# Genitourinary Infections

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## LEARNING OBJECTIVES

1. Distinguish the differences between acute cystitis (AC) and pyelonephritis, as well as between uncomplicated and complicated UTIs.
2. Evaluate the pharmacotherapy options used for UTIs and distinguish between appropriate and inappropriate use.
3. Evaluate recommendations from available clinical practice guidelines related to UTIs.
4. Analyze appropriate selection of empiric treatment options given increased antimicrobial resistance, particularly to the fluoroquinolones and trimethoprim/sulfamethoxazole.
5. Design a pharmacotherapy treatment plan for patients with AC, pyelonephritis, catheter-associated UTIs, and prostatitis.

### ABBREVIATIONS IN THIS CHAPTER

| | |
|---|---|
| AC | Acute cystitis |
| ASB | Asymptomatic bacteriuria |
| CA-ASB | Catheter-associated asymptomatic bacteriuria |
| CAUTI | Catheter-associated UTI |
| C&S | Culture & susceptibility |
| cUTI | Complicated UTI |
| MDRO | Multidrug-resistant organism |
| uUTI | Uncomplicated UTI |

*Table of other common abbreviations.*

## INTRODUCTION

Urinary tract infections are among the most common type of infectious diseases encountered in the ambulatory care setting. The lifetime incidence of UTIs in female adults is estimated to be as high as 50%–60%, with many women experiencing a recurrent infection within 1 year (Medina 2019). Urinary tract infections are most common in adolescents and women of childbearing age. Urinary tract infections are uncommon in men because of their inherently longer urethra, making bacterial ascension from the outside the body up the urethra much more difficult than in females. However, after age 65, the incidence of UTIs between males and females is about equal, primarily because of immunosenescence and male-specific risk factors, such as benign prostatic hypertrophy.

## CLASSIFICATION OF GENITOURINARY INFECTIONS

*Urinary tract infection* is a broad term that refers to an infection of any area of the urinary tract, ranging from the urethra to the kidneys. Table 1 shows the different types of UTIs. Most UTIs occur through the ascending pathway, by which uropathogens from the perirectal area colonize the urethral opening and ascend up the urethra to establish an infection in the bladder (acute cystitis [AC]) or transverse further to infect the kidneys (pyelonephritis). Because of the proximity of the urethra to the perirectal area, most UTIs are caused by enteric gram-negative organisms. In otherwise healthy women with AC and pyelonephritis, *Escherichia coli* accounts for more than 80% of infections; *Klebsiella pneumoniae* and *Proteus mirabilis* account for most other infections. Gram-positive organisms are unusual causes, though *Staphylococcus saprophyticus* can cause infections in otherwise healthy women. Some infections, such as urethritis, though technically considered UTIs, are generally caused by sexually

transmitted infections and are beyond the scope of this chapter. The descending or hematogenous pathway of infection occurs when bacteria from another infection site travel through the bloodstream to infect the urinary tract; however, this accounts for less than 5% of all UTIs (Fernandez 2020).

Urinary tract infections can broadly be classified as either uncomplicated (uUTIs) or complicated (cUTIs), but this terminology can be confusing because there is no standard definition for either term. In general, uUTIs occur in premenopausal, otherwise healthy women who have no underlying structural or anatomical anomaly that might predispose them to a UTI, such as vesicoureteral reflux. Any other type of patient is generally considered to have a cUTI. This includes male patients, patients with underlying structural/anatomical abnormalities, and older adults. Urinary tract infections can also be classified as either lower or upper, depending on the exact location of the infection. Acute cystitis is considered a lower UTI, whereas pyelonephritis is considered an upper UTI. A common misconception is that an upper UTI equates to a cUTI and a lower UTI indicates a uUTI, but the anatomic location of the infection does not relate to the complexity. For example, a male patient with AC would be considered to have a cUTI, whereas an otherwise healthy female with pyelonephritis would likely be considered to have an uncomplicated, though potentially severe, infection.

## BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Pathophysiology, risk factors, and common pathogens of UTIs
- Common microbiological causes of UTIs
- Common antimicrobial agents used in the treatment of UTIs
- Basic principles of antimicrobial stewardship and antimicrobial resistance

*Table of common laboratory reference values.*

## ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-e120.
- Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis 2019;68:e83-e110.
- Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. Clin Infect Dis 2010;50:625-63.

**Table 1.** Different Types of UTIs

| Type of UTI | Definition |
|---|---|
| Acute cystitis | Infection of the urinary bladder (lower UTI) with accompanying localized signs and symptoms of infection such as increased urinary frequency, dysuria, and nocturia. Usually diagnosed with a urine culture showing > 100,000 CFU/mL of a pathogenic organism |
| Pyelonephritis | Infection of the kidneys (upper UTI) with accompanying systemic signs and symptoms of infection, such as fever, flank pain, nausea/vomiting, and chills |
| Uncomplicated UTIs | No standard definition, but generally understood to be infections in healthy, premenopausal women who have no underlying structural or anatomical abnormalities |
| Complicated UTIs | No standard definition, but generally understood to be any infection that falls outside the usual understanding of an uncomplicated infection. Individuals with these infections include, but are not limited to, male patients, older adults, and patients with underlying structural or anatomical abnormalities of the urinary tract |
| Recurrent UTIs | ≥ 2 separate, culture-proven episodes of symptomatic UTI episodes within 6 mo or ≥ 3 episodes within 1 yr |

Information from: Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol 2019;11:1756287219832172; Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases. Clin Infect Dis 2011; 52:e103-e120.

### Acute Cystitis

Acute cystitis is the most common manifestation of UTIs in the ambulatory care setting. Signs and symptoms of AC are

localized and include dysuria, increased urinary frequency, urgency, and nocturia. In otherwise healthy, premenopausal women, AC can be diagnosed by signs and symptoms alone. However, confirmatory testing is often achieved through either a urine dipstick test or a urinalysis. The hallmark indication of infection is the presence of WBCs or leukocyte esterases, which are a byproduct of WBCs. The presence of leukocyte esterase is highly sensitive but not specific for UTIs; leukocyte esterase can be a useful antimicrobial stewardship tool because the lack of presence would rule out infection, and antimicrobial therapy could be avoided (Advani 2021). In addition, certain gram-negative bacteria, including the three organisms that primarily cause UTIs, reduce nitrates into nitrites in the urine, making the presence of nitrites highly suggestive of infection. The combination of a positive leukocyte esterase test and a positive nitrite test is highly suggestive of a UTI, particularly in a symptomatic patient. Urine cultures, though considered the "gold standard" for diagnosis, are not always performed in the ambulatory care setting to confirm AC because signs and symptoms and urinalyses are sufficient for diagnosis. When a urine culture is performed, greater than 100,000 CFU/mL of a pathogenic species is considered diagnostic in symptomatic women. Table 2 shows different diagnostic measures for UTIs.

An important area of concern for the ambulatory care pharmacist is distinguishing between patients with asymptomatic bacteriuria (ASB) and those experiencing true AC. Asymptomatic bacteriuria is the presence of bacteria in the

**Table 2.** Diagnostic Measures for UTIs

| Diagnostic Measure | Comments |
|---|---|
| Signs and symptoms | • In otherwise healthy, premenopausal women, signs and symptoms alone are enough to diagnose a UTI<br>• Typical signs and symptoms include dysuria, increased urinary frequency, and nocturia<br>• Signs and symptoms alone should not be used to diagnose pyelonephritis |
| Urine dipstick testing | • Sometimes called a rapid urine test because results are available in ~60 s<br>• Involves dipping a test strip into a urine sample in the clinic setting without the need to send the sample to the laboratory; hence, it is useful as a rapid screening tool<br>• Detects the presence of blood, protein, leukocyte esterase, and nitrites, among other substances<br>• Does not provide quantitative amounts; only detects the presence of the substances<br>• Should be performed on a clean-catch urine sample |
| Urinalysis | • Comprehensive urine test that detects the presence of all the substances that a urine dipstick test does, but provides quantitative amounts<br>• Also tests for parameters such as specific gravity, presence of epithelial cells, and bacteria, among others<br>• Must be performed by a laboratory, so results are not immediately available<br>• Should only be performed on a clean-catch urine sample and only in symptomatic patients because inaccurate results can lead to inappropriate diagnosis and antimicrobial prescribing<br>• Provides more specific information than a urine dipstick test |
| Urine culture | • Considered the gold standard for diagnosing a UTI<br>• > 100,000 CFU/mL of one or more pathogenic organisms is considered diagnostic in symptomatic females<br>• Results are usually available within 48–72 hours to identify a pathogen with antimicrobial susceptibility results<br>• Results must be interpreted in conjunction with clinical signs and symptoms of infection<br>• A positive urine culture in a patient *without* signs and symptoms of infection would be ASB<br>• A positive urine culture in a patient *with* signs and symptoms of infection would be a UTI (either AC or pyelonephritis)<br>• Urine cultures should always be obtained in patients with pyelonephritis<br>• For patients with AC, urine cultures can be performed; however, they are not required because some recommended empiric therapies would already be complete by the time the culture results are available |

AC = acute cystitis; ASB = asymptomatic bacteriuria.

Information from: Advani SD, Polage CR, Fakih MG. Deconstructing the urinalysis: a novel approach to diagnostic and antimicrobial stewardship. Antimicrob Steward Healthc Epidemiol 2021;1:e6; Fernandez JM, Coyle EA. Urinary tract infections and prostatitis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. McGraw-Hill, 2020:chap 134.

urine without accompanying signs and symptoms of infection. Asymptomatic bacteriuria is diagnosed with a urine culture showing greater than 100,000 CFU/mL of an organism and, under most circumstances, is not considered a true infection (Nicolle 2019). The presence of bacteria in the urine alone should never be considered diagnostic for a UTI, particularly in otherwise healthy, premenopausal women. Often, bacteria may be present in the urine because of a non–clean-catch urine sample. In addition, the clinical practice guidelines for the treatment of ASB recommend antibiotics only in limited situations, such as for the treatment of pregnant women and for patients with ASB about to undergo invasive urologic procedures.

### Pyelonephritis

Pyelonephritis occurs when pathogenic bacteria ascend from the urinary bladder up the ureters and establish infection in the kidneys. Compared with AC, pyelonephritis is a more severe, systemic infection that can result in severe complications, such as bacteremia and sepsis. The signs and symptoms associated with AC can also occur with pyelonephritis, but more systemic signs and symptoms, such as fever, chills, flank pain, and nausea/vomiting, can also occur in some patients with pyelonephritis. Pyelonephritis can be treated in either the outpatient or inpatient setting, depending on patient severity. In general, patients with unstable vital signs whose infection may be progressing toward sepsis should be admitted for treatment. Severe nausea and vomiting that result in dehydration may also warrant inpatient treatment. However, in the absence of these severe signs and symptoms, pyelonephritis can be treated in the ambulatory care setting with close monitoring of the patient. Inpatient management is not further discussed in this chapter. Unlike with AC, urine culture and susceptibility (C&S) testing should always be performed in a patient thought to have pyelonephritis to ensure correct pharmacotherapy.

### Catheter-Associated UTIs

Catheter-associated UTIs (CAUTIs) are most common in the hospital and long-term care settings, but they are also encountered in the ambulatory care setting in older adults and in patients with certain medical conditions, such as neurogenic bladder. Pathogens of the order Enterobacterales are the most common cause of CAUTIs, with *E. coli* being the most commonly identified pathogen; however, it accounts for only about one-third of cases. Other causative organisms include *Klebsiella*, *Serratia*, *Citrobacter*, *Enterobacter*, and *Pseudomonas* spp. In addition, the presence of the catheter predisposes to gram-positive organisms, such as *Staphylococcus aureus*, coagulase-negative staphylococci, and *Enterococcus* spp. Infections in patients with short-term catheters (less than 30 days) are usually monomicrobial, whereas infections in patients with long-term catheters (30 days or longer) are usually polymicrobial.

Placement of an indwelling urinary catheter provides a portal of entry for bacteria directly into the urinary tract; also, the catheters themselves can become colonized with bacteria after insertion, which is known as catheter-associated asymptomatic bacteriuria (CA-ASB). Almost all patients with indwelling catheters will have developed CA-ASB after 1 month, though some patients may develop it much faster. The infections of most patients with CA-ASB do not progress to a true CAUTI, but distinguishing between these two conditions is often quite difficult. Treating CA-ASB accounts for considerable inappropriate antibiotic use. One reason that CA-ASB and CAUTIs are difficult to distinguish is that patients with CAUTIs may not experience the typical signs and symptoms of a UTI. Rather, the signs and symptoms of CAUTIs may include fever, rigors, altered mental status, an acute worsening of mental status in a patient with baseline altered mental status, malaise/lethargy, flank pain, costovertebral angle tenderness, and pelvic discomfort. In some patients, these symptoms may be so subtle that they go unnoticed.

Using urinalysis results to diagnose a CAUTI is often unreliable because most patients with indwelling catheters will experience pyuria. Because a catheter is a foreign body, WBCs will naturally gravitate to the area, resulting in pyuria. Thus, pyuria should not be used as an indication for antimicrobial therapy in a patient with an indwelling catheter. In addition, patients with a catheter should not be screened for the presence of bacteria in the urine because it will almost always be positive. Catheter-associated ASB is defined by the presence of greater than 100,000 CFU/mL of at least one pathogenic organism in a single catheter urine specimen in a patient without UTI symptoms. A CAUTI is defined by the presence of UTI signs and symptoms plus 1000 CFU/mL of at least one pathogenic organism in a single catheter urine specimen. In patients thought to have a CAUTI who have a catheter that has been in place for more than 2 weeks, the catheter should be replaced and the urine culture obtained from the new catheter. This will provide the most accurate laboratory results and is also necessary for resolution of the infection. Catheter replacement is not required if the catheter has been in place less than 2 weeks, but some clinicians may still elect to replace the catheter.

### Prostatitis

Although the prostate gland plays no role in the production and voiding of urine, prostatitis is similar to UTIs in many ways. Although the pathogenesis of prostatitis is not completely understood, the reflux of infected urine into the prostate gland is almost certainly involved. As such, the pathogenic organisms associated with UTIs are also associated with prostatitis, with *E. coli* accounting for about 75% of cases. Prostatitis becomes more common with increased age, and as many as 50% of all men will develop prostatitis at some point. In addition, prostatitis is classified as either acute or chronic, which have distinctly different

presentations. Acute prostatitis is characterized by the sudden onset of fever, chills, localized rectal tenderness, dysuria, and increased urinary frequency. Chronic prostatitis is characterized by much more subtle and nonspecific symptoms, such as difficulty urinating, perineal pain, low back pain, or recurrent UTIs. These nonspecific symptoms may make diagnosis of chronic prostatitis more difficult. In contrast, acute prostatitis can be diagnosed through signs and symptoms and the presence of bacteriuria. Culturing prostate fluid is not generally recommended when acute prostatitis is suspected because obtaining the sample would require prostate massage, which can result in bacteremia. Obtaining a culture can be considered when chronic prostatitis is suspected, but diagnosis is more commonly made because of the diagnosis of recurrent UTIs with the same organism (Sharp 2010).

### UTIs in Special Populations

If a male younger than 65 years is diagnosed with a UTI, further investigation is necessary to assess for underlying anatomical or structural abnormalities that might predispose to a UTI. There are no specific guidelines or recommendations for treating male patients, and only limited primary literature exists; thus, treatments are usually extrapolated from data in otherwise healthy females. In general, male patients with AC are treated for longer durations than their female counterparts, but this is primarily based on clinical experience rather than available quality data. However, some evidence suggests that shorter courses of therapy are effective. One recent randomized controlled trial showed that ciprofloxacin or trimethoprim/sulfamethoxazole for 7 days was noninferior to 14 days of therapy with respect to symptom resolution 14 days after therapy in men experiencing afebrile UTIs (Drekonja 2021). Although UTIs are relatively common in older adults, available data on treatments are limited; thus, specific guidelines are unavailable, and like with male patients, treatment options are extrapolated from studies of otherwise healthy women. Also similar to male patients, treatment durations tend to be longer for older adults.

Pregnant women are at increased risk of experiencing UTIs secondary to changes in the urinary tract, such as decreased bladder tone and dilation of the renal pelvis and ureters. Because of the serious risks associated with UTIs during pregnancy, such as premature labor and fetal death, pregnant women should receive treatment, even in cases of ASB (Sheiner 2009). In general, the best recommended length of therapy for pregnant women is not known, but they are generally treated with longer courses of therapy than nonpregnant women with AC (Ovalle 2001).

## PHARMACOLOGIC THERAPIES USED IN THE TREATMENT OF UTIS

Most data for drug therapy used for UTIs are derived from studies of premenopausal, otherwise healthy women. Several different drug therapies can be used, each with distinct advantages and disadvantages. The main pharmacologic treatments used in the outpatient setting are discussed in the text that follows.

### Nitrofurantoin

Nitrofurantoin has many desirable properties conducive to UTI treatment. Nitrofurantoin is reduced by flavoproteins produced by bacteria to reactive metabolites that ultimately result in inhibition of bacterial protein synthesis, aerobic energy metabolism, DNA/RNA, and cell wall synthesis. In the urine, nitrofurantoin has bactericidal activity and is a broad-spectrum agent with in vitro activity against most organisms that commonly cause UTIs, including *E. coli* and *Klebsiella*, though it is not active against *Proteus* spp. Furthermore, nitrofurantoin is active against some multidrug-resistant gram-negative organisms and vancomycin-resistant *Enterococcus*. Although nitrofurantoin is broad spectrum, it does not significantly concentrate outside the urinary bladder; thus, normal microflora are not exposed to the drug, resulting in a low risk of collateral damage. Collateral damage refers to the ecological adverse effects of drug therapy in which broad-spectrum drugs affect the normal microflora of humans to a greater degree than narrower-spectrum drugs, resulting in increased antimicrobial resistance. Of note, nitrofurantoin does not concentrate well in the kidneys; hence, it is only appropriate for the treatment of AC, not pyelonephritis. Pulmonary fibrosis is a concern during long courses of treatment, such as for UTI prophylaxis, but is not generally a concern with usual courses of therapy for UTIs.

Of note, a historical recommendation was that nitrofurantoin was contraindicated in patients with a CrCl less than 60 mL/minute/1.73 $m^2$ because the prevailing thought was that appropriate renal filtration was required for the drug to concentrate in the urine and that adverse effects would be higher with decreasing renal function. However, more recent studies have shown that nitrofurantoin is both safe and effective in patients with a CrCl greater than 30 mL/minute/1.73 $m^2$. In 2015, the Beers criteria were updated to reflect this new evidence. Pharmacists can play a key role in disseminating and educating health care providers regarding this recommendation.

### Trimethoprim/Sulfamethoxazole

Historically, trimethoprim/sulfamethoxazole has been a mainstay in the treatment of UTIs because of its high concentration in the urinary bladder and kidneys and reliable activity against the most common bacterial causes of UTIs. However, this has also led to widespread overuse and misuse of trimethoprim/sulfamethoxazole, resulting in increased bacterial resistance of gram-negative organisms to this agent. Some areas of the country report such high resistance rates to trimethoprim/sulfamethoxazole that it is no longer a viable option for empiric treatment.

Trimethoprim/sulfamethoxazole works by interfering with the bacterial synthesis of folic acid. Although generally well tolerated, trimethoprim/sulfamethoxazole induces true allergic reactions in some patients and can increase serum potassium concentrations, particularly when combined with other drugs that cause the same effect, such as angiotensin-converting enzyme inhibitors. Because trimethoprim/sulfamethoxazole concentrates in areas of the body outside the urinary tract and has a broader spectrum of activity than nitrofurantoin, it has a higher propensity to cause collateral damage. Despite this, and assuming the pathogen is susceptible, trimethoprim/sulfamethoxazole is highly efficacious for treating both AC and pyelonephritis.

### Fosfomycin

Fosfomycin is a cell wall synthesis inhibitor with a broad spectrum of activity against many of the organisms commonly associated with UTIs. Fosfomycin is available as an oral powder that must be mixed with liquid before consumption. A unique feature of fosfomycin is that it can be administered as a one-time dose to treat AC caused by *E. coli* (Stein 1999). Because fosfomycin does not significantly concentrate in the kidneys, it should not be used for the treatment of pyelonephritis. Given its broad spectrum of activity and some absorption outside the urinary tract, fosfomycin has a higher propensity for collateral damage than nitrofurantoin, though probably not as high as trimethoprim/sulfamethoxazole. Although most uropathogens currently retain high susceptibility to fosfomycin, according to epidemiologic studies, fosfomycin susceptibility is not generally tested for in most clinical laboratories because of the currently recommended methods for testing (i.e., agar and disk diffusion).

Fosfomycin also has broad coverage against several multidrug-resistant organisms (MDROs), including vancomycin-resistant *Enterococcus* spp. and methicillin-resistant *S. aureus* (MRSA). Although these are uncommon causes of UTIs in the ambulatory care setting, fosfomycin is useful if one of these organisms is confirmed. Perhaps more importantly, fosfomycin also provides activity against extended-spectrum β-lactamase–producing organisms, with *E. coli* and *K. pneumoniae* being two of the most common organisms producing extended-spectrum β-lactamases. Although extended-spectrum β-lactamase–producing strains are also uncommon in the ambulatory care setting, the incidence is increasing and will likely continue to increase as uropathogens become more resistant to commonly used treatment agents. Thus, fosfomycin may play a more important role in the treatment of AC in the future. Of note, when using fosfomycin to treat an MDRO, there are no specific dosing recommendations, and several doses are likely required, even when treating AC. In addition, evidence is increasing that one dose of fosfomycin is inferior to nitrofurantoin for the treatment of uUTIs in women; thus, the current single-dose recommendation may change as more evidence is accumulated (Huttner 2018).

### β-Lactams

Different β-lactam agents, including penicillins, cephalosporins, and carbapenems, are effective in the treatment of both AC and pyelonephritis. Historically, the β-lactams were not considered first-line treatment for UTIs because they provide no greater efficacy than nitrofurantoin or trimethoprim/sulfamethoxazole. The β-lactams can be associated with higher rates of adverse effects, particularly GI and immune-mediated reactions. The β-lactams are generally prescribed for 3–7 days for AC and 7–10 days for pyelonephritis. The propensity of the β-lactams for collateral damage varies by agent, depending on the spectrum of activity. For example, the third-generation cephalosporins have a higher propensity than the first-generation agents.

Because of increased resistance to both trimethoprim/sulfamethoxazole and the fluoroquinolones (see the text that follows), the β-lactams have become more prominent treatments for UTIs, particularly given that gram-negative organisms have retained a relatively high susceptibility, though this may vary widely by location. For the treatment of AC, the β-lactams are probably best used as an alternative when nitrofurantoin or trimethoprim/sulfamethoxazole cannot be used. However, for the outpatient treatment of pyelonephritis, an immediate dose of intravenous or intramuscular ceftriaxone has become a mainstay of therapy (because of its prolonged half-life and the ability to administer a single dose in the clinic setting), followed by an oral β-lactam agent.

### Fluoroquinolones

The fluoroquinolones are highly effective for both AC and pyelonephritis when the organism is susceptible. The fluoroquinolones achieve high concentrations in the urinary bladder and kidneys and are bactericidal. Short courses of therapy (3 days) are highly effective for AC, and although longer courses are required for the treatment of pyelonephritis, the fluoroquinolones are considered the drug of choice for pyelonephritis because of their high efficacy. However, these qualities have resulted in widespread misuse of the fluoroquinolones, leading to widespread resistance of gram-negative organisms. Of the drugs discussed so far, the fluoroquinolones have the highest propensity for collateral damage because of their very broad spectrum of activity and ability to achieve high concentrations throughout the body (Paterson 2004). Consequently, the usefulness of the fluoroquinolones for the treatment of UTIs has dramatically decreased. These factors, together with their many potential adverse effects, support avoidance of the fluoroquinolones for AC treatment unless no other options exist. Of note, moxifloxacin is never appropriate for UTI treatment, even if the organism was susceptible, because adequate urinary concentrations are not achieved after its administration. Several fluoroquinolones have been studied in clinical trials, though ciprofloxacin and levofloxacin are used almost exclusively in clinical practice.

### Aminoglycosides

Aminoglycosides such as gentamicin and tobramycin are highly effective in the treatment of UTIs, particularly pyelonephritis. The aminoglycosides achieve excellent concentrations in the kidneys and have maintained reliable activity against gram-negative organisms. Although the aminoglycosides are primarily used in the inpatient setting for the treatment of pyelonephritis because of intravenous administration, they can also be used for outpatient treatment when administered as an initial one-time dose. If used in this way, the aminoglycosides should be dosed as a 24-hour regimen, with subsequent doses of a different agent administered orally. This is similar to how ceftriaxone is used in the outpatient treatment of pyelonephritis. Because of their high risk of nephrotoxicity, the aminoglycosides should be avoided in any patient with underlying renal dysfunction. However, the risk of nephrotoxicity is low when aminoglycosides are administered as a one-time initial dose. The aminoglycosides are not generally used in the treatment of AC except in limited circumstances when the infection is caused by an MDRO.

## CLINICAL PRACTICE GUIDELINES

Currently, there are three clinical practice guidelines related to the treatment of UTIs: (1) treatment of AC and pyelonephritis in premenopausal women (Gupta 2011), (2) treatment of ASB (Nicolle 2019), and (3) treatment of CAUTIs (Hooten 2010). As mentioned earlier, no guidelines exist to guide the treatment of males, older adults, or other unique patient populations. However, research in these areas is limited. The guidelines for the treatment of AC and pyelonephritis are being updated, given that they were last published in 2011, and some recommendations are likely outdated, particularly as they pertain to antimicrobial resistance. Because ASB should not be treated except in very limited circumstances (pregnancy and before urologic procedures), it is not discussed further.

### AC in Otherwise Healthy, Premenopausal Women

Three agents are guideline recommended first line for the treatment of AC: nitrofurantoin, trimethoprim/sulfamethoxazole, and fosfomycin (Gupta 2011). Each treatment is given an equal rating of evidence but differs with respect to dosing, frequency, and therapy duration. Pivmecillinam is also recommended as a first-line therapy, but its availability is limited to a few European countries, and it is not discussed further. The β-lactams and fluoroquinolones are recommended as second-line therapies. Table 3 lists the antimicrobials used in the treatment of AC and summarizes the information for each.

Of the three recommended first-line therapies, nitrofurantoin poses the least risk of collateral damage and is therefore least likely to induce the development of antimicrobial resistance. This, combined with its reliable efficacy and favorable safety and tolerability profile, particularly when used for only 5 days, should give nitrofurantoin strong consideration as the preferential agent for the treatment of AC. However, of the three first-line therapies, nitrofurantoin requires the longest length of therapy at 5 days and may not be suitable for all patients, particularly when adherence may be of concern.

Trimethoprim/sulfamethoxazole has historically been the recommendation of choice for the treatment of AC because of its reliable efficacy when the pathogen is susceptible and was recommended in the original Infectious Diseases Society of America guidelines. Although the propensity of trimethoprim/sulfamethoxazole for collateral damage is greater than that of nitrofurantoin, it is not thought to be as high as that of the fluoroquinolones or extended-spectrum cephalosporins. Trimethoprim/sulfamethoxazole is recommended for 3-day courses because longer durations have not been shown to be more effective than those lasting 3 days. Pharmacists can play an important role in educating other health care providers regarding the length of therapy for trimethoprim/sulfamethoxazole because clinicians often unnecessarily prescribe longer durations in practice, even for otherwise healthy women.

The main caveat with the use of trimethoprim/sulfamethoxazole is that empiric therapy is not recommended when local resistance rates to uropathogens are 20% or higher. Resistance rates of uropathogens to trimethoprim/sulfamethoxazole are a global concern, and resistance in the United States is almost certainly higher now than in 2011 when the guidelines were last updated. The European Association of Urology no longer recommends trimethoprim/sulfamethoxazole as a first-line therapy for AC because of high resistance rates in Europe. In addition, and unlike in the health system setting where antibiograms are often used, clinicians in the ambulatory care setting may not have access to local resistance patterns in the community, making the choice of trimethoprim/sulfamethoxazole uncertain. When local resistance patterns are unknown, trimethoprim/sulfamethoxazole should generally be avoided. This combination of factors makes trimethoprim/sulfamethoxazole a less desirable empiric option for the treatment of AC than historically recommended. However, when local uropathogen resistance is known to be less than 20% or if the infecting organism is known to be susceptible, trimethoprim/sulfamethoxazole can be an appropriate treatment.

The final first-line recommended agent is fosfomycin dosed as 3 g (one packet) orally as a one-time dose. The possibility of administering a one-time dose may be very attractive to both patients and prescribers, particularly when adherence is a concern, given that the dose can be administered directly in the clinic setting. However, the cost of fosfomycin is usually higher than that of other first-line options, and fosfomycin is often not covered by insurance formularies, which may limit its use. In addition, although the one-time dose is effective, fosfomycin does not appear to be as effective as trimethoprim/sulfamethoxazole and nitrofurantoin in the treatment

**Table 3.** Antimicrobials Used in the Empiric Treatment of AC

| | Antimicrobial | Dose | Frequency | Duration | Comments |
|---|---|---|---|---|---|
| First-line agents | Nitrofurantoin | 100 mg | Twice daily | 5 days | • Lowest risk of collateral damage<br>• Well tolerated |
| | TMP/SMX | 1 double-strength tablet (160 mg/ 800 mg) | Twice daily | 3 days | • Only use empirically when local uropathogen resistance is < 20%<br>• Avoid use if local resistance rates are unknown |
| | Fosfomycin | 3 g (one packet) | Once | N/A | • Useful for patients with adherence issues, but the single dose may be less effective and is expensive<br>• Useful for MDROs, but treatment requires several doses |
| Second-line agents | Fluoroquinolones: Ciprofloxacin | 250 mg immediate release or 500 mg extended release | Twice daily for the immediate release, once daily for the extended release | 3 days | • Highly effective when the organism is susceptible, but resistance is dramatically increasing<br>• Associated with rare but serious adverse effects |
| | Levofloxacin | 250 mg | Once daily | | • Highest risk of collateral damage<br>• Use only when a first-line agent cannot be used |
| | β-Lactams: Various agents are used, including amoxicillin/ clavulanate, cephalexin, cefaclor, cefdinir, and cefpodoxime | Varies depending on drug selected | Varies depending on drug selected | 3–7 days | • Slightly less effective than first-line agents, but high resistance to other drugs often warrants use |

MDRO = multidrug-resistant organism; N/A = not applicable; TMP/SMX = trimethoprim/sulfamethoxazole.

Information from: Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-e120.

of AC. A recent study showed that nitrofurantoin was significantly more likely to result in both microbiologic and clinical cure than fosfomycin (Huttner 2018). This was a multinational, open-label, analyst-blinded, randomized controlled trial with an objective to compare the clinical and microbiologic efficacy of nitrofurantoin and fosfomycin in women with uncomplicated cystitis. Participants were randomized in a 1:1 fashion to receive either nitrofurantoin (100 mg orally three times daily for 5 days; n=255) or fosfomycin (3 g orally as a single dose; n=258), with follow-up occurring at days 14 and 28 after therapy completion for clinical evaluation and urine culture collection. A total of 475 patients completed the trial. In the nitrofurantoin group, 171 of 244 patients (70%) achieved clinical resolution at day 28; in the fosfomycin group, 139 of 241 patients (58%) achieved clinical resolution at day 28 (p=0.004). Microbiologic cure occurred in 74% of patients in the nitrofurantoin group and 63% in the fosfomycin group (p=0.04). The results of this trial call into question whether fosfomycin should remain a first-line treatment for AC or should instead be relegated to second-line use when nitrofurantoin cannot be used. Of note, this trial used nitrofurantoin at a higher daily dose (100 mg orally three times daily) than currently recommended (100 mg orally twice daily); thus, the lower recommended dose should be compared with single-dose fosfomycin in a clinical trial to more accurately compare the efficacy with what is done in clinical practice.

Given the results of this trial, a strong case can be made for the preferential use of nitrofurantoin over fosfomycin for the treatment of AC. Despite its lower efficacy, fosfomycin is still useful for the treatment of AC in certain circumstances, particularly when adherence is a concern and for cases caused by MDROs.

The oral β-lactams are recommended second line for the treatment of AC. The β-lactams specifically recommended by the clinical practice guidelines include amoxicillin/clavulanate, cefdinir, cefaclor, and cefpodoxime, but the guidelines note that other agents, such as cephalexin, may also be appropriate. Amoxicillin and ampicillin, though historically used for the treatment of AC, are no longer recommended as empiric or targeted therapy because of widespread resistance among uropathogens and the overall poor efficacy of these agents. The recommended therapy duration for a β-lactam is 3–7 days. However, because studies of these agents used different therapy durations, the choice of duration may vary from clinician to clinician. In addition, no particular β-lactam is preferred to another; thus, the choice of which to use is also based on clinician preference, patient-specific factors (e.g., allergies), and local resistance patterns, if known.

The β-lactams should only be used for the treatment of AC when one of the first-line options is not available, because of several factors. The use of broad-spectrum β-lactams, particularly the cephalosporins, is associated with a high degree of collateral damage, including the emergence of extended-spectrum β-lactamase–producing organisms and the development of *Clostridioides difficile* infections, among others. In addition, the β-lactams are generally considered to have lower efficacy for the treatment of AC, though clinical trials directly comparing the β-lactams with all other first-line agents are lacking. One clinical trial compared cefpodoxime 100 mg orally twice daily for 3 days with trimethoprim/sulfamethoxazole 160/800 mg orally twice daily for 3 days. On days 4–7 after completion of therapy, 100% of women who received trimethoprim/sulfamethoxazole and 98% of women who received cefpodoxime achieved both clinical and microbiological cure, though the small sample size (n=133) limited the statistical power to detect differences between groups (Kavatha 2003). However, studies that have compared the β-lactams with the fluoroquinolones generally show lower efficacy for the β-lactams. One study compared amoxicillin/clavulanate 500/125 mg orally twice daily for 3 days with ciprofloxacin 250 mg orally twice daily for 3 days. After 4 months of follow-up, 58% of women in the amoxicillin/clavulanate group experienced clinical cure compared with 77% of women in the ciprofloxacin group ($p<0.001$) (Hooton 2005). One possible explanation for the decreased efficacy of the β-lactams is that they show lower rates of eradication of uropathogens from the vaginal canal, and the persistence of these pathogens in the vaginal reservoir has been postulated as a mechanism of infection. Of note, however, despite their potentially lower efficacy, the β-lactams are increasingly being used for the treatment of AC because of increased antimicrobial resistance to other agents. When β-lactams must be used, agents with a narrower spectrum of activity and a lower risk of collateral damage, such as first-generation cephalosporins, are preferable, though this may not always be possible when therapy is empiric.

The fluoroquinolones have extensively been studied for the treatment of AC and show high efficacy when the pathogen is susceptible. Because 3 days of therapy is highly effective, longer durations are not needed when treating AC. Similar to the extended-spectrum β-lactams, fluoroquinolone overuse has been associated with the development of MDROs and *C. difficile* infections. Fluoroquinolone use has also been associated with higher rates of MRSA infections. The fluoroquinolones also have several boxed warnings for rare but serious adverse drug reactions, such as tendon rupture, neurologic problems, and aortic dissection. In 2016, the FDA updated the safety information for the fluoroquinolones to note that the risk of adverse effects outweighs the benefits in patients with certain uncomplicated infections, including AC (FDA 2016). Given these issues, the fluoroquinolones should only be used for the treatment of AC when no other options are available.

### Pyelonephritis in Otherwise Healthy, Premenopausal Women

The clinical practice guidelines recommend several options for the outpatient treatment of pyelonephritis: the fluoroquinolones, trimethoprim/sulfamethoxazole, the β-lactams, and the aminoglycosides. The current guidelines heavily recommend the fluoroquinolones for pyelonephritis treatment because of their high efficacy when the pathogen is susceptible. However, like with the treatment of AC, antimicrobial resistance with the fluoroquinolones is of increasing concern. Selection of an appropriate empiric antibiotic for pyelonephritis is particularly important because of the systemic nature of infection and the probability of progression if not appropriately treated. As such, the clinical practice guidelines recommend empiric fluoroquinolone use only when local fluoroquinolone resistance of uropathogens is less than 10%. In such situations of low resistance, three treatment options are preferred: ciprofloxacin 500 mg orally twice daily for 7 days, with or without an initial intravenous dose of ciprofloxacin 400 mg; ciprofloxacin 1000 mg extended release orally once daily for 7 days; or levofloxacin 750 mg orally once daily for 5 days. These regimens are derived from clinical trials that showed higher efficacy with the fluoroquinolones than with trimethoprim/sulfamethoxazole and the cephalosporins. The oral fluoroquinolones should be considered the treatment of choice for the outpatient treatment of pyelonephritis when the local uropathogen resistance is less than 10%.

However, many areas of the country and the world have uropathogen resistance well exceeding 10%. In such cases or when local resistance patterns are unknown, several

alternative treatments exist. Alternative treatments involve either a one-time intravenous dose of ceftriaxone 1 g or a consolidated 24-hour dose of an aminoglycoside (e.g., 5–7 mg/kg of either gentamicin or tobramycin), followed by an oral fluoroquinolone. There is often confusion among clinicians regarding why the fluoroquinolone is given at all when fluoroquinolone resistance is of concern. The rationale is that because the fluoroquinolones are the most efficacious agents for use when the pathogen is susceptible, the long-acting parenteral agent should provide coverage until C&S results are available, but the fluoroquinolone would already be initiated in the patient should the pathogen be susceptible. Some experts recommend continuing the parenteral agent until C&S results are available, but this approach has little evidence and may not be feasible in the outpatient setting. In addition, intramuscular injections can be used if the intravenous route is not possible, but again, data are limited to support this practice.

Other options in situations of high local fluoroquinolone resistance include trimethoprim/sulfamethoxazole and the oral **β**-lactams. If either of these options is selected as empiric therapy, a one-time dose of ceftriaxone or a consolidated aminoglycoside should always be administered to help ensure appropriate empiric coverage until C&S results are available. As with the treatment of AC, antimicrobial resistance to trimethoprim/sulfamethoxazole is of increasing clinical concern, so empiric use should ideally be avoided; however, trimethoprim/sulfamethoxazole is highly efficacious when the pathogen is susceptible. The recommended dose and duration of trimethoprim/sulfamethoxazole for the treatment of pyelonephritis is 1 double-strength tablet orally twice daily for 14 days; unlike with AC, data with pyelonephritis are

## Patient Care Scenario

**A 27-year-old woman presents to the primary care clinic with concerns of burning during urination and needing to get up several times a night to urinate for the past 2 nights. Her vital signs in the clinic include temperature 97.9°F, blood pressure 114/78 mm Hg, heart rate 72 beats/minute, and respiratory rate 12 breaths/minute. A urine dipstick test is positive for both leukocyte esterase and nitrites. The provider on duty diagnoses AC and asks for the pharmacist's recommendation for the most appropriate antibiotic. This is the third time this year she has presented with a UTI. The patient was successfully treated both prior times with cephalexin 250 mg orally every 6 hours for 7 days, though she claims to have missed several doses during each treatment. She has no known drug allergies. The pharmacist does not know the local resistance rates for area uropathogens. What would be the most appropriate treatment for the patient at this time? Does the patient require continuous prophylaxis for UTIs?**

### ANSWER

**This patient presents with uncomplicated AC, given that she is an otherwise healthy, premenopausal woman with classic signs and symptoms of AC. The urine dipstick test is positive for leukocyte esterase and nitrites, indicating she is experiencing a UTI. She has no systemic signs or symptoms, and her vital signs are normal; hence, pyelonephritis is highly unlikely. The patient is experiencing a recurrent UTI because this is the third time in 1 year she has been diagnosed with a UTI. Because of her current infection, she must receive treatment for it. Although urine cultures are not required for most women experiencing AC, a culture would be appropriate for this patient because this is a recurrent infection, and a culture result might help guide future empiric therapy if she has a subsequent infection. Even in patients with recurrent infections, the recommendations for treatment are generally the same as for someone experiencing an initial infection, meaning the first-line treatment is nitrofurantoin, trimethoprim/sulfamethoxazole, or fosfomycin. Trimethoprim/sulfamethoxazole would not be appropriate in this scenario because local resistance patterns are unknown; hence, there is no way to know whether resistance to trimethoprim/sulfamethoxazole is less than 20%. The patient could likely receive either nitrofurantoin or fosfomycin, with either being appropriate for her. However, because she appears to have had adherence issues in the past, fosfomycin might be preferred because it is a one-time dose, even though its efficacy may be lower than that of nitrofurantoin. Although the patient previously received an oral β-lactam, this was likely inappropriate because she is able to receive a first-line agent; hence, there is no reason to prescribe an oral β-lactam again. Regarding whether the patient should receive prophylaxis for future infections, she meets the criteria to receive it, given that she is experiencing recurrent UTIs. However, this decision is best made using shared clinical decision-making with her primary provider.**


1. Advani SD, Polage CR, Fakih MG. Deconstructing the urinalysis: a novel approach to diagnostic and antimicrobial stewardship. Antimicrob Steward Healthc Epidemiol 2021;1:e6.7.
2. Anger J, Lee U, Ackerman AL, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. J Urol 2019;202:282-9.
3. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-e120.

limited to support shorter therapy durations with trimethoprim/sulfamethoxazole. The oral β-lactams are also not preferred for empiric therapy because of their lower efficacy compared with the fluoroquinolones, but high antimicrobial resistance to other agents sometimes necessitates their use. The guidelines do not recommend any specific oral β-lactams for the treatment of pyelonephritis. However, when being used as empiric therapy, broader-spectrum agents, such as second- or third-generation cephalosporins, should likely be considered to increase the likelihood of susceptibility. Figure 1 is an algorithm for the treatment of pyelonephritis.

### CAUTI Guidelines

The clinical practice guidelines for the treatment of CAUTIs were last updated in 2009 (Hooton 2010), and at the time of writing this chapter, were not being updated. Most of the guidelines focus on catheter care and other activities for which pharmacists are unlikely to have significant

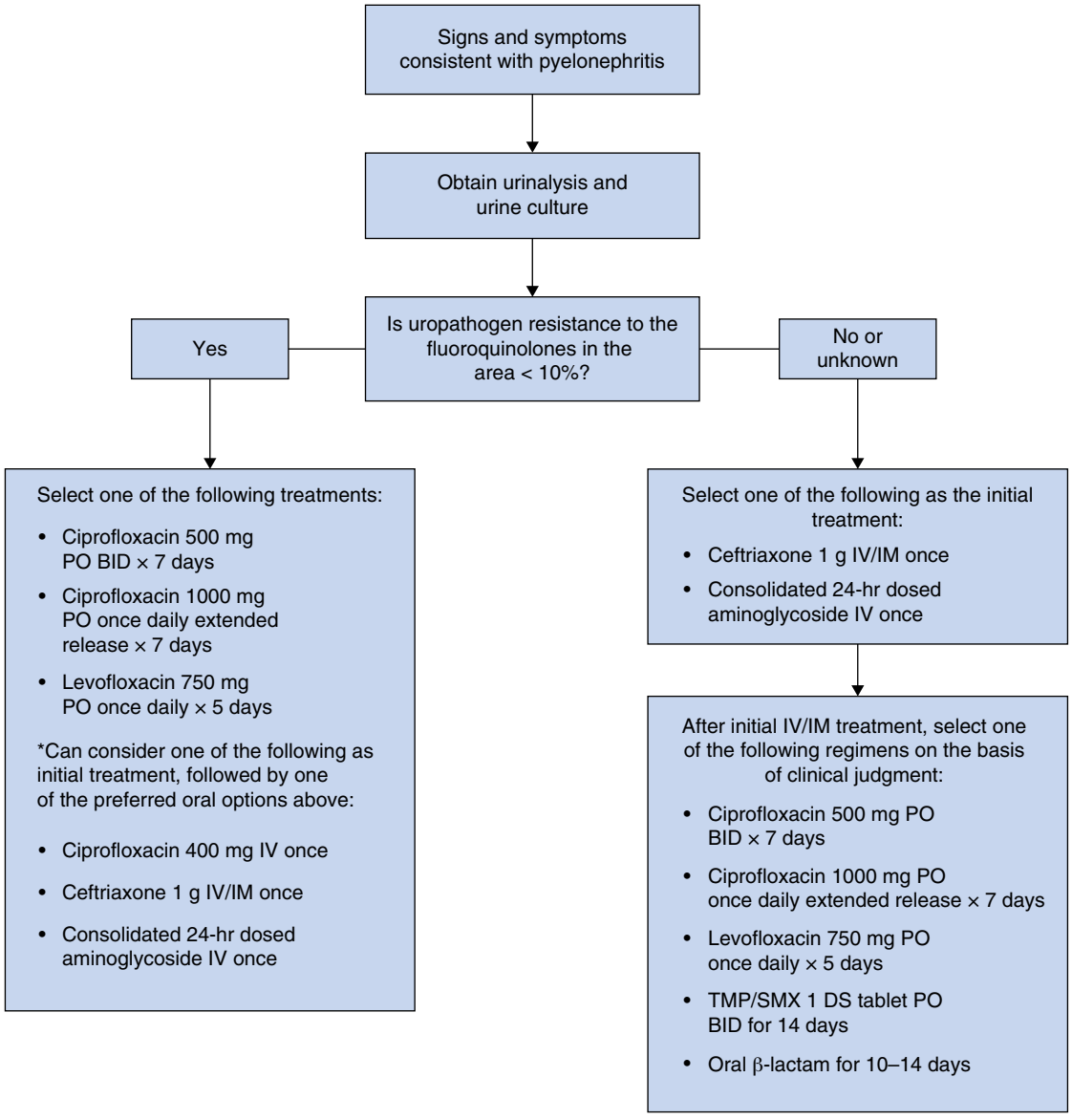


**Figure 1.** Pyelonephritis treatment algorithm for the non-hospitalized patient.

BID = twice daily; DS = double-strength; IM = intramuscular(ly); IV = intravenous(ly); PO = oral(ly); TMP/SMX = trimethoprim/sulfamethoxazole.

Information from: Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-e120.

involvement. Recommendations for the use of specific antimicrobials are not provided because of the very limited data from clinical trials. Selection of an empiric antibiotic should ideally be guided by local antimicrobial resistance information. Possible empiric options include, but are not limited to, all of the antimicrobials described earlier for the treatment of AC. Urine C&S testing should always be performed when treating a CAUTI to guide ultimate antimicrobial therapy (Hooton 2010).

The CAUTI guidelines provide some specific guidance on therapy duration. Most patients who have prompt resolution of symptoms after starting antimicrobial therapy can be treated for 7 days. In those who have a delayed response, 10–14 days is more appropriate. Because no specific definition of what constitutes a prompt or delayed response is provided, clinicians must use their judgment on a case-by-case basis. According to the results of one trial, a 5-day course of levofloxacin may be appropriate for patients who are not severely ill (Peterson 2008). Women younger than 65 who develop a CAUTI without upper urinary tract symptoms after the catheter has been removed can be treated with a 3-day antimicrobial regimen.

## PROSTATITIS TREATMENT RECOMMENDATIONS

No clinical practice guidelines for the treatment of prostatitis exist, likely because of the scarcity of clinical trials related to prostatitis treatment. The antimicrobial agents that penetrate and concentrate well in prostatic tissue are the fluoroquinolones, followed closely by trimethoprim/sulfamethoxazole (Wagenlehner 2006). Thus, the fluoroquinolones and trimethoprim/sulfamethoxazole are generally considered the treatments of choice for prostatitis (Lipsky 2010). Of interest, sulfamethoxazole penetrates poorly into prostatic tissue, and trimethoprim alone can be used for treatment. However, with increased antimicrobial resistance to the fluoroquinolones and trimethoprim/sulfamethoxazole, other options are needed. Although alternative options have less evidence, they include nitrofurantoin, amoxicillin/clavulanate, and cephalosporins such as cephalexin, cefuroxime, or cefixime. Clinicians must use their judgment when selecting an appropriate empiric agent and consider patient-specific factors and local antimicrobial resistance patterns, if known. Given that trimethoprim/sulfamethoxazole and the fluoroquinolones concentrate best in prostatic fluid, they should be considered as first-line agents unless antimicrobial resistance is likely or suspected. Urine C&S results can help guide the selection of a targeted antibiotic, so urine cultures should be obtained in all patients when prostatitis is suspected. Although no drug dosing recommendations exist specifically for prostatitis, the upper end of the dosing range for the chosen drug should be used to ensure adequate penetration into prostatic tissue. Acute prostatitis should be treated for at least 2 weeks, and treatment must often be extended to 4 weeks if patients are slow to show clinical improvement. Chronic prostatitis is treated for a longer duration, usually 6–8 weeks, but treatment may require up to 12 weeks in some cases (Murphy 2009).

## RECOMMENDATIONS FOR SPECIAL POPULATIONS

As mentioned earlier, well-designed clinical trials for patient populations that do not fall into the category of otherwise healthy, premenopausal women are lacking; thus, no specific treatment guidelines or recommendations are available. For male patients who experience a UTI, treatment should be provided, but the underlying cause of the UTI should also be thoroughly investigated because the cause could be an underlying structural or anatomical abnormality. In general, the same drug therapies for healthy females can apply to both male patients and older adults. Other recommendations likely apply as well. For example, if the patient resides in an area where uropathogen resistance to trimethoprim/sulfamethoxazole is greater than 20%, trimethoprim/sulfamethoxazole should not be used empirically. In addition, the fluoroquinolones should be avoided unless no other options exist. Male patients and older adults with a suspected UTI should undergo C&S testing to help guide antimicrobial therapy. Traditionally, male patients and older adults have been treated with longer courses of therapy than healthy females, though exact durations are based on clinician preference and lack evidence to support longer courses, and a recent trial showed that 7 days of therapy was noninferior to 14 days in men (Drekonja 2021).

Pregnant women should only receive drugs that are generally considered safe in pregnancy. The β-lactams are considered safe and have historically been the drugs of choice for the treatment of UTIs in pregnancy. Nitrofurantoin is considered safe until the last 30 days of pregnancy, when it should be avoided because of an increased risk of neonatal jaundice. Fosfomycin crosses the placenta but appears to be safe. However, because of less clinical experience than other drugs, fosfomycin should be reserved as an alternative therapy to the β-lactams or nitrofurantoin. The fluoroquinolones can inhibit cartilage and bone development, and trimethoprim/sulfamethoxazole is associated with congenital malformations and an increased risk of kernicterus; hence, these drugs should be avoided.

## TREATMENT OF RECURRENT UTIS

Recurrent UTIs are common in the ambulatory care setting. Around 20%–40% of otherwise healthy women who experience one episode of AC are likely to experience another, and 25%–50% of these patients will experience subsequent recurrent episodes. A recurrent UTI is defined as two separate, culture-proven episodes of symptomatic AC within

6 months, or three episodes within 1 year. In 2019, the American Urological Association, the Canadian Urological Association, and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction released the first clinical practice guidelines for the management of recurrent uUTIs in women (Anger 2019). The guidelines note that the treatment for recurrent UTIs should not generally be different from that for a first incident, and current first-line therapy of nitrofurantoin, trimethoprim/sulfamethoxazole, and fosfomycin should be used depending on local resistance patterns. Unlike a first episode of a UTI, cultures should be performed before initiating antimicrobial therapy when a recurrent UTI is suspected. Shared clinical decision-making can be used to determine whether antimicrobial therapy can be deferred until urine C&S results have returned to decrease the use of inappropriate antimicrobials. If antimicrobial therapy cannot be delayed until C&S results have returned, selection of an empiric antimicrobial should be based on prior C&S results and local resistance patterns.

Under certain circumstances, antimicrobial prophylaxis may be initiated to prevent recurrent UTIs. The decision to initiate prophylaxis is complex, with consideration given to the benefits to the patient of preventing recurrences while balancing the risks of increased antimicrobial resistance. No specific recommendation is made for when to initiate prophylaxis, so the decision must be shared between the patient and the clinician. Many different antimicrobials and regimens have been evaluated for prophylaxis (Table 4), and the guidelines do not recommend one agent over another. The choice of which antimicrobial to prescribe for prophylaxis should be based on factors such as previous C&S results and local resistance patterns as well as patient-specific factors. The most evidence from clinical trials appears to be with nitrofurantoin. Strong consideration should be given for nitrofurantoin because of the low risk of collateral damage and tolerability. However, with nitrofurantoin, pulmonary and hepatic toxicities can occur and are more common with prolonged use; thus, a different prophylactic agent should likely be prescribed for patients with underlying chronic lung and liver problems. The fluoroquinolones should not be used for prophylaxis because of the risk of high resistance, the high propensity for collateral damage, and the risk of adverse effects. The duration of antimicrobial prophylaxis varies but is typically 6–12 months. However, after discontinuing prophylaxis, recurrent UTIs resume for most women. For this reason, some women continue prophylaxis for years, though there is little evidence for this practice and the effect on antimicrobial resistance is unknown. In practice, women receiving prophylaxis should be assessed and monitored every few months for efficacy and the need for continued prophylaxis. Trial discontinuations of prophylaxis can be tried, with prophylaxis reinitiated if UTIs recur. For women who experience postcoital UTIs, single-dose antimicrobial prophylaxis before or after intercourse can help prevent infections. Intermittent dosing of these antimicrobials is associated with fewer adverse effects than continual prophylactic or treatment courses. See Table 4 for antimicrobial options.

**Table 4.** Oral Antimicrobials Used for Prophylaxis in Recurrent UTIs

| Continuous Prophylaxis | Pre- or Postcoital Prophylaxis[a] |
|---|---|
| • Trimethoprim 100 mg once daily<br>• TMP/SMX 40 mg/200 mg (½ single-strength tablet) once daily<br>• TMP/SMX 40 mg/200 mg (½ single-strength tablet) three times per week<br>• Nitrofurantoin 50 mg daily<br>• Nitrofurantoin 100 mg daily<br>• Cephalexin 125 mg once daily<br>• Cephalexin 250 mg once daily<br>• Fosfomycin 3 g every 10 days | • TMP/SMX 40 mg/200 mg (½ single-strength tablet)<br>• TMP/SMX 80 mg/400 mg (single-strength tablet)<br>• Nitrofurantoin 50 mg<br>• Nitrofurantoin 100 mg<br>• Cephalexin 250 mg |

[a]Patients should take a single dose either immediately before or immediately after sexual intercourse.

Information from: Anger J, Lee U, Ackerman AL, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. J Urol 2019;202:282-9.

Finally, non-antimicrobials for preventing recurrent UTIs can be considered. Non-antimicrobials have many advantages, particularly from an antimicrobial stewardship standpoint. Cranberry products have long been touted as a measure to prevent UTIs, for which several randomized controlled trials have been conducted in recent years. These trials have used a variety of cranberry formulations, including juices, cocktails, and tablets, and several trials have shown positive benefits with the cranberry products. Currently, evidence is insufficient to recommend a specific product or formulation over another, but any formulation that a patient can tolerate can be offered as a prophylactic measure. Few risks are associated with cranberry products; however, juices may be high in sugar content, so caution should be used in patients with diabetes. Another option that can be considered in peri- and postmenopausal women is local vaginal estrogen therapy, such as creams, which is associated with a reduction in recurrent UTIs. Vaginal estrogen therapy is also extremely safe, with minimal systemic absorption. Different formulations of vaginal estrogen products are available, and no preference is given to one product over another.

## CONCLUSION

Urinary tract infections are a common reason for receipt of antimicrobial therapy in the ambulatory care setting. There

are several different types of UTIs, of which AC and pyelonephritis are the most common. The treatment of UTIs, including prostatitis, is becoming more challenging because of increased antimicrobial resistance in uropathogens to drugs that have traditionally been used as recommended treatments (e.g., trimethoprim/sulfamethoxazole and the fluoroquinolones). Patients with ASB do not generally require antimicrobial therapy except in certain limited situations. Clinical practice guidelines for the treatment of AC and pyelonephritis in otherwise healthy women are available, but they are outdated because of increased global antimicrobial resistance. However, these guidelines are currently being updated and may be released in 2022, though the exact date is uncertain. Guidelines are also available for the treatment of CAUTIs, but they do not recommend specific antimicrobial therapy; instead, empiric therapy should be based on local susceptibility patterns. Because of a lack of well-designed controlled trials, guidelines are not available for special populations, such as older adults and males. However, these patients can be treated similarly to women, but with longer courses of therapy. Pharmacists play an important role in the management of UTIs and can educate other health care providers about appropriate treatment. To provide appropriate treatment, pharmacists must be familiar with the local resistance patterns of uropathogens.

### Practice Points

**Pharmacists working in the ambulatory care setting often encounter patients requiring treatment for UTIs. Increased antimicrobial resistance among uropathogens to agents once commonly used for UTI treatment, particularly trimethoprim/sulfamethoxazole and the fluoroquinolones, has made treatment more challenging. Pharmacists must be familiar with local resistance patterns in order to treat these infections appropriately.**

- **Pharmacists must be able to distinguish between ASB and AC to know when antimicrobial therapy is indicated.**
- **For the treatment of AC, first-line agents for empiric therapy are nitrofurantoin, trimethoprim/sulfamethoxazole, and fosfomycin.**
- **Trimethoprim/sulfamethoxazole should not be used as empiric therapy for AC if local uropathogen resistance is greater than 20%.**
- **The β-lactams and fluoroquinolones can be used as alternative agents for the treatment of AC, but only if use of a first-line agent is not possible.**
- **The drugs of choice to treat pyelonephritis are the fluoroquinolones because of their highly improved efficacy when the pathogen is susceptible. However, high resistance rates now limit their use.**
- **In areas where local uropathogen resistance to the fluoroquinolones is greater than 10%, a one-time dose of ceftriaxone or a consolidated 24-hour aminoglycoside should be administered first, followed by an oral fluoroquinolone. Trimethoprim/sulfamethoxazole or an oral β-lactam can be used in place of fluoroquinolones.**
- **Empiric treatment of CAUTIs should be based on local susceptibility data, and pharmacists should ensure the patient is experiencing a true CAUTI and not a CA-ASB.**
- **Trimethoprim/sulfamethoxazole and the fluoroquinolones concentrate well in prostatic tissue and should be the drugs of choice for the treatment of prostatitis, but high resistance may limit their use. The oral β-lactams or nitrofurantoin can be used as an alternative.**
- **UTIs in men and older adults are generally treated similarly to infections in women, but longer treatment courses may be required.**
- **Women who experience recurrent UTIs can use shared clinical decision-making to determine whether antimicrobial prophylaxis is appropriate.**

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# Self-Assessment Questions

1. A 21-year-old woman presents to her university medical clinic with concerns of painful urination and increased urinary frequency. She has no significant medical history, and her vital signs include temperature 98.4°F, blood pressure 110/72 mm Hg, heart rate 64 beats/minute, and respiratory rate 12 breaths/minute. A urine dipstick test is positive for both leukocyte esterase and nitrites. Which one of the following organisms most likely caused this patient's UTI?

   A. *K. pneumoniae*
   B. *Pseudomonas aeruginosa*
   C. *S. aureus*
   D. *Enterococcus faecalis*

2. A 36-year-old woman with a medical history of prediabetes is undergoing evaluation with a urinalysis to test for the presence of glucose. Although the glucose test was negative, the patient had WBCs, leukocyte esterase, and bacteria in her urine. The patient denies any signs and symptoms of a UTI. A urine culture shows greater than 100,000 CFU/mL of *P. mirabilis* after 48 hours. Which one of the following is best to recommend for this patient?

   A. Prescribe an antimicrobial according to the susceptibility results from the urine culture.
   B. Re-collect the urine sample and counsel the patient on how to obtain a clean-catch specimen.
   C. Do not prescribe antimicrobials or obtain further laboratory testing.
   D. Initiate nitrofurantoin 100 mg orally twice daily for 5 days.

3. A 27-year-old woman presents to the acute care clinic for evaluation. She has had painful urination and nocturia for the past 3 days; however, she has not sought treatment because she thought it would get better on its own. Now, she "feels hot," and her lower back has begun to hurt. A clean-catch urinalysis shows the presence of bacteria and is positive for WBCs and nitrites. The patient's vital signs include temperature 102.1°F, blood pressure 136/84 mm Hg, heart rate 82 beats/minute, and respiratory rate 14 breaths/minute. She is diagnosed with pyelonephritis and able to drink some fluids in the clinic room. She has a medical history of asthma in childhood and has no known drug allergies. Uropathogen resistance in the area to the fluoroquinolones is 7%. Which one of the following is best to recommend for this patient?

   A. Admit to the hospital for further treatment.
   B. Initiate nitrofurantoin 100 mg orally twice daily for 5 days.
   C. Administer ceftriaxone 1 g intravenously once, then initiate ciprofloxacin 500 mg orally twice daily for 7 days.
   D. Initiate levofloxacin 750 mg orally daily for 5 days.

4. A 45-year-old woman (height 64 inches, weight 72 kg) with no known drug allergies is undergoing evaluation for pyelonephritis, and it is determined that she does not require hospitalization. No local antibiogram is available, and ceftriaxone is currently on a national manufacturer backorder. Which one of the following is best to recommend for this patient?

   A. Ciprofloxacin 400 mg intravenously once
   B. Gentamicin 150 mg intravenously once
   C. Levofloxacin 500 mg intravenously once
   D. Tobramycin 450 mg intravenously once

5. A 71-year-old man has a medical history significant for hypertension, dyslipidemia, and type 2 diabetes. Over the past year, he has had three UTIs, all caused by *E. coli* (resistant to ampicillin but susceptible to all other tested antibiotics). He also has concerns about difficulty urinating and has had low back pain for several months. He is ultimately diagnosed with chronic prostatitis. Which one of the following is the best to recommend for this patient?

   A. Ciprofloxacin 500 mg orally every 12 hours for 4 weeks
   B. Amoxicillin/clavulanate 500 mg/125 mg orally every 8 hours for 12 weeks
   C. Levofloxacin 750 mg orally once daily for 8 weeks
   D. Trimethoprim/sulfamethoxazole 1 double-strength tablet orally every 12 hours for 3 weeks

6. A 23-year-old man has been experiencing intermittent burning on urination for a few weeks and presents to his PCP for evaluation. He has no contributory medical history. A urine dipstick test is positive for both leukocyte esterase and nitrites. His vital signs are all within normal limits. Local resistance rates of uropathogens to trimethoprim/sulfamethoxazole are around 15%. Which one of the following is the best to recommend for this patient?

   A. Obtain a urine culture; initiate trimethoprim/sulfamethoxazole 1 double-strength tablet orally twice daily for 7 days; refer to urology for further evaluation.
   B. Initiate ciprofloxacin 500 mg orally twice daily for 7 days; no further tests are needed.
   C. Obtain a urine culture; initiate cefdinir 300 mg orally twice daily for 10 days.

D. Initiate moxifloxacin 400 mg orally once daily for 7 days; no further tests are needed; refer to urology for further evaluation.

**Questions 7 and 8 pertain to the following case.**

J.G. is a 77-year-old man who resides at a long-term care facility. He has a complex medical history with several comorbidities. He requires a permanent indwelling Foley catheter, which is changed on a monthly basis. He has no known drug allergies. One week after his last catheter change, routine quarterly laboratory tests were obtained which include a comprehensive metabolic panel, CBC, and urinalysis. The urinalysis shows the presence of leukocyte esterase but is negative for nitrites. The patient has no symptoms of a UTI and is at his normal baseline mental status.

7. Which one of the following is best to recommend for J.G.?

   A. Replace the catheter now and initiate empiric antimicrobials.
   B. Do not replace the catheter now but initiate empiric antimicrobials.
   C. Replace the catheter now but do not initiate empiric antimicrobials.
   D. Do not replace the catheter and do not initiate empiric antimicrobials.

8. Two weeks later, J.G. experiences a temperature of 101.1°F and has altered mental status from his baseline. Which one of the following is the best to recommend for J.G.?

   A. Replace the catheter now and obtain a urinalysis and urine culture from the new catheter; initiate a broad-spectrum antimicrobial according to the local antibiogram until the urine culture returns.
   B. Do not obtain new laboratory tests because they were obtained 2 weeks ago and do not replace the catheter; initiate a broad-spectrum antimicrobial according to the local antibiogram until the urine culture returns.
   C. Replace the catheter now and obtain a urinalysis and urine culture from the new catheter; initiate an antimicrobial only if the urine culture returns positive for a pathogenic organism.
   D. Obtain a urinalysis and urine culture from the catheter already in place; initiate a broad-spectrum antimicrobial according to the local antibiogram until the urine culture returns.

9. A 26-year-old woman has had four UTIs over 8 months. No cultures were obtained for the first two infections, but the most recent infections grew *E. coli* resistant to ampicillin, trimethoprim/sulfamethoxazole, and cefazolin. She presents to her PCP today for a routine yearly examination but wants to discuss the possibility of antimicrobial prophylaxis against UTIs. Which one of the following best assesses this patient's candidacy for antimicrobial prophylaxis?

   A. She is not currently a candidate for antimicrobial prophylaxis.
   B. She is a candidate for antimicrobial prophylaxis; initiate trimethoprim/sulfamethoxazole 40 mg/200 mg (½ single-strength tablet) orally once daily.
   C. She is a candidate for antimicrobial prophylaxis; initiate nitrofurantoin 100 mg orally once daily.
   D. She is a candidate for antimicrobial prophylaxis; initiate cephalexin 250 mg orally once daily.

10. A 31-year-old woman is experiencing recurrent UTIs after sexual intercourse. After discussion with her PCP, she has agreed to try postcoital prophylaxis with nitrofurantoin 100 mg. She presents to the pharmacy to obtain the prescription and asks to be counseled on use of the medication. Which one of the following is the best educational point regarding prophylaxis to share with this patient?

    A. Take 1 capsule immediately before and immediately after intercourse.
    B. Take 1 capsule immediately after intercourse.
    C. Take 1 capsule every evening.
    D. Take 1 capsule three times weekly.

11. A 51-year-old man presents to the acute care clinic with concerns of self-reported fever, chills, rectal pain, and dysuria for the past 24 hours. He has never had these symptoms before. Acute prostatitis is diagnosed, and a urine culture returns with the following result: greater than 100,000 CFUs of *K. pneumoniae*.

| Drug | Minimum Inhibitory Concentration (mg/L) | Interpretation |
|---|---|---|
| Ampicillin | ≥ 8 | R |
| Ampicillin/sulbactam | < 2 | S |
| Cefazolin | 16 | R |
| Cefepime | ≤ 1 | S |
| Ceftriaxone | ≤ 1 | S |
| Ciprofloxacin | > 4 | R |
| Gentamicin | ≤ 2 | S |
| Imipenem | ≤ 2 | S |
| Nitrofurantoin | ≤ 16 | S |
| Piperacillin/ tazobactam | ≤ 4 | S |
| Trimethoprim/ sulfamethoxazole | ≤ 2 | S |

Given the culture results, which one of the following is best to recommend for this patient?

A. Amoxicillin/clavulanate for 4 weeks
B. Levofloxacin for 4 weeks
C. Trimethoprim/sulfamethoxazole for 4 weeks
D. Cephalexin for 4 weeks

12. A 22-year-old otherwise healthy woman presents to the outpatient pharmacy with a prescription for trimethoprim/sulfamethoxazole, 1 double-strength tablet orally twice daily for 7 days for AC. The pharmacist filling the prescription knows that *E. coli* resistance to trimethoprim/sulfamethoxazole in the area is around 28%. Which one of the following is the most appropriate action for the pharmacist to take for this patient?

    A. Call the prescriber for a new prescription for ciprofloxacin.
    B. Call the prescriber to get the length of therapy reduced to 3 days.
    C. Fill the prescription as written and counsel the patient on possible adverse drug events.
    D. Call the prescriber to change the antibiotic to nitrofurantoin 100 mg orally every 12 hours for 5 days.

13. A 69-year-old woman presents to an urgent care facility with concerns of dysuria, frequency of urination, and urgency to urinate over the past 3 days. She also reports some left flank pain, which she rates as 4/10 and says it has not affected her activities of daily living. She denies nausea, vomiting, and diarrhea. Her vital signs include temperature 101.2°F, blood pressure 114/68 mm Hg, heart rate 72 beats/minute, and respiratory rate 14 breaths/minute. Her medical history is significant for hypertension, gastroesophageal reflux disease, and type 2 diabetes. She has no known drug allergies. Local resistance patterns from the community are unknown. A urine culture is pending, and the results from her urinalysis are as follows:

| | Reference Range | Result |
|---|---|---|
| Appearance | Clear | Hazy |
| Bacteria | None | Many |
| Color | Clear | Amber |
| Leukocyte esterase | None | 3+ |
| Nitrites | Negative | Positive |
| Specific gravity | 1.002–1.030 | 1.016 |
| Urine bilirubin | None | None |
| Urine glucose | None | None |
| Urine pH | 5.0–7.0 | 5.2 |
| Urine protein | None | None |
| Urine WBC | None | 30 cells/high-power field |

Which one of the following is the best to recommend for this patient?

    A. Admit to the hospital and begin treatment with ceftriaxone 1 g intravenously once daily.
    B. Administer trimethoprim/sulfamethoxazole 80/400 mg orally every 12 hours for 14 days in the outpatient setting.
    C. Administer fosfomycin 3 g orally every 24 hours for three doses in the outpatient setting.
    D. Administer ceftriaxone 1 g intravenously once, then initiate ciprofloxacin 500 mg orally every 12 hours for 7 days.

14. A 45-year-old woman presents to the pharmacy to ask about using cranberry products to prevent recurrent UTIs. Which one of the following is the best educational point to share with this patient?

    A. Cranberry products should not be used because they have not been shown efficacious for preventing UTIs.
    B. Only cranberry juice has been shown efficacious in preventing UTI recurrences.
    C. Some studies have shown cranberry products to be efficacious, but evidence is insufficient to recommend one specific formulation over another.
    D. Cranberry products can contribute to the development of antimicrobial resistance and should not be recommended for use.

15. A 53-year-old man presents to his PCP for burning and painful urination for the past 24 hours. He currently has no other concerns. His vital signs include temperature 98.2°F, blood pressure 120/74 mm Hg, heart rate 68 beats/minute, and respiratory rate 12 breaths/minute. A urine dipstick test is positive for leukocyte esterase and nitrites, and his PCP diagnoses a UTI. Which one of the following best classifies this patient's UTI?

    A. Lower UTI, uncomplicated
    B. Upper UTI, complicated
    C. Lower UTI, complicated
    D. Upper UTI, uncomplicated

## Learner Chapter Evaluation: Genitourinary Infections

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.
12. The activity met the stated learning objectives.
13. If any objectives were not met, please list them here.

### OTHER COMMENTS

14. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
15. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter: