

Urinary Tract Infections

Nancy M. Toedter, Pharm.D. Assistant Professor of Clinical Pharmacy Practice
University of Louisiana at Monroe College of Pharmacy

ISSUES:

- UTIs are one of the most common infectious diseases encountered today, contributing significantly to healthcare costs.
- UTIs are most prevalent in women, and causative organisms usually originate from the fecal flora of the host.
- The antimicrobial choice for treatment of UTIs must take into consideration the spectrum of activity, potential toxicities, and current resistance patterns.

Urinary tract infections (UTIs) are one of the most commonly occurring medical problems, causing considerable morbidity and healthcare costs. In the United States, UTIs account for approximately seven million office visits to physicians each year, and over one million hospitalizations annually are attributed to or complicated by UTIs. Overall annual healthcare costs due to UTIs are estimated to exceed \$1 billion.¹ Although UTIs can occur in persons of all ages, sexually active young women are more commonly affected. It is estimated that 40% of women will develop UTI sometime during their lifetime, and 20% of women reporting UTI will have multiple recurrences.^{2,3} As these figures demonstrate, UTIs are a major health problem, and appropriate management can help minimize morbidity and costs associated with them.

Definitions

The general term "urinary tract infection" refers to the presence of microorganisms in the urinary tract, which includes the bladder, kidneys, collecting systems, or prostate. Most UTIs are caused by bacteria, although fungi and viruses may occasionally be involved.⁴ UTIs may be classified by anatomic site of involvement or may be categorized as uncomplicated versus complicated. Regarding anatomic designations, UTIs are divided into lower tract infections (cystitis, urethritis, prostatitis, and epididymitis) and upper tract infections (acute or chronic pyelonephritis).¹ The other method of classification divides UTIs into uncomplicated versus complicated infections. Uncomplicated UTIs generally occur in sexually active, nonpregnant adult women who do not have structural or functional abnormalities of the urinary tract. This is the more common type of UTI and is most responsive to antibiotics.^{1,5} Complicated UTIs, on the other hand, are harder to treat and occur in patients with structurally or functionally abnormal urinary tracts. This includes patients with renal stones, indwelling urinary catheters, prostatic hypertrophy, obstruction, or diabetes. Infections occurring in elderly, children, men, or pregnant women as well as hospital-acquired UTIs are also considered complicated.^{1,5,6}

Bacteriuria refers to the presence of bacteria in the urine. The term "significant bacteriuria" has been used to differentiate true infection from contamination, and historically, bacterial counts greater than or equal to 100,000 organisms/ml indicated a true infection while counts less than 100,000 organisms/ml represented contamination.⁷ This traditional threshold of greater than or equal to 100,000 bacteria/ml has been challenged because 30-50% of women with acute cystitis have less than 100,000 bacteria/ml. In those symptomatic women with low bacterial colony counts, the infection may be in an early phase and may not yet be established in the bladder; this is often termed "urethral syndrome." Additionally, the infection may be subsiding, or the patient may have recently urinated or may be taking a diuretic.^{3,5,6} Therefore, significant bacteriuria may be better defined based on patient population and method of urine collection, and this definition may be expanded to include the following criteria:⁸

- $>10^2$ CFU coliforms/ml or $> 10^5$ CFU noncoliforms/ml in a symptomatic female
- $>10^3$ CFU bacteria/ml in a symptomatic male
- $>10^5$ CFU bacteria/ml in asymptomatic patients on two consecutive specimens
- $>$ Any growth of bacteria on suprapubic catheterization in a symptomatic patient
- $>10^2$ CFU bacteria/ml in a catheterized patient (CFU = colony-forming units)

Pathophysiology

Bacteria can invade the urinary tract through three possible routes: the ascending, hematogenous, and lymphatic pathways. Most infections occur via the ascending pathway, with bacteria moving from the urethra to the bladder (cystitis) and continuing up the ureter to the kidney (pyelonephritis). The short length of the female urethra along with its close proximity to the perirectal area promote urethral colonization, and sexual intercourse may then force bacteria into the bladder. Hematogenous spread of organisms rarely occurs, accounting for less than 5% of documented UTIs. Infection of the kidneys by this route usually results from bacteremia with invasive pathogens, such as *Staphylococcus aureus*. Finally, the lymphatic pathway appears to have an insignificant role in the pathogenesis of UTIs. Although lymphatic communications exist between the bowel/kidney and bladder/kidney, there is no evidence that organisms enter the kidney via this route.^{1,4,7,9}

Once bacteria do reach the urinary tract, various factors can influence the development of infection. The normal urinary tract possesses several defense mechanisms to prevent infection. For example, the urine possesses antibacterial activity; a low pH, high urea and organic acid concentrations, and a high osmolality are all factors that can inhibit microorganisms. Additionally, micturition involves removal of contaminated urine, and certain antiadherence mechanisms present in the bladder, such as urinary mucus, prevent bacteria from colonizing and infecting the urinary tract. On the other hand, bacteria can possess certain virulence factors that increase their likelihood of causing an infection. An example is the presence of fimbriae, or rigid hair-like appendages, that allow bacteria to adhere to uroepithelial cells.^{4,7}

Predisposing Factors

Certain risk factors have been identified which increase the chances of developing UTIs. Age and gender are two such factors. Elderly patients are at increased risk due to impaired bladder emptying, obstruction secondary to prostatic disease, bladder catheterization, and increased perineal soiling. Regarding gender, adult women are thirty times more likely than men to develop UTI. Sexual intercourse is another risk factor, as this may facilitate migration of pathogens into the bladder. The use of a diaphragm and spermicide for contraception also present an increased risk; not only can the diaphragm cause urinary obstruction, but the spermicide can also cause a change in vaginal flora. Delayed postcoital micturition and pregnancy are other risk factors. Postmenopausal women may also be predisposed to infection due to an increase in vaginal pH, which alters endogenous flora. Hospitalized patients, those with urinary catheters, and those with neurologic disorders as well as patients with diabetes mellitus are also at increased risk for development of UTIs.^{1,4,9,10}

Etiology

Most UTIs are caused by a single pathogen, usually enteric gram-negative bacteria originating from the fecal flora of the host. The most common cause of uncomplicated, community-acquired UTIs is *Escherichia coli*, accounting for more than 80% of infections. *Staphylococcus saprophyticus* is the second most common pathogen, particularly among young, sexually active females, accounting for 5-15% of community-acquired episodes. This pathogen is generally considered more aggressive than *E. coli* because about 50% of the women present with upper tract involvement, and infections due to this organism are more likely to be recurrent, relapsing, and persistent. Occasionally, other Enterobacteriaceae, such as *Proteus mirabilis* or *Klebsiella* spp. are isolated in uncomplicated UTIs.^{1,3,7,11}

Complicated UTIs, including nosocomial infections, are caused by more varied organisms and are generally more resistant than those causing uncomplicated infections. Although *E. coli* is still frequently isolated, it causes less than 50% of infections. Other organisms that are frequently isolated include *Proteus* spp., *Klebsiella pneumoniae*, *Enterobacter* spp., *Pseudomonas aeruginosa*, staphylococci, and enterococci. *Enterococcus faecalis* is now the second-most frequently isolated bacteria in hospitalized patients. This may be due to indwelling urinary catheter use or overuse of third-generation cephalosporins, which have no activity against enterococci. *Candida* spp. also cause UTIs, particularly in the critically ill and chronically catheterized patient as well as those patients receiving broad-spectrum antibiotics.^{1,6,7,9}

Clinical Presentation

The clinical presentation of UTI can be separated into those symptoms associated with lower tract and upper tract infections. Lower tract symptoms have an abrupt onset and result from bacteria irritating the urethral and bladder mucosa, causing dysuria, urgency, and frequency. Patients sometimes report

suprapubic pain or heaviness, and occasionally, hematuria is present. The urine may be cloudy and foul smelling. Systemic symptoms, such as fever and leukocytosis, are generally absent with acute cystitis.^{7,9,12}

Clinical findings of upper tract infections typically involve systemic symptoms, including fever, chills, nausea, vomiting, flank pain, costovertebral angle tenderness, and malaise. Leukocytosis and hematuria are also usually present. Lower tract symptoms (urgency, frequency, and dysuria) are often present and may even precede fever and upper tract symptoms by one to two days.^{7,9,12}

Not all patients with UTIs present with these classic symptoms. Elderly patients, for example, may present with altered mental status, loss of appetite, lethargy, nausea, vomiting, or abdominal pain. Infants may also present with nonspecific symptoms, including poor feeding, vomiting, and fever. Additionally, both upper and lower tract infections can be asymptomatic. Asymptomatic UTIs occur most commonly in elderly patients, children, pregnant patients, and those with indwelling catheters.^{6,7,9,12}

Diagnosis

In addition to symptoms, diagnosis of UTIs depends on examination of the urine, specifically performing a urinalysis and, if indicated, a urine culture. In order for laboratory evaluation to be useful, proper collection of urine is necessary. There are three methods of urine collection: midstream clean-catch method, urinary catheterization, and suprapubic bladder aspiration. The midstream clean catch is the preferred method for routine urine collection and is the most practical for outpatient use because it utilizes voided urine. When patients are uncooperative or are unable to void, catheterization or suprapubic bladder aspiration may be indicated. These alternative methods utilize catheterized urine or urine aspirated directly from the bladder.^{7,9,10}

A definitive diagnosis of UTI depends on the presence of pyuria and bacteriuria, which can be determined from a urinalysis. A macroscopic examination of the urine is initially performed, followed by a microscopic analysis. A macroscopic analysis involves describing the urine color, measuring its specific gravity, and estimating pH, glucose, protein, ketone, blood, and bilirubin content. Cloudy or turbid urine often suggests UTI, and hematuria as well as proteinuria may be present with UTIs. The urinary pH may increase because of by-products produced by urea-splitting bacteria, such as *Proteus* spp. A microscopic examination of the urine sediment, on the other hand, describes the presence and quantity of erythrocytes, leukocytes, epithelial cells, crystals, casts, and bacteria. Pyuria (greater than 10 WBCs/mm³ of urine) is often seen in symptomatic patients, and WBC casts often suggest pyelonephritis.^{3,6,7,13,14}

Urine dipstick tests are also available which can rapidly screen urine for the presence of pyuria and bacteriuria by detecting leukocyte esterase and nitrite, respectively. The leukocyte esterase test detects the enzyme leukocyte esterase,

which is unique to granulocytic cells, such as leukocytes, and indicates the presence of WBCs (pyuria). The nitrite dipstick test detects the presence of nitrite, which is formed when gram-negative bacteria reduce nitrate that is normally present in the urine. It should be noted that not all bacteria reduce nitrates to nitrites. This includes gram-positive organisms and *Pseudomonas aeruginosa*, which may thus give false-negative results with this test.^{3,7,9} These urine dipstick tests are now available for home testing of UTIs. The UTI Urine Nitrite Test Strips screen for the presence of nitrites only, while the Azo Test Strips detect both leukocytes and nitrites. Patients should be cautioned that false-negative results could occur with these tests if they are taking tetracycline or large doses of vitamin C. Additionally, phenazopyridine can stain the test strip and make it harder to read.^{15,16}

Consequently, the urine culture is the most reliable method for diagnosing UTIs. This quantifies the number of bacteria present and allows identification of the infecting pathogen and subsequent susceptibility testing. Urine cultures may not be necessary in women with acute, uncomplicated cystitis but should be performed when a complicated infection or pyelonephritis is suggested.^{7,14}

Treatment

When selecting an antimicrobial agent for treatment of UTI, various factors should be considered. These include spectrum of activity, pharmacokinetics favoring decreased dosing frequency, underlying disease states or complicating host factors, patient allergies, ability to achieve adequate urinary concentrations (including adequate tissue levels in the kidney if pyelonephritis is being treated), potential for adverse effects or drug interactions, prevalence of antimicrobial resistance patterns among common UTI pathogens, and cost.^{5,14} Practitioners should become aware of current patterns of antimicrobial resistance among organisms causing uncomplicated UTIs since resistance among these uropathogens is growing. Reports that 25-35% (or higher) of *E. coli* isolates may be resistant to ampicillin, amoxicillin, or sulfonamides have resulted in decreased usage of these antibiotics as empiric therapy.^{9,11} Of greater concern is that a recent study among women with uncomplicated cystitis showed an increasing prevalence of *E. coli* resistance (up to 18%) to trimethoprim and trimethoprim-sulfamethoxazole (TMP-SMX), commonly used agents for treating acute cystitis; resistance to nitrofurantoin and ciprofloxacin remained extremely low.¹⁷

Several nonspecific therapies have been used in preventing UTIs and as an adjunct to antibiotics in treating UTIs. Increased fluid intake is one such strategy, as this may result in removal of uropathogens by frequent voiding. Postcoital micturition may also flush bacteria from the bladder and urethra. Ascorbic acid may acidify the urine, thus increasing the antibacterial activity of urine. More commonly, cranberry juice has been used to acidify the urine and has also been shown to prevent *E. coli* from adhering to the uroepithelium, thereby preventing infection. Additionally, urinary tract analgesics, such as phenazopyridine, may be used to relieve dysuria. It has no antibacterial activity and is generally only used

for one or two days. Patients should be warned that phenazopyridine may discolor the urine to a red-orange-brown color, which can stain clothing. Finally, estrogen therapy may prove useful in postmenopausal women with frequent UTIs, as estrogens may decrease vaginal pH, thus increasing vaginal colonization with lactobacilli and suppressing vaginal growth of Enterobacteriaceae.^{5,9,18,19,20}

Acute Cystitis

Treatment options for acute, uncomplicated cystitis include single-dose therapy and three- or seven-day antibiotic regimens. In the past, it was considered standard therapy to treat cystitis with 7-10 days of antibiotics. However, it is now apparent that acute cystitis is a superficial mucosal infection that can be treated with much shorter courses of therapy, such as single-dose and three-day regimens. These short-course regimens offer the advantages of fewer side effects, improved compliance, and lower cost.^{9,14}

Single-dose therapy results in high urinary concentrations that persist for at least 12-24 hours and eliminate bacteria when confined to the bladder. This regimen should only be used in young women of childbearing age who have no complicating factors present; it should not be used in treating upper tract infections or in pregnant women, elderly women, diabetics, or males. Single-dose therapy is often associated with lower cure rates and a higher risk of recurrence, most likely due to the inability of single-dose antibiotics to eradicate *E. coli* from the fecal and vaginal reservoir, which is the source for the ascending route of infection. Of single-dose therapies, the most effective results have been achieved with TMP-SMX (2 double-strength tablets), various fluoroquinolones, or fosfomycin (Monurol 3g). Lower cure rates have been reported with single doses of beta-lactams, primarily due to the high incidence of ampicillin- and amoxicillin-resistant organisms and faster elimination rates associated with beta-lactams. It is also noteworthy that with single-dose regimens, *E. coli* seems to be eliminated more effectively than *S. saprophyticus*. Another drawback to single-dose regimens is the patients' perception about the adequacy of their therapy, since symptoms of UTI often persist beyond the day of treatment.^{2,5,9,10,11,12,18}

Three-day regimens are more effective than single-dose therapy and offer comparable efficacy to seven-day regimens but with fewer side effects and lower cost. Unlike single-dose therapy, three or more days of antibiotic therapy generally eradicate *E. coli* from the fecal and vaginal reservoir. Greater cure rates have been associated with trimethoprim, TMP-SMX, and various fluoroquinolones, including ciprofloxacin, ofloxacin, norfloxacin, and levofloxacin. The new quinolone, gatifloxacin (Tequin), also is effective in complicated and uncomplicated UTIs.²¹ Amoxicillin and first-generation cephalosporins are generally not good choices for empiric therapy due to the high prevalence of organisms resistant to these agents. Additionally, three-day regimens of nitrofurantoin have resulted in higher treatment failures due to its short plasma half-life; therefore, it should be given for at least seven days for treatment of

acute cystitis. Based on cost and efficacy, a three-day regimen of TMP-SMX should be considered first-line for empiric therapy in uncomplicated cystitis. The fluoroquinolones, although highly effective and well tolerated, should primarily be used in patients who are allergic to sulfonamides, who are suspected of having antimicrobial-resistant pathogens, or who reside in an area with a high prevalence of TMP-SMX resistance.^{2,3,5,11,22}

Seven-day antibiotic regimens, once considered the standard of therapy, are now generally reserved for infections in patients with complicating factors. These include male sex, a history of a previous UTI caused by resistant bacteria, diabetes, symptoms present for more than seven days, pregnancy, age over 65 years, urinary tract abnormality, or immunosuppression. Short-course therapy is not recommended in these patients, as these complicating factors may compromise three-day cure rates.^{5,9,11,18}

Recurrent Cystitis

Recurrent UTIs are common among young, otherwise healthy females, occurring in more than 20% of women. Although such recurrences may occasionally be due to a relapse (persistent infection with the same organism), most recurrences represent episodes of reinfection (infection with different organisms). In cases of relapse, a urine culture and susceptibility testing should be done, and the patient should be placed on an antibiotic for a longer treatment course, such as 2-6 weeks. For reinfections, three management strategies have been used: continuous low-dose antimicrobial prophylaxis, postcoital prophylaxis, or patient-initiated therapy. Women should be questioned about their method of contraception since diaphragm-spermicide use may contribute to recurrent infections. If UTIs are associated with sexual activity, voiding after intercourse may prove beneficial. Finally, in postmenopausal women with recurrent infections, intravaginal estrogen cream may decrease the incidence of UTI.^{2,9,11,19,22}

Acute Uncomplicated Pyelonephritis

Women with acute uncomplicated pyelonephritis may be categorized into those who are sick enough to require hospitalization for parenteral therapy and those who can be safely managed as an outpatient with oral therapy. Urine cultures are indicated in all patients with suspected pyelonephritis, and blood cultures should also be obtained in hospitalized patients. When selecting antimicrobial therapy, consideration must be given that the antibiotic achieve adequate concentrations in both urine and kidney tissue. Therefore, drugs such as nitrofurantoin should not be used in treating pyelonephritis because it does not achieve reliable tissue concentrations. The usual duration of therapy for pyelonephritis is fourteen days.^{2,5,6,11,18}

Empiric therapy should include an agent with a broad spectrum of coverage. For patients with mild to moderate infections (no nausea or vomiting), oral agents such as TMP-SMX, the fluoroquinolones, or extended-spectrum cephalosporins

may be used. However, patients who are more severely ill and are experiencing nausea/vomiting or dehydration may require parenteral therapy. Intravenous agents often used for initial treatment include third-generation cephalosporins, fluoroquinolones, extended-spectrum penicillins, or aminoglycosides. As the patient improves clinically, therapy may be converted to an oral regimen to complete the fourteen-day course.^{2,5,6,11,18}

Conclusion

UTIs are one of the most common infectious diseases and are seen in both the inpatient and outpatient settings. An understanding of the pathogenesis, diagnosis, clinical course, and treatment regimens are essential in managing this disease state. Knowledge of antimicrobial spectrum of activity along with current resistance patterns, drug cost, and potential medication side effects may help guide antimicrobial selection. Nonpharmacologic modalities should also be used in treatment. Gaining a better understanding of this disease state can result in more optimal patient outcomes.

References

1. Bacheller CD, Bernstein JM. Urinary tract infections. *Med Clin North Am.* 1997;81(3):719-30.
2. Orenstein R, Wong ES. Urinary tract infections in adults. *Am Fam Physician.* 1999;59(5):1225-34.
3. Faro S, Fenner DE. Urinary tract infections. *Clin Obstet Gynecol.* 1998;41(3):744-54.
4. Wisinger DB. Urinary tract infection: current management strategies. *Postgrad Med.* 1996;100(5):229-36, 239.
5. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am.* 1997;11(3):551- 81.
6. Barnett BJ, Stephens DS. Urinary tract infection: an overview. *Am J Med Sci.* 1997;314(4):245-9.
7. Mullenix TA, Prince RA. Urinary tract infections and prostatitis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach.* 4th ed. Stamford, Connecticut; Appleton & Lange, 1999:1779-94.
8. Johnson CC. Definitions, classification, and clinical presentation of urinary tract infections. *Med Clin North Am.* 1991;75(2):241-52.

9. Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 4th ed. New York; Churchill Livingstone, 1995:662-90.
10. Hatton J, Hughes M, Raymond CH. Management of bacterial urinary tract infections in adults. *Ann Pharmacother*. 1994;28:1264-72.
11. Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med*. 1993;329(18):1328-34.
12. Romac DR. Urinary tract infections. In: Herfindal ET, Gourley DR, eds. *Textbook of Therapeutics: Drug and Disease Management*. 6th ed. Baltimore; Williams & Wilkins, 1996:1307-25.
13. Sahai JV, Fendler KJ. Urinary tract infections. In: Koda-Kimble MA, Young LY, eds. *Applied Therapeutics: The Clinical Use of Drugs*. 5th ed. Vancouver, Washington; Applied Therapeutics, Inc. 1992:43.1-43.23.
14. Tice AD. Short-course therapy of acute cystitis: a brief review of therapeutic strategies. *J Antimicrob Chemother*. 1999;43(Suppl A):85-93.
15. UTI Urine Nitrite Test Strips. Consumers Choice Systems, Inc. Bellevue, Washington: 1996. Product information.
16. Azo Test Strips. PolyMedica Corporation. Woburn, MA: 1997. Product information.
17. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA*. 1999;281(8):736-38.
18. Perdue BE, Plaisance KI. Treatment of community-acquired urinary tract infections. *Am Pharm*. 1995;NS35(12):37-45.
19. Stapleton A, Stamm WE. Prevention of urinary tract infection. *Infect Dis Clin North Am*. 1997;11(3):719-33.
20. Avorn J, Monane M, Gurwitz JH, et al. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA*. 1994;271(10):751-54.
21. Tequin (gatifloxacin). Bristol-Myers Squibb Company. Princeton, NJ: 1999. Product information.
22. Hooton TM, Stamm WE. Management of acute uncomplicated urinary tract infection in adults. *Med Clin North Am*. 1991;75(2):339- 57.

