situations where resistance to 1 or more of the drugs is higher.

There are also barriers to the application of guidelines in clinical practice. Guidelines can be difficult to apply because subtle differences in women with UTI sometimes affect outcome of treatment. For example, in women who are essentially healthy and have no prior urinary tract disease, the development and sequelae of UTI are different from those in women who have some preexisting urinary problems (Table). To account for these differences, studies of UTI now differentiate between simple or complicated infection based on the absence or presence of documented or suspected structural or physiologic abnormalities of the urinary tract. However, choosing which of the approaches to adopt from guidelines (simple or complicated UTI) might vary depending on the weight ascribed to the complicating factors present. For example, there is no information to suggest the presence of abnormal urinary anatomy or physiology in Patient 1. In view of this, she has simple cystitis that should respond quickly to any one of a number of treatments, including the 3-day course of treatment recommended in the guidelines. On the other hand, Patient 2 recently completed a course of antibiotics and might have some bladder-emptying problems related to diabetic neuropathy. It may be difficult to classify her infection as simple or complicated without further information, such as whether she can empty her bladder completely.

Even in a reasonably healthy population of ambulatory patients, previous health status can influence the bacteriologic outcome of cystitis. A randomized clinical trial of 3-day treatment regimens in 688 adult women with UTI showed a 96% rate of eradication of bacteria in women with excellent health versus an 83% eradication in women whose health was only fair (P < 0.01) [11]. Since poorer outcomes in general are more likely when the infection involves the upper urinary tract, some of the differences in this study might be explained by occult pyelonephritis that was not specifically looked for and would be expected to be present more commonly in the least healthy of this cohort.

An additional barrier to using guidelines (especially older ones) is that a growing pool of antimicrobials is available for treating UTI. For example, some currently available drugs such as fluoroquinolones and fosfomycin were not tested in older studies. We now know that some doses or durations of treatment (eg, ampicillin for 14 days for cystitis) are no longer consonant with modern standards of care. Newer drugs may be more or less safe, effective, or costly than older ones, but it is not always possible to compare each newer drug to each older one in a randomized clinical trial of sufficient power to show all the important differences.

- Is further follow-up needed for either patient?

Follow-up for the woman with a symptomatic UTI is simple. If all symptoms have resolved, the treatment is considered successful and no further office visit or diagnostic testing is needed. Both patients had good responses and would not need office follow-up. It would be sufficient to have telephone contact to ensure that the treatment was successful [4,5]. The success rate with TMP/SMX in the IDSA study [4] was 93%, and the majority of treatment failures were symptomatic (ie, failures were based on patients reporting continued symptoms). Similar success and failure rates were found in a large UK primary care database study of women treated between 1992 to 1999 (104,099 infections) [22]. In this study, the failure rate (ie, need for a second course of therapy) was 14% at 28 days after the diagnosis of UTI was made [22]. Of all the drugs used, TMP/SMX was the least likely to fail; ciprofloxacin and cefadroxil were of comparable efficacy but were used much less often than TMP/SMX.

- Can the diagnosis and treatment of UTI be pared down even further?

A telephone-based clinical practice guideline approach to UTI was implemented by a large HMO [23]. Nurses were instructed on how to make the diagnosis of UTI through a telephone interview and then to offer an office visit or to prescribe appropriate medicine on the spot. This study was done in an effort to promote cost containment, and by avoiding some office visits and laboratory costs, it was successful. The follow-up showed that there was no excess in office visits for incompletely treated UTI. Compared with an earlier period of study in physicians’ offices, the nurses showed increased compliance with established treatment protocols for UTI.
However, many clinical practices are not suited to this form of patient care because it requires a cadre of trained, available nurses to handle inquiries and to prescribe treatment.

- When should resistance to various antimicrobials be factored into the decision to initiate therapy?

Antimicrobial Resistance
Rates of resistance are not uniform, even within a country. One study looked at resistance patterns among uropathogens obtained in ambulatory adolescent and adult women in the United States in 1998 [21]. More than 100,000 isolates of bacteria were analyzed, and among E. coli strains there was a TMP/SMX resistance rate of 22% in the western states and only 10% in the eastern states. A gradual rise in resistance to TMP/SMX has occurred over the mid-1990s, with resistance rates rising from 8% in 1992 to 16% in 1996 [24]. There also has been a rise in resistance to ampicillin, cephalaxin, and each of the components of TMP/SMX but no change in resistance to fluoroquinolones or nitrofurantoin. Given the range of resistance to the first-line agents, it can be difficult to know which drugs are likely to be most useful without recent, regional resistance data (see Sidebar, page 223). With accurate and up-to-date knowledge that resistance has become an important regional problem, the primary care provider might have a lower threshold for urine culture or might use another empiric agent that seems more likely to result in clinical success. The elements that go into these decisions can be described [27], but evidence-based data are still somewhat lacking. A regional TMP/SMX resistance rate greater than 20% in E. coli should direct the physician to alternate initial therapy; a rate between 10% and 20% might prompt consideration of other medication in patients with the least ability to tolerate inadequate treatment [4]. In vitro resistance is associated with much lower success rates, although some patients will still respond when the laboratory reports resistance. Cystitis response in the setting of TMP/SMX resistance is variable, but one study showed 50% bacteriologic and 60% clinical response in 10 women with bacterial isolates resistant to TMP/SMX [11].

- If Patient 1 had presented for a routine office examination without urinary symptoms but a urine sample revealed pyuria and a significant number of bacteria on quantitative culture, would antibiotic therapy be the next step?

Asymptomatic Bacteriuria
Asymptomatic bacteriuria refers to the presence of significant numbers of bacteria in the urine in the total absence of symptoms such as urinary burning, frequency, or urgency. In young, healthy women, the prevalence of asymptomatic bacteriuria is 5% to 6% [28]. In a study [28] it was shown that the vast majority of cases of asymptomatic bacteriuria disappear spontaneously, although the likelihood of developing cystitis within 1 week of the detection of asymptomatic bacteriuria was 8 times higher than the risk of having a sterile urine culture within 1 week. In this setting, therefore, asymptomatic bacteriuria is a common but un alarming entity that has a small chance of progressing to symptomatic disease. Underlying conditions known to be associated with higher rates of asymptomatic bacteriuria are pregnancy, post-bladder catheter removal, advanced age (eg, older than 65 years), and diabetes mellitus. There is evidence favoring treatment of asymptomatic bacteriuria during pregnancy [29,30] and following bladder catheter removal [31]. Since the patient has neither of these conditions, antimicrobial therapy would not be the next step. In diabetes and old age, attempted treatment of bacteriuria is unhelpful in preventing subsequent infections and exposes patients to the potential toxicity of antimicrobials and the cost of repeated office visits and urine tests [32,33].

Patient 2: Second Presentation
Three months after her UTI resolves, the patient notes the onset of dysuria and urinary frequency over a period of 2 days. At the time of the office visit, she appears uncomfortable but has no fever or constitutional symptoms. On urinalysis done in the hospital laboratory, dipstick testing is positive for leukocyte esterase and microscopic analysis shows a large number of white blood cells. The physician prescribes another course of TMP/SMX after sending a urine culture. This time, the culture shows more than 100,000 colony-forming units of Klebsiella pneumoniae. This organism is resistant to ampicillin but susceptible to all other antibiotics tested.

- What is the approach to management of recurrent UTIs?

Recurrent UTI
Recurrent of UTI is a common problem, with rates reported as high as 44% at 1 year [34]. Recurrent symptoms following apparent cure of a UTI can represent a relapse of the previous infection or a reinfection. In this case, the patient clearly has a reinfection since the organism isolated was a species different from that of the prior infection. To document a relapse, it is essential to demonstrate not only the same species of bacteria in both infections but also similarities of strain. This step is rarely done in clinical laboratories, with the exception of antibiotic resistance profiles. Even strains of bacteria that
EPIDEMIC UTI?

The conventional notion of UTI in adults posits that cystitis is caused by endogenous bacterial flora. Uropathogenic bacteria first colonize the gut before moving to the introitus of the vulva and then up into the bladder. This aspect of passing along an endogenous bacterium from the bowel to the bladder via the external genitalia makes it improbable that UTI would occur in epidemics, since the development of UTI is a complex ballet between potentially pathogenic bacteria, susceptible hosts, and a variety of situational risk factors (eg, sexual activity, spermicide use). Yet an epidemic of UTI has recently been noted in a cohort of college students [25]. Furthermore, this epidemic encompassed women in at least 3 states ranging from Michigan to Minnesota to California.

This epidemic was first noted to be occurring when a larger than expected number of TMP/SMX–resistant E. coli (21%) were recognized by a university health service in northern California in the latter part of 1999 and early 2000. Upon careful study, the antibiotic-resistant E. coli were also related to one another by serotype, presence of urinary virulence factors, and specific DNA sequences. While the strains causing infection in California, Minnesota, and Michigan were not identical, they clearly were closely related and quite unlike strains obtained from women with fully antibiotic susceptible urinary isolates of E. coli. This clonal group of E. coli was quite different from other strains of E. coli that had been isolated from college students (or other women) with cystitis in the past. The women involved in this epidemic did not know each other and had not traveled to a common location. Information about their specific dietary and sexual habits was not available. Studies of E. coli in fecal flora during the epidemic period showed that this new strain was present in both men and women in California. In more limited environments (eg, members of a family or sexual partners), uropathogenic E. coli have been shared among householders or people with intimate contact, but the source of this new clonal group of E. coli is not immediately apparent.

Community-wide epidemics of UTI are quite uncommon but not unheard of. In a previously described outbreak of pyelonephritis and bacteremia in 1986 [26], a previously unrecognized multidrug-resistant E. coli clone caused fairly severe UTI in south London and eventually in other parts of Europe and the United States. In this epidemic, the great morbidity of the infection as well as the resistance pattern of the organism were evidence that something unusual was occurring. Comparison of the 1986 organism to the one described in several U.S. states in 1999/2000 shows that they are clearly different. Yet both epidemics shared organisms that were somewhat drug resistant and fully equipped with a raft of virulence factors to cause UTI.

How can these observations be useful in the future? First, they might provide further motivation to limit the use of antibiotics (especially TMP/SMX and others that are commonly found in the resistance profiles of these organisms) for trivial (viral) diseases since they may favor the selection and retention of resistant bacteria. This advice might apply to all use of TMP/SMX and not just use in UTI because selection of resistant fecal flora could occur well before a UTI develops. Second, these observations may help us focus on environmental sources of E. coli (eg, meat, food handlers) that might be the source of uropathogenic strains. The reduction of potentially uropathogenic E. coli in food production, preparation, and service might reduce the total number of UTIs. Measures to improve overall food purity might reduce the number of UTIs as well as the number of cases of diarrhea caused by salmonella, campylobacter, and E. coli. Third, these observations suggest that we should study molecular determinants of E. coli that are not antibiotic resistant since these might be causing silent epidemics that might be detected and controlled. The result of these interventions might reduce the total burden of UTI on women by reducing community-wide gastrointestinal carriage of uropathogenic bacteria.
and after obtaining cultures it is reasonable to start empiric therapy according to known local drug susceptibility [36]. Selection of resistant fecal and genital strains after a 3-day course of therapy is rare, but obtaining a culture for all recurrences will quickly identify these occasions.

**Patient 2: Follow-up**

Although she feels completely well at the conclusion of her second course of antibiotics, the patient is frustrated and asks, “Why does this keep happening to me? Can’t something be done to prevent another one of these infections?”

- Are there safe, effective interventions to prevent further recurrences of UTI?

**Prevention of Recurrent UTI**

The timing and frequency of recurrent UTI is unpredictable, and most of the known risk factors for UTI are difficult to control. Efforts to reduce the adhesion of uropathogenic bacteria to the genitourinary epithelium by the ingestion of cranberry juice have been mildly effective [37]. The use of a lactobacillus GG beverage was not helpful in preventing UTI [37]. Changes in vaginal pH, particularly due to the use of spermicide (often accompanying diaphragms), has been associated with an increased risk of UTI in several studies [3,38]. Sexual activity can predispose to UTI [3], and this may be especially problematic with newer sex partners. In postmenopausal women, not taking estrogen replacement therapy is a risk factor for recurrent UTI [39]. Topical or systemic estrogens will reduce the rate of recurrent UTI in these women [40].

The controversy over seeking an anatomic explanation for recurrent UTI is not fully resolved, but in adults it is rare to identify correctable lesions [41]. For this patient, bladder function could be abnormal if she also has an autonomic neuropathy from the diabetes. Obstructions to urine flow, poor emptying of the bladder and ureters, reflux of urine from the bladder to the ureter, and anatomic variations of the urethra can be found as causes of recurrent infection, but standard techniques (eg, radiographic imaging, cystoscopy) have a low yield in identifying such lesions [41]. Relatively common problems such as incomplete bladder emptying because of neural injury or disease are often difficult or impossible to correct.

Antimicrobial prevention of recurrent infections has been more clearly worked out. Women with frequent, uncomplicated recurrences (usually 2 or more infections in a 6-month period) may benefit from 1 of 3 antibiotic therapy strategies: continuous low-dose prophylaxis [42], postcoital prophylaxis [43], or preemptive short-course treatment (without medical consultation) at first sign of infection [44]. Each of these strategies reduces the frequency and morbidity of UTI, but there are no controlled trials comparing them. Self-directed therapy appeals to many women, and there is evidence that women who have experienced UTI can self-diagnose and treat with impressive accuracy and good outcomes [45]. In this study, 172 women were given the opportunity to initiate levofloxacin therapy at the first indication of a UTI. Roughly half of the women studied had a UTI after enrolling in the study (on average, 2 per woman for those who had UTI), and the urinalysis and/or urine culture was positive in 95% of these episodes. Clinical and microbiologic cures were attained in 92% and 96% of cases, respectively. Whether prophylaxis is offered or not, there tends to be a slow trend toward cessation of recurrent infections in women without anatomic or physiologic reasons to have recurrent UTI [7]. For women on continuing prophylaxis or postcoital prophylaxis, it might make sense to stop this treatment every year or so to see if the propensity for recurrent infections has faded.

Patient 2 will need to be aware of her urinary infection pattern and perhaps be evaluated for possible bladder dysfunction. Doing so may entail consultation with a urologist who can assess her urodynamics and help determine the best way to maintain good voiding patterns. She might consider prophylactic antibiotics, but it also might be prudent to see what happens after this second infection before committing to a long-term course of antibiotics.

**Conclusion**

In clinical practice, the delay to initiation of therapy for UTI should be minimal. The medications used for treatment of UTI are very well studied and well tolerated, especially in the short treatment courses used for cystitis. Further investigation may be needed in women who do not respond to initial therapy or who return with recurrent infection. The majority of these women will have simple reasons for their failure to respond, and a longer course of medicine or a different antibiotic is usually sufficient. For the woman who has frequent recurrences, more intensive evaluation by an infectious diseases specialist or a urologist can be helpful. But in the absence of other medical illness or obviously altered urinary anatomy or physiology, there are some simple strategies to help. Adjusting birth control practices, considering estrogens for the postmenopausal woman, and initiating antibiotic prophylaxis or early treatment have proven successful in the vast majority of recurrent UTI cases.

Meta-analyses can provide useful information about demographic and behavioral risk factors for UTI as well as point out differences in outcome that may be undetectable in smaller studies [46]. For example, in a meta-analysis covering 6 double-blinded clinical trials (over 3000 patients), not
using a diaphragm, treatment for ≥3 days, symptoms for <2 days, and African-American race were associated with better outcomes. Patients infected with bacteria categorized as Klebsiella or “other” had a worse prognosis.

Even when guidelines are available and widely disseminated, they can be difficult for physicians to follow. A recent study showed that there are significant discrepancies in the way that physicians have been treating UTI, and that these differences are better accounted for by differences in medical specialty than by differences in the characteristics of the women being treated [18]. A study [18] involving a large ambulatory care database from the 1990s (1989–1998) showed that family physicians favored treating UTI with TMP/SMX, internists favored fluoroquinolones, and gynecologists favored nitrofurantoin. While guidelines are not expected to be followed 100% of the time (variations in patient preferences, local drug price differences, formulary variability), the breadth of discrepancies of this study is interesting and might help frame the way that future guidelines are developed and implemented.

The unanswerable question is whether changing patterns of bacterial resistance will make some of the current strategies unwise in the future. The published literature even from the late 1990s shows surprisingly good efficacy for TMP/SMX, a drug for which increasing resistance on the part of uropathogens has been reported in recent years. Whether this decline of in vitro activity has not yet been captured in clinical trials or is a transient or not clinically important problem has not been fully determined. For example, recommendations of long-term (up to 5 years) prophylaxis with low-dose TMP/SMX for suppression of frequently recurring UTI, which was successful in a small study [47], might no longer be appropriate. Even the current approach of not using urine culture and sensitivity tests for first-time infection might be reconsidered if treatment failures become too frequent. The other strategy to minimize costs might be to use fluoroquinolones as the primary treatment agents. Drug acquisition costs would be higher, but the cost of laboratory testing and the delay in decision making might be avoided, thus lowering the total cost of therapy. But while the current susceptibility patterns show a good likelihood of efficacy with fluoroquinolones, there could be significant emergence of resistance to these drugs as has already occurred in Neisseria gonorrhoeae and Campylobacter jejuni. While there is some evidence that fluoroquinolone-resistant E. coli might be less invasive (and thus less worrisome) than fluoroquinolone-susceptible strains, this will only be known over time [48].

It is somewhat worrisome to note that no new classes of oral medicines for UTI other than fluoroquinolones and fosfomycin have been developed in the past 15 years. Because fluoroquinolone resistance, when it occurs, tends to be sustained for all members of the class, resistance to these agents could make necessary the use of more inconvenient and expensive parenteral therapy. What would happen if therapy for cystitis was not offered at all? We have no recent clinical data about this option, and it would be unethical to study this option given the excellent, safe and effective treatments available. However, a controlled trial in Denmark in the 1960s randomized women with cystitis into an active treatment arm or a placebo arm [49]. In this double-blinded study, the majority of women had sterile urine within a few weeks, although recrudescence was fairly common. It seems unlikely that we will run out of good treatment options for cystitis in the near future, but vigilance of antibiotic resistance patterns is prudent. Further clinical trials will be needed to assess the optimal diagnostic and treatment strategies should resistance to current first-line agents become commonplace.

Corresponding author: Thomas Fekete, MD, Section of Infectious Diseases, Temple University School of Medicine, 3401 N. Broad St., Philadelphia, PA 19140.

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References


