Chapter 139: Urinary Tract Infections

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 51, Urinary Tract Infections and Prostatitis.

KEY CONCEPTS

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1. Urinary tract infections (UTIs) can be classified as uncomplicated and complicated. *Uncomplicated* refers to an infection in an otherwise healthy, premenopausal female who lacks structural or functional abnormalities of the urinary tract. Most often complicated infections are associated with a predisposing lesion of the urinary tract; however, the term may be used to refer to all other infections, except for those in the otherwise healthy, premenopausal adult female.

2. Recurrent UTIs are considered either reinfections or relapses. Reinfection usually happens more than 2 weeks after the last UTI and is treated as a new uncomplicated UTI. Relapse usually happens within 2 weeks of the original infection and is a relapse of the original infection because of unsuccessful treatment of the original infection, a resistant organism, or anatomical abnormalities.

3. The majority (75%-90%) of uncomplicated UTIs are caused by *Escherichia coli* and the remainder are caused primarily by *Staphylococcus saprophyticus*, *Proteus* spp., and *Klebsiella* spp. Complicated infections may be associated with other gram-negative organisms and *Enterococcus faecalis.*

4. Symptoms of lower UTIs include dysuria, urgency, frequency, nocturia, and suprapubic heaviness, whereas upper UTIs involve more systemic symptoms such as fever, nausea, vomiting, and flank pain.

5. Significant bacteriuria has been defined as bacterial counts of greater than 10^5 organisms (colony-forming unit [CFU])/mL (10^8 CFU/L) of a midstream clean catch urine. However, this is too general and significant bacteriuria in patients with symptoms of UTI may be defined as greater than 10^2 organisms (CFU)/mL (10^5 CFU/L).

6. The goals of treatment of UTIs are to eradicate the invading organism(s), prevent or treat systemic consequences of infections, prevent the recurrence of infection, and prevent antimicrobial resistance.

7. Uncomplicated UTIs can be managed most effectively with short-course therapy (3 days) with either trimethoprim–sulfamethoxazole, one dose of fosfomycin, or 5 days of nitrofurantoin. Fluoroquinolones should be reserved for suspected pyelonephritis or complicated infections.

8. When choosing appropriate antibiotic therapy, practitioners need to be cognizant of antibiotic resistance patterns, particularly to *E. coli.* Trimethoprim–sulfamethoxazole has diminished activity against *E. coli* in some areas of the country, with reported resistance in some areas greater than 20%.

9. Acute bacterial prostatitis can be managed with many agents that have activity against the causative organism. Chronic prostatitis requires prolonged therapy with an agent that penetrates the prostatic tissue and secretions. Therapy with fluoroquinolone or trimethoprim–sulfamethoxazole is preferred for up to 6 weeks.

BEYOND THE BOOK

BEYOND THE BOOK

EY, a 28-year-old pregnant female presents to her OB clinic for a routine week 18 appointment. Her past medical history is unremarkable except for seasonal allergies. In the clinic, she is hemodynamically stable with a BP 130/72 mm Hg, HR 78 BPM, RR 16, and temperature 97.5°F (36.4°C). Her home medications include a daily maternal multivitamin and diphenhydramine PRN. The patient denies any dysuria, urinary frequency, costovertebral angle tenderness, or suprapubic pain.

1. Should this patient be screened for urinary tract infection?
2. Which of the following clinical or laboratory features places this patient at an increased risk of a complicated UTI?
    a. Age
    b. Pyuria
    c. Pregnancy
    d. Positive leukocyte esterase
3. Which of the following would be most appropriate in managing EY's bacteriuria?
    a. Ciprofloxacin 500 mg orally twice daily for 3 days
    b. Antibiotics not indicated now
    c. Trimethoprim/sulfamethoxazole 800/160 mg twice daily for 10 days
    d. Nitrofurantoin 100 mg orally twice daily for 7 days.
4. Three days later, EY calls the clinic because she has a low-grade fever (99.5°F [37.5°C]) and is complaining of having pyuria, frequent urination, and intermittent back pain. She has been busy the past few days and has not had a chance to pick up her prescription. The culture from the urinalysis from 3 days ago has grown out *E. coli* that is sensitive to ciprofloxacin, nitrofurantoin, fosfomycin, and trimethoprim/sulfamethoxazole. Which of the following is the best recommendation for EY now?
    a. Trimethoprim/sulfamethoxazole 800/160mg twice daily for 14 days
    b. Start the prescription from 3 days ago
    c. Levofloxacin 250 mg orally daily for 7 days
    d. Piperacillin/tazobactam 3.375 g IV every 6 hours for 7 days

INTRODUCTION

Infections of the urinary tract represent a wide variety of syndromes, including urethritis, cystitis, prostatitis, and pyelonephritis. Urinary tract infections (UTIs) are the most commonly occurring bacterial infections and one of the most common reasons for antibiotic exposure, especially in females of childbearing age.[1-3] Approximately 60% of females will develop a UTI during their lifetime with about one-fourth having a recurrence within a year.[2] Infections in males occur much less frequently until the age of 65 years at which point the incidence rates in males and females are similar.

UTI is defined as the presence of microorganisms in the urinary tract that cannot be accounted for by contamination. The organisms present have the potential to invade the tissues of the urinary tract and adjacent structures. Infection may be limited to the growth of bacteria in the urine, which frequently may not produce symptoms. UTI can present as several syndromes associated with an inflammatory response to microbial invasion and can range from asymptomatic bacteriuria (ASB) to pyelonephritis with bacteremia or sepsis.

UTIs are classified as lower and upper UTIs. Typically, they have been described by anatomic site of involvement. Lower tract infections correspond to cystitis (bladder), and pyelonephritis (an infection involving the kidneys) represents upper tract infection.

1 Also, UTIs are designated as uncomplicated or complicated. Uncomplicated infections occur in individuals who lack structural or functional abnormalities of the urinary tract which interfere with the normal flow of urine or voiding mechanism. These infections occur in premenopausal females of childbearing age (15-45 years) who are otherwise normal, healthy individuals. Infections in males generally are not classified as uncomplicated because these infections are rare and most often represent a structural or neurologic abnormality.

Complicated UTIs are usually the result of a predisposing lesion of the urinary tract, such as a congenital abnormality or distortion of the urinary tract, a stone, indwelling catheter, prostatic hypertrophy, obstruction, or neurologic deficit that interferes with the normal flow of urine and urinary tract defenses. Complicated infections occur in both genders and frequently involve the upper and lower urinary tract.

2 Recurrent UTIs in healthy nonpregnant females—two or more UTIs occurring within 6 months or three or more UTIs within 1 year—are a common problem. They are characterized by multiple symptomatic infections with asymptomatic periods occurring between each episode and may be either reinfections or relapses. Reinfections are caused by a different organism than originally isolated and account for the majority of recurrent UTIs. Relapses are the development of repeated infections with the same initial organism and usually indicate a persistent infectious source.[2]

ASB is a common finding, particularly among those 65 years of age and older when there is significant bacteriuria (more than 10^5 bacteria/mL [10^8/L] of urine) in the absence of signs or symptoms. Symptomatic abacteriuria or acute urethral syndrome consists of symptoms of frequency and dysuria in the absence of significant bacteriuria. This syndrome is commonly associated with *Chlamydia* infections.

Significant abacteriuria is a term used to distinguish the presence of microorganisms that represent true infection versus contamination of the urine as it passes through the distal urethra prior to collection. Historically, bacterial counts equal to or greater than 100,000 organisms/mL (10^8/L) of urine in a "clean-catch" specimen were judged to indicate true infection.[4-6] Counts less than 100,000 organisms/mL (10^8/L) of urine, however, may represent true infection in certain situations, for example, with concurrent antibacterial drug administration, rapid urine flow, low urinary pH, or upper tract obstruction.[6] Table 139-1 lists the clinical definitions of significant bacteriuria, which are dependent on the clinical setting and the method of specimen collection.[6] These criteria allow for more appropriate specificity and sensitivity in documenting infection under differing clinical circumstances.

TABLE 139-1

Diagnostic Criteria for Significant Bacteriuria

- ≥10^2 CFU coliforms/mL (10^5 CFU/L) or ≥10^5 CFU noncoliforms/mL (10^8 CFU/L) in a symptomatic female
- ≥10^4 CFU bacteria/mL (10^7 CFU/L) in a symptomatic male
- ≥10^5 CFU bacteria/mL (10^8 CFU/L) in asymptomatic individuals on two consecutive specimens
- Any growth of bacteria on suprapubic catheterization in a symptomatic patient
- ≥10^{2-5} CFU bacteria/mL (10^{5-8} CFU/L) in a catheterized patient

CFU, colony-forming unit.

EPIDEMIOLOGY

The prevalence of UTIs varies with age and gender. In newborns and infants up to 6 months of age, the prevalence of abacteriuria is approximately 1% and is more common in boys. Most of these infections are associated with structural or functional abnormalities of the urinary tract and also have been correlated with noncircumcision.[7] Between the ages of 1 and 6 years, UTIs occur more frequently in females. The prevalence of abacteriuria in females and males of this age group is 3% to 7% and 1% to 2%, respectively.[7,8] Infections occurring in preschool boys usually are associated with congenital abnormalities of the urinary tract. These infections are difficult to recognize because of the age of the patient, but they often are symptomatic. In

addition, the majority of renal damage associated with UTI develops at this age.[7,8]

Through grade school and before puberty, the prevalence of UTI is approximately 1%, with 5% of females reported to have significant bacteriuria prior to leaving high school. This percentage increases dramatically to 1% to 4% after puberty in nonpregnant females primarily as a result of sexual activity. Approximately one in five women will suffer a symptomatic UTI at some point in their lives. Many females have recurrent infections with a significant proportion having a history of childhood infections. In contrast, the prevalence of bacteriuria in adult males is low (less than 0.1%).[9]

In the older adults, the ratio of bacteriuria in women and men is dramatically altered and is approximately equal in persons older than 65 years. The overall incidence of UTI increases substantially in this population with the majority of infections being asymptomatic. The rate of infection increases further for older adults who are residing in nursing homes, particularly those who are hospitalized frequently. A variety of factors increase the risk of infection including structural and anatomical changes such as benign prostatic hypertrophy in males and prolosapse in women resulting in either urinary retention or incontinence, respectively. Patients suffering from fecal incontinence as a complication of advanced dementia or neuromuscular disease including strokes are also at increased risk. Urinary instrumentation (catheterization) along with some medications such as the sodium-glucose co-transporter inhibitors also creates an environment that is more supportive of UTIs.[10]

ETIOLOGY

3 The bacteria causing UTIs usually originate from bowel flora of the host. Although virtually every organism is associated with UTIs, certain organisms predominate as a result of specific virulence factors. The most common cause of uncomplicated UTIs is *Escherichia coli*, which accounts for 80% to 90% of community-acquired infections. Additional causative organisms in uncomplicated infections include *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, *Proteus* spp., *Pseudomonas aeruginosa*, and *Enterococcus* spp.[11] Because *S. epidermidis* is frequently isolated from the urinary tract, it should be considered initially a contaminant. Repeat cultures should be performed to help confirm the organism as a real pathogen.

Organisms isolated from individuals with complicated infections are more varied and generally are more resistant than those found in uncomplicated infections. *E. coli* is a frequently isolated pathogen, but it accounts for less than 50% of infections. Other frequently isolated organisms include *Proteus* spp., *K. pneumoniae*, *Enterobacter* spp., *P. aeruginosa*, staphylococci, and enterococci. Enterococci represent the second most frequently isolated organisms in hospitalized patients.[11-13] In part, this finding may be related to the extensive use of third-generation cephalosporin antibiotics, which are not active against the enterococci. Vancomycin-resistant *E. faecalis* and *E. faecium* (vancomycin-resistant enterococci) have become more widespread, especially in patients with long-term hospitalizations or underlying malignancies. Vancomycin-resistant enterococci are major therapeutic and infection control issues because these organisms are susceptible to few antimicrobials.[12,13] *S. aureus* infections may arise from the urinary tract, but they are more commonly a result of bacteremia producing metastatic abscesses in the kidney. *Candida* spp. are common causes of UTI in the critically ill and chronically catheterized patient. Most UTIs are caused by a single organism; however, in patients with stones, indwelling urinary catheters, or chronic renal abscesses, multiple organisms may be isolated. Depending on the clinical situation, the recovery of multiple organisms may represent contamination and a repeat evaluation should be done.

PATHOPHYSIOLOGY

Route of Infection

Organisms typically gain entry into the urinary tract via three routes: the ascending, hematogenous (descending), and lymphatic pathways. The female urethra usually is colonized by bacteria believed to originate from the fecal flora. The short length of the female urethra and its proximity to the perirectal area make colonization of the urethra likely. Other factors that promote urethral colonization include the use of spermicides and diaphragms as methods of contraception.[2,3] Although there is evidence in females that bladder infections follow colonization of the urethra, the mode of ascent of the microorganisms is incompletely understood. Massage of the female urethra and sexual intercourse allow bacteria to reach the bladder.[14] Once bacteria have reached the bladder, the organisms quickly multiply and can ascend the ureters to the kidneys. This sequence of events is more likely to occur if vesicoureteral reflux (reflux of urine into the ureters and kidneys while voiding) is present. UTIs are more common in females than in males because the anatomic differences in location and length of the urethra tend to support the ascending route of infections as the primary acquisition route.

Infection of the kidney by hematogenous spread of microorganisms usually occurs as the result of dissemination of organisms from a distant primary infection in the body. Infections via the descending route are uncommon and involve a relatively small number of invasive pathogens. Bacteremia caused by *S. aureus* may produce renal abscesses. Additional organisms include *Candida* spp., *Mycobacterium tuberculosis*, *Salmonella* spp., and enterococci. Of particular interest, it is difficult to produce experimental pyelonephritis by IV administration of common gram-negative organisms such as *E. coli* and *P. aeruginosa*. Overall, less than 5% of documented UTIs results from hematogenous spread of microorganisms.

There appears to be little evidence supporting a significant role for renal lymphatics in the pathogenesis of UTIs. There are lymphatic communications between the bowel and kidney, as well as between the bladder and kidney. There is no evidence, however, that microorganisms are transferred to the kidney via this route. After bacteria reach the urinary tract, three factors determine the development of infection: the size of the inoculum, the virulence of the microorganism, and the competency of the natural host defense mechanisms. Most UTIs reflect a failure in host defense mechanisms.

Host Defense Mechanisms

The normal urinary tract generally is resistant to invasion by bacteria and is efficient in rapidly eliminating microorganisms that reach the bladder. The urine under normal circumstances is capable of inhibiting and killing microorganisms. The factors thought to be responsible include a low pH, extremes in osmolality, high urea concentration, and high organic acid concentration. Bacterial growth is further inhibited in males by the addition of prostatic secretions.[14,15]

The introduction of bacteria into the bladder stimulates micturition with increased diuresis and efficient emptying of the bladder. These factors are critical in preventing the initiation and maintenance of bladder infections. Patients who are unable to void urine completely are at greater risk of developing UTIs and frequently have recurrent infections. Also, patients with even small residual amounts of urine in their bladder respond less favorably to treatment than patients who are able to empty their bladders completely.[16]

An important virulence factor of bacteria is their ability to adhere to urinary epithelial cells resulting in colonization of the urinary tract, bladder infections, and pyelonephritis. Various factors that act as anti-adherence mechanisms are present in the bladder preventing bacterial colonization and infection. The epithelial cells of the bladder are coated with a urinary mucus or slime called *glycosaminoglycan*. This thin layer of surface mucopolysaccharide is hydrophilic and strongly negatively charged. When bound to the uroepithelium, it attracts water molecules and forms a layer between the bladder and urine. The anti-adherence characteristics of the glycosaminoglycan layer are nonspecific and when the layer is removed by dilute acid solutions, rapid bacterial adherence results.[17]

In addition, the Tamm–Horsfall protein is a glycoprotein produced by the ascending limb of Henle and distal tubule that is secreted into the urine and contains mannose residues. These mannose residues bind *E. coli* that contain small surface-projecting organelle on their surfaces called *pili* or *fimbriae*. Type 1 fimbriae are mannose-sensitive, and this interaction prevents the bacteria from binding to similar receptors present on the mucosal surface of the bladder. Other factors that possibly prevent adherence of bacteria include immunoglobulins (Ig) G and A, which are synthesized systemically and in the kidney with upper tract infections. The role of Igs in preventing bladder infection is less clear. Patients with reduced urinary levels of secretory IgA are, however, at increased risk of infections of the urinary tract.

After bacteria have invaded the bladder mucosa, an inflammatory response is stimulated with the mobilization of polymorphonuclear leukocytes (PMNs) and resulting phagocytosis. PMNs are primarily responsible for limiting the tissue invasion and controlling the spread of infection in the bladder and kidney. They do not play a role in preventing bladder colonization or infections and actually contribute to renal tissue damage.

Other host factors that may play a role in the prevention of UTIs are the presence of *Lactobacillus* in the vaginal flora and circulating estrogen levels. In premenopausal women, circulating estrogen supports the vaginal tract growth of lactobacilli, which produce lactic acid to help maintain a low vaginal pH, thereby preventing *E. coli* vaginal colonization.[18] Topical estrogens are used for the prevention of UTI in postmenopausal women who have more than three recurrent UTI episodes per year and are not on oral estrogens.[19]

Bacterial Virulence Factors

Pathogenic organisms have differing degrees of pathogenicity (virulence), which play a role in the development and severity of infection. Bacteria that adhere to the epithelium of the urinary tract are associated with colonization and infection. The mechanism of adhesion of gram-negative bacteria, particularly *E. coli*, is related to bacterial fimbriae that are rigid, hair-like appendages of the cell wall.[9] These fimbriae adhere to specific glycolipid

components on epithelial cells. The most common type of fimbriae is type 1, which binds to mannose residues present in glycoproteins. Glycosaminoglycan and Tamm–Horsfall protein are rich in mannose residues that readily trap those organisms that contain type 1 fimbriae, which are then washed out of the bladder.[20] Other fimbriae are mannose-resistant and are associated more frequently with pyelonephritis, such as P fimbriae, which bind avidly to specific glycolipid receptors on uroepithelial cells. These bacteria are resistant to washout or removal by glycosaminoglycan and are able to multiply and invade tissue, especially the kidney. In addition, PMNs, as well as secretory IgA antibodies, contain receptors for type 1 fimbriae, which facilitate phagocytosis, but are lacking receptors for P fimbriae.

Other virulence factors include the production of hemolysin and aerobactin.[21] Hemolysin is a cytotoxic protein produced by bacteria that lyses a wide range of cells, including erythrocytes, PMNs, and monocytes. *E. coli* and other gram-negative bacteria require iron for aerobic metabolism and multiplication. Aerobactin facilitates the binding and uptake of iron by *E. coli*; however, the significance of this property in the pathogenesis of UTIs remains unknown.[22]

PREDISPOSING FACTORS TO INFECTION

The normal urinary tract typically is resistant to infection and colonization by pathogenic bacteria. In patients with underlying structural abnormalities of the urinary tract, the typical host defenses previously discussed usually are lacking or compromised. There are several known abnormalities of the urinary tract system that interfere with its natural defense mechanisms, the most important of which is obstruction. Obstruction can inhibit the normal flow of urine disrupting the natural flushing and voiding effect in removing bacteria from the bladder and resulting in incomplete emptying. Common conditions that result in residual urine volumes include prostatic hypertrophy, urethral strictures, calculi, tumors, bladder diverticula, and drugs such as anticholinergic agents. Additional causes of incomplete bladder emptying include neurologic malfunctions associated with stroke, diabetes, spinal cord injuries, tabes dorsalis, and other neuropathies. Vesicoureteral reflux represents a condition in which urine is forced up the ureters to the kidneys. Urinary reflux is associated not only with an increased incidence of UTIs and pyelonephritis but also with renal damage.[8,16] Reflux may be the result of a congenital abnormality or, more commonly, bladder overdistension from obstruction. Other risk factors include urinary catheterization, mechanical instrumentation, pregnancy, and the use of spermicides and diaphragms.

CLINICAL PRESENTATION

4 The presenting signs and symptoms of UTIs in adults are recognized easily. Females frequently will report gross hematuria. Systemic symptoms, including fever, typically are absent in this setting. Unfortunately, large numbers of persons with significant bacteriuria are asymptomatic. These individuals may be normal, healthy persons, older adults, children, pregnant persons, and persons with indwelling catheters. Attempts at differentiating upper tract from lower tract infections on the basis of symptoms alone are not reliable.

CLINICAL PRESENTATION: Urinary Tract Infections in Adults

Signs and Symptoms

- Lower UTI: Dysuria, urgency, frequency, nocturia, and suprapubic heaviness
- Gross hematuria
- Upper UTI: Flank pain, fever, nausea, vomiting, and malaise

Physical Examination

- Upper UTI: Costovertebral tenderness

Laboratory Tests

- Bacteriuria
- Pyuria (WBC count more than 10/mm^3 [10 × 10^6/L])
- Nitrite-positive urine (with nitrite reducers)
- Leukocyte esterase-positive urine
- Antibody-coated bacteria (upper UTI)

Older adults frequently do not experience specific urinary symptoms, but they will present with altered mental status, change in eating habits, or gastrointestinal (GI) symptoms. In addition, patients with indwelling catheters or neurologic disorders commonly will not have lower tract symptoms. Instead, they may present with flank pain and fever. Many of the aforementioned patients, however, frequently will develop upper tract infections with bacteremia and no or minimal urinary tract symptoms.

Symptoms alone are unreliable for the diagnosis of bacterial UTIs. The key to the diagnosis of UTI is the ability to demonstrate significant numbers of microorganisms in an appropriate urine specimen to distinguish contamination from infection. The type and extent of laboratory examination required depends on the clinical situation.

Urine Collection

Examination of the urine is the cornerstone of laboratory evaluation for UTIs. There are three acceptable methods of urine collection. The first is the *midstream clean-catch method.* After cleaning the urethral opening area in both men and women, 20 to 30 mL of urine is voided and discarded. The next part of the urine flow is collected and should be processed immediately (refrigerated as soon as possible). Specimens that are allowed to sit at room temperature for several hours may result in falsely elevated bacterial counts. The midstream clean-catch is the preferred method for the routine collection of urine for culture. When a routine urine specimen cannot be collected or contamination occurs, alternative collection techniques must be used.

The two acceptable alternative methods include catheterization and suprapubic bladder aspiration. Catheterization may be necessary for patients who are uncooperative or who are unable to void urine. If catheterization is performed carefully with the aseptic technique, the method yields reliable results. However, the introduction of bacteria into the bladder may result and the procedure is associated with infection in 1% to 2% of patients. Suprapubic bladder aspiration involves inserting a needle directly into the bladder and aspirating the urine. This procedure bypasses the contaminating organisms present in the urethra and any bacteria found using this technique generally are considered to represent significant bacteriuria.[23-26] Suprapubic aspiration is a safe and painless procedure that is most useful in newborns, infants, paraplegics, seriously ill patients, and others in whom infection is suspected and routine procedures have provided confusing or equivocal results.

Bacterial Count

5 The diagnosis of UTI is based on the isolation of significant numbers of bacteria from a urine specimen. Microscopic examination of a urine sample is an easy-to-perform and reliable method for the presumptive diagnosis of bacteriuria. The examination may be performed by preparing a Gram stain of unspun or centrifuged urine. The presence of at least one organism per oil-immersion field in a properly collected uncentrifuged specimen correlates well with more than 100,000 CFU/mL (10^5 CFU/mL or 10^8 CFU/L) of urine. For detecting smaller numbers of organisms, a centrifuged specimen is more sensitive. Such examinations detect more than 10^5 bacteria (CFU)/mL (10^8 CFU/L) with a sensitivity of greater than 90% and a specificity of greater than 70%.[23,24] A quantitative count of greater than or equal to 10^5 CFU/mL (10^8 CFU/L) is considered indicative of a UTI; however, up to 50% of women will present with clinical symptoms of a UTI with lower counts (10^3 CFU/mL) (10^6 CFU/L).[4]

Pyuria, Hematuria, and Proteinuria

Microscopic examination of the urine for leukocytes is used to determine the presence of pyuria. The presence of pyuria in a symptomatic patient correlates with significant bacteriuria.[25] Pyuria is defined as a white blood cell (WBC) count of greater than 10 WBC/mm^3 (10×10^6/L) of urine. A count of 5 to 10 WBC/mm^3 (5×10^6 to 10×10^6/L) is accepted as the upper limit of normal. It should be emphasized that pyuria is nonspecific and signifies only the presence of inflammation and not necessarily infection. Thus, patients with pyuria may or may not have infection. Sterile pyuria has long been associated with urinary tuberculosis, as well as chlamydial and fungal urinary infections. Hematuria, microscopic or gross, is frequently present in patients with UTI, but is nonspecific. Hematuria may indicate the presence of other disorders, such as renal calculi, tumors, or glomerulonephritis. Proteinuria is found commonly in the presence of infection.

Chemistry

Several biochemical tests have been developed for screening urine for the presence of bacteria. A common dipstick test detects the presence of nitrite in the urine, which is formed by bacteria that reduce nitrate normally present in the urine. False-positive tests are uncommon. False-negative tests are more common and are frequently caused by the presence of gram-positive organisms or *P. aeruginosa* that do not reduce nitrate.[26] Other causes of false tests include low urinary pH, frequent voiding, and dilute urine.

The leukocyte esterase dipstick test is a rapid screening test for detecting the presence of pyuria. Leukocytes esterase is found in primary neutrophil granules and indicates the presence of WBCs. The leukocyte esterase test is a sensitive and highly specific test for detecting more than 10 WBC/mm^3 (10×10^6/L) of urine. When the leukocyte esterase test is used with the nitrite test, the reported positive predictive value and specificity are 79% and 82%, respectively, for the detection of bacteriuria.[27,28] These tests can be useful in the outpatient evaluation of uncomplicated UTIs. However, urine culture is still the “gold standard” test in determining the presence of UTIs.

Culture

The most reliable method of diagnosing UTI is by quantitative urine culture. Urine in the bladder is normally sterile making it possible to differentiate contamination of the urine from infection by quantifying the number of bacteria present in a urine sample. This criterion is based on a properly collected midstream clean-catch urine specimen. Patients with infection usually have greater than 10^5 bacteria/mL (10^8/L) of urine. However, as many as one-third of females with symptomatic infection have less than 10^5 bacteria/mL (10^8/L). Also, a significant portion of patients with UTIs, either symptomatic or asymptomatic, have less than 10^5 bacteria/mL (10^8/L) of urine.

Several laboratory methods are used to quantify bacteria present in the urine. The most accurate method is the pour-plate technique. This method is unsuitable for a high-volume laboratory because it is expensive and time-consuming. The streak-plate method is an alternative that involves using a calibrated-loop technique to streak a fixed amount of urine on an agar plate. This method is used most commonly in diagnostic laboratories because it is simple to perform and less costly.

After identification and quantification are complete, the next step is to determine the susceptibility of the organism. There are several methods by which bacterial susceptibility testing may be performed. Knowledge of bacterial susceptibility and achievable urine concentration of the antibiotics puts the clinician in a better position to select an appropriate agent for treatment.

Infection Site

History and physical examination are of little value in predicting the site of infection. The most direct method to determine the location of infection within the urinary system and differentiate upper tract from lower tract involvement is a ureteral catheterization procedure as described by Stamey and colleagues.[29] The method involves the passage of a catheter into the bladder and then into each ureter, where quantitative cultures are obtained. Although this method provides direct quantitative evidence for UTI, it is invasive, technically difficult, and expensive. The Fairley bladder washout technique is a modification of the Stamey procedure that involves Foley catheterization only.[30] After the catheter is passed into the bladder, bladder samples are obtained, and the bladder is washed out with culture samples taken at 10, 20, and 30 minutes. The procedure shows that up to 50% of patients have renal involvement, regardless of signs and symptoms. Other investigators found 10% to 20% of tests to be equivocal.[30]

Noninvasive methods of localization may be more acceptable for routine use; however, they have limited clinical value. Patients with pyelonephritis can have abnormalities in urinary concentrating ability. The use of concentrating ability for localization of UTIs, however, is associated with high false-positive and false-negative responses and is not useful clinically.[26] The antibody-coated bacteria test is an immunofluorescent method that detects bacteria coated with Ig in freshly voided urine indicating upper UTI. The sensitivity and specificity of this test to localize the site of infection are reported to average 88% and 76%, respectively.[31] Because of the high incidence of false-positive and false-negative results, antibody-coated bacteria testing is not used routinely in the management of UTIs.

Virtually all patients with uncomplicated lower tract infections can be cured with a short course of antibiotic therapy and this assumption sometimes can be used to distinguish between patients with lower and upper tract infections. Patients who do not respond or who relapse may do so because of upper tract involvement. It is rarely necessary to localize the site of infection to direct the clinical management of such patients.

PATIENT CARE PROCESS

Patient Care Process for Urinary Tract Infection

Collect

- Patient characteristics (eg, age, sex, pregnant, immunocompetent)
- Patient symptoms (see Clinical Presentation box)
- Patient medical history (including history of past UTIs)
- Social history (eg, sexually active) and dietary habits
- Current medications including nonprescription and/or herbal products, dietary supplements
- Objective data

- Vital signs: blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2 saturation, temperature
- Labs including white blood cell count (WBC), serum creatinine (SCr)
- Urinalysis (eg, nitrite or leukocyte esterase +) +/− culture and sensitivity data
- Urine dipstick test
- Physical exam (eg, abdominal tenderness, costovertebral tenderness)

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg >110 bpm)
- Mental status
- Urinary catheter present

Plan

- Drug therapy regimen including drug name, dose, route, frequency, and duration (see Tables 134-2, 134-3, and 134-4)
- Monitoring parameters including efficacy (eg, afebrile, WBC, urinalysis, resolution of symptoms), decrease in urinary discomfort and safety (eg, signs and symptoms of antibiotic hypersensitivity, SCr, WBC, hemodynamics)
- Patient education (eg, purpose of treatment, personal hygiene, drug-specific information, medication administration instructions, when to follow-up if no improvement observed; see Table 139-3)
- Self-monitoring for resolution of symptoms (eg, urinary discomfort, flank pain, fever, mental status changes)
- Referrals to other providers when appropriate (eg, urologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up if necessary

Follow-up: Monitor and Evaluate

- Resolution of urinary symptoms (eg, burning, discomfort during urination, flank pain, tenderness)
- Normalization of labs (eg, WBC, SCr)
- Urinalysis presence of adverse effects (eg, rash, diarrhea)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate if patient does not respond adequately to treatment

**Collaborate with patient, caregivers, and other healthcare professionals.*

TREATMENT

Desired Outcomes

6 The goals of UTI treatments are (a) to eradicate the invading organism(s), (b) to prevent or to treat systemic consequences of infection, (c) to prevent the recurrence of infection, and (d) to decrease the potential for collateral damage with too broad of antimicrobial therapy.

Management

The management of a patient with a UTI includes initial evaluation, selection of an antibacterial agent, and duration of therapy and follow-up evaluation. The initial selection of an antimicrobial agent for the treatment of UTI is based primarily on the severity of the presenting signs and symptoms, the site of infection and whether the infection is determined to be uncomplicated or complicated. Other considerations include antibiotic susceptibility, side-effect potential, cost, current antimicrobial exposure, and the comparative inconvenience of different therapies.[1]

Various pharmacologic factors may affect the action of antibacterial agents. Certainly, the ability of the agent to achieve appropriate concentrations in the urine is of utmost importance. Factors that affect the rate and extent of excretion through the kidney include the patient's glomerular filtration rate and whether or not the agent is actively secreted. Filtration depends on the molecular size and degree of protein binding of the agent. Agents such as sulfonamides, tetracyclines, and aminoglycosides enter the urine via filtration. As the glomerular filtration rate is reduced, the amount of drug that enters the urine is reduced. Most β-lactam agents and quinolones are filtered and are actively secreted into the urine. For this reason, most of these agents achieve high urinary concentrations despite unfavorable protein-binding characteristics or the presence of renal dysfunction.

The ability to eradicate bacteria from the urine is related directly to the sensitivity of the microorganism and the achievable concentrations of the antimicrobial agent in the urine. Unfortunately, most susceptibility testing is directed at achievable concentrations in the blood. There is a poor correlation between achievable blood concentrations of antimicrobial agents and the eradication of bacteria from the urine.[32] In the treatment of lower tract infections, plasma concentrations of antibacterial agents may not be important, but achieving appropriate plasma concentrations appears critical in patients with bacteremia and renal abscesses.

Nonspecific therapies have been advocated in the treatment and prevention of UTIs. Fluid hydration has been used to produce rapid dilution of bacteria and removal of infected urine by increased voiding. A critical factor appears to be the amount of residual volume remaining after voiding. As little as 10 mL of residual urine can alter the eradication of infection significantly.[16] Paradoxically, increased diuresis also may promote susceptibility to infection by diluting the normal antibacterial properties of the urine. Often in clinical practice, the concentrations of antimicrobial agents in the urine are so high that dilution has little effect on efficacy.

The antibacterial activity of the urine is related to the low pH, which is the result of high concentrations of various organic acids. Large volumes of cranberry juice increase the antibacterial activity of the urine and prevent the development of UTIs.[3,33] Apparently, the fructose and other unknown substances (condensed tannins, proanthocyanidin) in cranberry juice may act to interfere with adherence mechanisms of some pathogens, thereby preventing infection or reinfection. Acidification of the urine by cranberry juice does not appear to play a significant role. Although there are a number of favorable studies, the benefit of ingested cranberry juice appears to be minimal and larger studies involving oral tablets or capsules need to be done to prove effectivness.[35-38] Females with repeated UTIs who receive the recommended 36 mg/d of proanthocyanidins (found in cranberry products) may gain some benefit but studies remain largely inconclusive.[36-40] The use of other agents (ascorbic acid) to acidify the urine to try to hinder bacterial growth does not achieve significant enough acidification. Consequently, attempts to acidify urine with systemic agents are not recommended. Lactobacillus potentially helps keep the vaginal pH in the normal range (pH 4-4.5); therefore, regulating genitourinary bacteria aiding in the prevention of UTIs.[41] In addition, *Lactobacillus* probiotics may aid in the prevention of female UTIs by decreasing the vaginal pH, thereby decreasing *E. coli* colonization.[19,33,34] In postmenopausal women, estrogen replacement may be of help in the prevention of recurrent UTIs. After 1 month of topical estrogen replacement, vaginal *Lactobacillus* as well as vaginal pH and *E. coli* colonization decrease.[18,33]

Phenazopyridine hydrochloride is nonprescription urinary anesthetic/analgesic that can be used for symptom relief in UTIs. It is frequently used by patients as self-medication to alleviate the dysuria associated with UTIs. The use of phenazopyridine in the treatment of UTIs is controversial. It has no antimicrobial properties and has a number of adverse effects such as red-orange discoloration of body fluids, rash, anaphylaxis, and rare effects such as hemolytic anemia, methemoglobinemia, and acute renal failure. In addition, its use can mask the symptoms of an untreated or inappropriately treated UTI. Unfortunately, there are not any guidelines for its role in the treatment of UTIs; however, experts agree that if phenazopyridine is used,

only use the recommended dose (maximum 200 mg three times a day) and limited to 1 to 2 days for symptomatic relief of the dysuria with UTIs.[41,42] In addition, it should be used with the combination of appropriate antibiotic therapy.

Pharmacologic Therapy

Ideally, the antimicrobial agent chosen should be well tolerated, well absorbed, achieve high urinary concentrations, and have a spectrum of activity limited to the known or suspected pathogen(s). Table 139-2 lists the most common agents used in the treatment of UTIs along with comments concerning their general use. Table 139-3 presents an overview of various therapeutic options for outpatient therapy of UTI. Table 139-4 describes empirical treatment regimens for selected clinical situations.

TABLE 139-2

Commonly Used Antimicrobial Agents in the Treatment of UTIs

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Oral Therapy			
Trimethoprim–sulfamethoxazole	Rash, Stevens–Johnson Syndrome, renal failure, photosensitivity, hematologic (neutropenia, anemia, etc.)	Serum creatinine, BUN, electrolytes, signs of rash, and CBC	This combination is highly effective against most aerobic enteric bacteria except *P. aeruginosa*. High urinary tract tissue concentrations and urine concentrations are achieved, which may be important in complicated infection treatment. Also effective as prophylaxis for recurrent infections
Nitrofurantoin	GI intolerance, neuropathies, and pulmonary reactions	Baseline serum creatinine and BUN	This agent is effective as both a therapeutic and prophylactic agent in patients with recurrent UTIs. Main advantage is the lack of resistance even after long courses of therapy
Fosfomycin trometamol	Diarrhea, headache, and angioedema	No routine tests recommended	Single-dose therapy for uncomplicated infections, low levels of resistance, use with caution in patients with hepatic dysfunction
Fluoroquinolones			
Ciprofloxacin Levofloxacin	Hypersensitivity, photosensitivity, GI symptoms, dizziness, confusion, and tendonitis (black box warning)	CBC, baseline serum creatinine, and BUN	The fluoroquinolones have a greater spectrum of activity, including *P. aeruginosa*. These agents are effective for pyelonephritis and prostatitis. Avoid in pregnancy and children. Moxifloxacin should not be used owing to inadequate urinary concentrations
Amoxicillin–clavulanate	Hypersensitivity (rash, anaphylaxis), diarrhea,	CBC, signs of rash, or hypersensitivity	Due to increasing *E. coli* resistance, amoxicillin–clavulanate is the preferred penicillin for uncomplicated cystitis

	superinfections, and seizures		
Cephalosporins Cefaclor Cefpodoxime-proxetil	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	There are no major advantages of these agents over other agents in the treatment of UTIs, and they are more expensive. These agents are not active against enterococci
Parenteral Therapy			
Aminoglycosides Gentamicin Tobramycin Amikacin	Ototoxicity, nephrotoxicity	Serum creatinine and BUN, serum drug concentrations, and individual pharmacokinetic monitoring	These agents are renally excreted and achieve good concentrations in the urine. Amikacin generally is reserved for multidrug-resistant bacteria
Penicillins			
Ampicillin–sulbactam Piperacillin–tazobactam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	These agents generally are equally effective for susceptible bacteria. The extended-spectrum penicillins are more active against *P. aeruginosa* and enterococci and often are preferred over cephalosporins. They are useful in renally impaired patients or when an aminoglycoside is to be avoided
Cephalosporins			
Ceftriaxone Ceftazidime Cefepime Ceftozolane/tazaobactam Ceftazidime/avabactam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Second- and third-generation cephalosporins have a broad spectrum of activity against gram-negative bacteria, but are not active against enterococci and have limited activity against *P. aeruginosa*. Ceftazidime and cefepime are active against *P. aeruginosa*. They are useful for nosocomial infections and urosepsis due to susceptible pathogens
Carbapenems/monobactams Imipenem–cilistatin Meropenem Meropenem/vaborbactam Doripenem Ertapenem Aztreonam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Carbapenems have a broad spectrum of activity, including gram-positive, gram-negative, and anaerobic bacteria. Imipenem, meropenem, and doripenem are active against *P. aeruginosa* and enterococci, but ertapenem is not. Aztreonam is a monobactam that is only active against gram-negative bacteria, including some strains of *P. aeruginosa*. Generally useful for nosocomial infections when aminoglycosides are to be avoided and in penicillin-sensitive patients
Fluoroquinolones Ciprofloxacin Levofloxacin	Hypersensitivity, photosensitivity, GI symptoms,	CBC, baseline serum creatinine, and	These agents have broad-spectrum activity against both gram-negative and gram-positive bacteria. They provide urine and high-tissue concentrations and are actively secreted in reduced renal function

	dizziness, confusion, and tendonitis (black box warning)	BUN	

BUN, blood urea nitrogen; CBC, complete blood count; GI, gastrointestinal; UTIs, urinary tract infections.

TABLE 139-3

Overview of Outpatient Antimicrobial Therapy for Lower Tract Infections in Adults

Indications	Antibiotic	Oral Dose	Interval[a]	Duration
Lower tract infections				
Uncomplicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	3 days
	Nitrofurantoin monohydrate	100 mg	Twice a day	5 days
	Fosfomycin trometamol	3 g	Single dose	1 day
	Ciprofloxacin	250 mg	Twice a day	3 days
	Levofloxacin	250 mg	Once a day	3 days
	Amoxicillin–clavulanate Pivmecillinam	500 mg 400 mg	Every 8 hours Twice a day	5-7 days 3 days
Complicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	7-10 days
	Ciprofloxacin	250-500 mg	Twice a day	7-10 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	7-10 days
Recurrent infections	Nitrofurantoin	50 mg	Once a day	6 months
	Trimethoprim–sulfamethoxazole	1/2 SS tablet	Once a day	6 months
Acute pyelonephritis	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	14 days
	Ciprofloxacin	500 mg	Twice a day	14 days
		1,000 mg ER	Once a day	7 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	14 days

DS, double strength; SS, single strength.

[a]Dosing intervals for normal renal function.

TABLE 139-4

Evidence-Based Empirical Treatment of UTIs and Prostatitis

Diagnosis	Pathogens	Treatment Recommendation	Comments
Acute uncomplicated cystitis	*Escherichia coli*, *Staphylococcus saprophyticus*	1. Nitrofurantoin × 5 days (A,I)[m] 2. Trimethoprim–sulfamethoxazole × 3 days (A,I)[a] 3. Fosfomycin trometamol × 1 dose (A,I)[a] 4. Fluoroquinolone × 3 days (A,I)[a] 5. β-Lactams × 3-7 days (B,I)[a] 6. Pivmecillinam × 3-7 days (A,I)	Short-course therapy more effective than single dose Reserve fluoroquinolones as alternatives to development of resistance (A-III)[a] β-Lactams as a group are not as effective in acute cystitis then trimethoprim–sulfamethoxazole or the fluoroquinolones, do not use amoxicillin or ampicillin[a] Pivmecillinam not available in the United States
Pregnancy	As above	1. Amoxicillin–clavulanate × 7 days 2. Cephalosporin × 7 days 3. Trimethoprim–sulfamethoxazole × 7 days	Avoid trimethoprim–sulfamethoxazole during the third trimester
Acute pyelonephritis			
Uncomplicated	*E. coli*	1. Quinolone × 7 days (A,I)[a] 2. Trimethoprim–sulfamethoxazole (if susceptible) × 14 days (A,I)[a]	Can be managed as outpatient
	Gram-positive bacteria	1. Amoxicillin or amoxicillin–clavulanic acid × 14 days	
Complicated	*E. coli* *P. mirabilis* *K. pneumoniae* *P. aeruginosa* *Enterococcus faecalis*	1. Quinolone × 14 days 2. Extended-spectrum penicillin plus aminoglycoside	Severity of illness will determine duration of IV therapy; culture results should direct therapy Oral therapy may complete 14 days of therapy
Prostatitis	*E. coli* *K. pneumoniae* *Proteus* spp. *P. aeruginosa*	1. Trimethoprim–sulfamethoxazole × 4-6 weeks 2. Quinolone × 4-6 weeks	Acute prostatitis may require IV therapy initially Chronic prostatitis may require longer treatment periods or surgery

UTI, urinary tract infection.

[a]Strength of recommendations: A, good evidence for; B, moderate evidence for; C, poor evidence for and against; D, moderate against; E, good evidence against. Quality of evidence: I, at least one proper randomized, controlled study; II, one well-designed clinical trial; III, evidence from opinions, clinical experience, and expert committees.

Data from Reference 1.

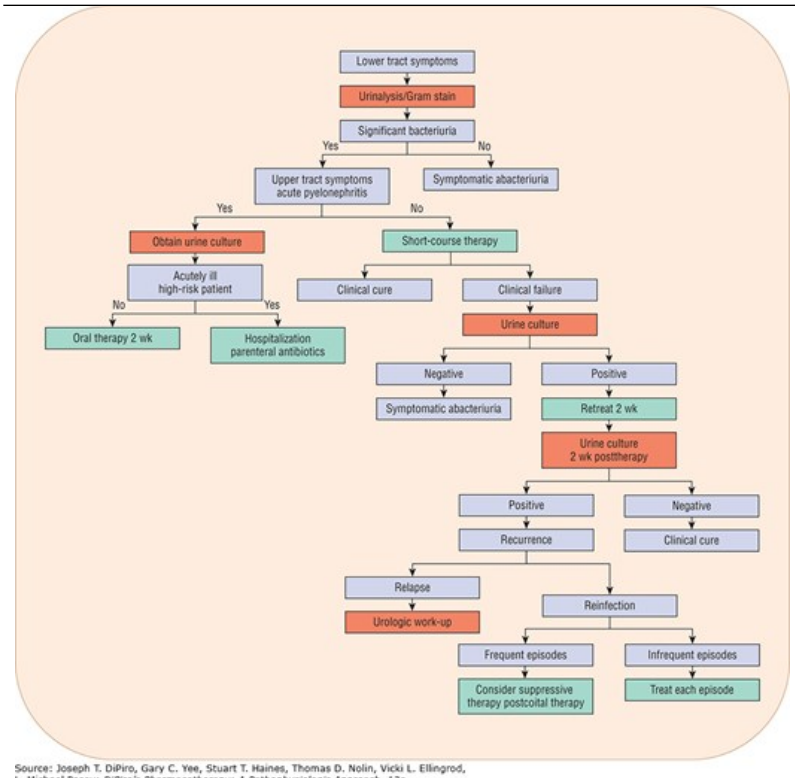
8 The therapeutic management of UTIs is best accomplished by first categorizing the type of infection: acute uncomplicated cystitis, symptomatic abacteriuria, ASB, complicated UTIs, recurrent infections, or prostatitis. In choosing the appropriate antibiotic therapy, aware of the increasing resistance of *E. coli* and other pathogens to many frequently prescribed antimicrobials.[44] Resistance to *E. coli* is as high as 37% for amoxicillin and ampicillin.[1,45] Most *E. coli* remain susceptible to trimethoprim–sulfamethoxazole, although resistance is continuing to increase and has been reported as high as 27%.[46] Although resistance to the fluoroquinolones remains low, these agents are being used more frequently and the incidence of fluoroquinolone-resistant *E. coli* is increasingly being reported and is of great concern.[45-51] Current or recent antibiotic exposure is the most significant risk factor associated with *E. coli* resistance and with the extensive use of the fluoroquinolones and trimethoprim–sulfamethoxazole for various infections, including UTIs, resistance will continue to increase.[45-50] In addition, broad-spectrum antimicrobials such as fluoroquinolones and broad-spectrum cephalosporins have a high impact on GI flora, increasing the risk of collateral damage (term used to refer to ecological adverse effects of antibiotic therapy) or the selection of resistant *E. coli* pathogens.[45-48,51,52] In light of rising resistance and in order to decrease the overuse of broad-spectrum antimicrobials, agents such as nitrofurantoin and fosfomycin are now considered first-line treatments along with trimethoprim–sulfamethoxazole in acute uncomplicated cystitis. Both nitrofurantoin and fosfomycin have little effects on the gut flora and *E. coli* susceptibility still remains high.[52-56] With the increased use of nitrofurantoin and fosfomycin since the 2010 guidelines, clinicians are starting to evaluate the success rate of resolution of uncomplicated lower UTIs in women when single-dose fosfomycin versus nitrofurantoin are used. More research will need to be done to establish that one therapy is more effective than the other.[57] Antibiotic therapy should be determined based on the geographic resistance patterns, as well as the patient's recent history of antibiotic exposure.

Acute Uncomplicated Cystitis

Acute uncomplicated cystitis is the most common form of UTI. These infections typically occur in females of childbearing age and often are related to sexual activity. Although the presence of dysuria, frequency, urgency, and suprapubic discomfort frequently is associated with lower tract infection, a significant number of patients have upper tract involvement as well.[3] Because these infections are predominantly caused by *E. coli*, antimicrobial therapy initially should be directed against this organism. Other common causes include *S. saprophyticus* and occasionally *K. pneumoniae* and *Proteus mirabilis*. Because the causative organisms and their susceptibility generally are known, many clinicians advocate a cost-effective approach to management. This approach includes a urinalysis and initiation of empirical therapy without a urine culture (Fig. 139-1).[1] Therefore, the susceptibility patterns of the geographic area drive the choice of empiric therapy.

FIGURE 139-1

Management of urinary tract infections in females.



The goal of treatment for uncomplicated cystitis is to eradicate the causative organism and to reduce the incidence of recurrence caused by relapse or reinfection. The ability to reduce the chance of recurrence depends on the agent's efficacy in eradicating the uropathogenic bacteria from the vaginal and GI reservoir. In the past, conventional therapy consisted of an effective oral antibiotic administered for 7 to 14 days. However, acute cystitis is a superficial mucosal infection that can be eradicated with much shorter courses of therapy (3 days). Advantages of short-course therapy include increased adherence, fewer side effects, decreased cost, and less potential for the development of resistance.

7 Three-day courses of trimethoprim–sulfamethoxazole or a fluoroquinolone (eg, ciprofloxacin or levofloxacin, not moxifloxacin) are superior to single-dose therapies.[55,58-60] Although the fluoroquinolones have shown excellent efficacy in acute cystitis, the guidelines recommend reserving these agents for patients with suspected or possible pyelonephritis due to the collateral damage risk. Instead, a 3-day course of trimethoprim–sulfamethoxazole, a 5-day course of nitrofurantoin, or a one-time dose of fosfomycin should be considered as first-line therapy.[1,53-61] In areas where there is more than 20% resistance of *E. coli* to trimethoprim–sulfamethoxazole, nitrofurantoin or fosfomycin should be used. Amoxicillin or ampicillin should not be used due to the high incidence of resistant *E. coli*. Instead, if a β-lactam must be used, amoxicillin–clavulanate, cefdinir, cefaclor, or cefpodoxime proxetil for 3 to 7 days are the preferred choices. For most adult females, short-course therapy is the treatment of choice for uncomplicated lower UTIs. Short-course therapy is inappropriate for patients who have had previous infections caused by resistant bacteria, for male patients, and for patients with complicated UTIs. If symptoms recur or do not respond to therapy, a urine culture should be obtained and conventional therapy with a suitable agent instituted.[1]

Symptomatic Abacteriuria

Symptomatic abacteriuria or acute urethral syndrome represents a clinical syndrome in which females present with dysuria and pyuria, but the urine culture reveals less than 10^5 bacteria/mL (10^8/L) of urine. Acute urethral syndrome accounts for more than half the complaints of dysuria seen in the community today. Infections typically involve small numbers of coliform bacteria, including *E. coli*, *Staphylococcus* spp., or *Chlamydia trachomatis*. Additional causes include *Neisseria gonorrhoeae*, *Gardnerella vaginalis*, and *Ureaplasma urealyticum.*

Most patients presenting with pyuria will, in fact, have infection that requires treatment. If antimicrobial therapy is ineffective, a culture should be obtained. If the patient reports recent sexual activity, therapy for *C. trachomatis* should be considered. Chlamydial treatment should consist of 1 g azithromycin or doxycycline 100 mg twice daily for 7 days. Often, concomitant treatment of all sexual partners is required to cure chlamydial infections

and prevent reacquisition (see Chapter 140, “Sexually Transmitted Diseases”).

Asymptomatic Bacteriuria

ASB is the finding of two consecutive urine cultures with more than 10^5 organisms/mL (10^8/L) of the same organism in the absence of urinary symptoms. Most patients with ASB are older females. Also, pregnant females frequently present with ASB. Although these individuals typically respond to treatment, relapse and reinfection are common and chronic ASB is difficult to eradicate.

The management of ASB depends on the age of the patient and whether or not the person is pregnant. In children, because of a greater risk of developing renal scarring and long-standing renal damage, treatment should consist of the same conventional courses of therapy as used for symptomatic infection. The greatest risk of renal damage occurs during the first 5 years of life.[62-63] In nonpregnant females, therapy is controversial; however, treatment has little effect on the natural course of infections. Two groups characterize ASB in the elderly: those with persistent bacteriuria and those with intermittent bacteriuria.

Several studies in hospitalized older adults, however, have not found antimicrobial therapy to be efficacious for abacteruria.[64-67] Thorough investigation of other causes of acute functional or cognitive changes or decline that may point to possible infection is encouraged in order to avoid unnecessary use of antibiotics which may lead to adverse consequences. However, persons with bacteriuria along with other systemic signs suggesting severe infection should be treated empirically with broad spectrum antimicrobial therapy until other causes are ruled out.[64] A number of questions remain unanswered due to limited data. For example: What is the effect of eradication of bacteriuria on life expectancy? What are the cost-effectiveness and risk-to-benefit ratio of therapy? What is the effect on morbidity? Certainly with the information available and the high adverse reaction rate in the elderly, vigorous treatment and screening programs cannot be advocated.

Complicated Urinary Tract Infections

Acute Pyelonephritis

A presentation of high-grade fever (more than 38.3°C [100.9°F]) and severe flank pain should be treated as acute pyelonephritis and warrants aggressive management. Severely ill patients with pyelonephritis should be hospitalized and IV antimicrobials administered initially (see Table 139-4). However, milder cases may be managed with orally administered antibiotics in an outpatient setting. Signs and symptoms of nausea, vomiting, and dehydration may require hospitalization.

At the time of presentation, a Gram stain of the urine should be performed along with a urinalysis, culture, and sensitivity tests. The Gram stain should indicate the morphology of the infecting organism(s) and help direct the selection of an appropriate antibiotic. However, the precise identity and susceptibility of the infecting organism(s) will be unknown initially, warranting empirical therapy. The goals of treatment include the achievement of therapeutic concentrations of an antimicrobial agent in the bloodstream and urinary tract to which the invading organism is susceptible and sufficient therapy to eradicate residual infection in the tissues of the urinary tract.

In the mild-to-moderate symptomatic patient in whom oral therapy is considered, an effective agent should be administered for 7 to 14 days, depending on the agent used.[1,68-73] Oral antibiotics that are highly active against the probable pathogens and that are sufficiently bioavailable are preferred. Fluoroquinolones (ciprofloxacin or levofloxacin) orally for 7 to 10 days are the first-line choice in mild-to-moderate pyelonephritis. Other options include trimethoprim–sulfamethoxazole for 14 days. If amoxicillin–clavulanate or an oral cephalosporin is used, it is recommended to give an initial long-acting parenteral antimicrobial such as ceftriaxone first and continue the oral agent for 10 to 14 days. If a Gram stain reveals gram-positive cocci, *Enterococcus faecalis* should be considered and treatment directed against this potential pathogen (ampicillin). Close follow-up of outpatient treatment is mandatory to ensure success.

In the seriously ill patient, parenteral therapy should be administered initially. Therapy should provide a broad spectrum of coverage and should be directed toward bacteremia or sepsis, if present. A number of antibiotic regimens have been used as empirical therapy, including an IV fluoroquinolone, an aminoglycoside with or without ampicillin, and extended-spectrum cephalosporins with or without an aminoglycoside and carbapenems.[1,74] Other options include aztreonam, the β-lactamase inhibitor combinations (eg, ampicillin–sulbactam, piperacillin–tazobactam, cetazidime/avabactam and cefetolozone/tazobactam), carbapenems (eg, imipenem, meropenem, doripenem, or ertapenem), novel boronic acid-based beta-lactamase inhibitor (eg, meropenem-vaborbactam), and IV trimethoprim–sulfamethoxazole.[74-76] If the patient has been hospitalized within

the past 6 months, has a urinary catheter, or is a nursing home resident, the possibility of *P. aeruginosa* and enterococci, as well as multiple resistant organisms, should be considered. In this setting, broader spectrum coverage is recommended such as an extended spectrum beta-lactam/beta-lactamase inhibitor or carbapenem. Ertapenem should not be used in this situation owing to its inactivity against enterococci and *P. aeruginosa*.[72]

Effective therapy should stabilize the patient within 12 to 24 hours. A significant reduction in urine bacterial concentrations should occur in 48 hours. If bacteriologic response has not occurred, an alternative agent should be considered based on susceptibility testing. If the patient fails to respond clinically within 3 to 4 days or has persistently positive blood or urine cultures, further investigation is needed to exclude bacterial resistance, possible obstruction, papillary necrosis, intrarenal or perinephric abscess, or some other disease process. Usually by the third day of therapy, the patient is afebrile and significantly less symptomatic. In general, after the patient has been afebrile for 24 hours, parenteral therapy may be discontinued and oral therapy instituted to complete a 2-week course. Follow-up urine cultures should be obtained 2 weeks after completion of therapy to ensure a satisfactory response and detect possible relapse.

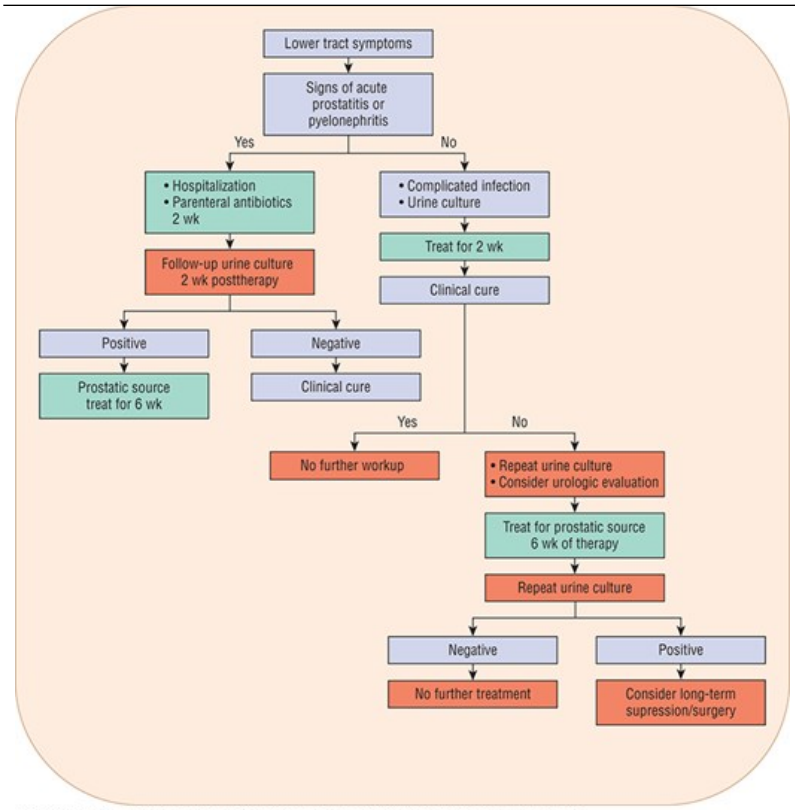
Urinary Tract Infections in Males

The management of UTIs in males is distinctly different and often more difficult than in females. Infections in male patients are considered to be complicated because endogenous bacteria in the presence of functional and/or structural abnormalities that disrupt the normal defense mechanisms of the urinary tract cause them. The incidence of infections in males younger than 60 years is much less than the incidence in females. During the adult years, the occurrence of infection can be related directly to some manipulation of the urinary tract. The most common causes are instrumentation of the urinary tract, catheterization, and renal and urinary stones. Uncomplicated infections are rare, but they may occur in young males as a result of homosexual activity, noncircumcision, and having sex with partners who are colonized with uropathogenic bacteria. As the patient ages, the most common cause of infection is related to bladder outlet obstruction because of prostatic hypertrophy. In addition, the prostate gland may become infected and provide a nidus for recurrent infection in males.

The conventional view is that therapy in males requires prolonged treatment (Fig. 139-2). A urine culture should be obtained before treatment because the cause of infection in males is not as predictable as in females. Single-dose or short-course therapy is not recommended in males. Considerably fewer data are available comparing various antimicrobial agents in males as compared with females. If gram-negative bacteria are presumed, trimethoprim–sulfamethoxazole or the quinolone antimicrobials should be considered because these agents achieve high renal tissue, urine, and prostatic concentrations.[77]

FIGURE 139-2

Management of urinary tract infections in males.



Initial therapy should be for 10 to 14 days. Factors associated with treatment success are isolation of a single organism, the absence of significant obstruction or anatomic abnormalities, a normally functioning urinary tract, and the absence of prostatic involvement. Parenteral therapy may be required in certain situations, such as in severely ill patients, in the presence of acute prostatitis or epididymitis and in patients who cannot tolerate oral medications. A comparison of 2-week versus 6-week therapy in males with recurrent infections who were given trimethoprim–sulfamethoxazole had cure rates of 29% and 62%, respectively.[78] Other investigators advocate longer treatment periods in males, as well.[79] Follow-up cultures at 4 to 6 weeks after treatment are important in males to ensure bacteriologic cure. Many patients require longer periods of treatment and possible alterations in antibiotics, depending on culture and sensitivity results and clinical response.

Recurrent Infections

Recurrent episodes of UTI account for a significant portion of all UTIs. Of the individuals suffering from recurrent infections, 80% can be considered reinfections, that is, the recurrence of infection by an organism different from the organism isolated from the preceding infection. These persons most commonly are females and recurrence develops in approximately 20% of females with cystitis. Reinfections can be divided into two groups: those with less than three episodes per year and those who develop more frequent infections. Treatment strategies are continuing to develop, as well as, an understanding of the role of the microbiome.[80,81] An excellent overview of the various treatment modalities for recurrent UTI in females has been published.[81]

Management strategies depend on predisposing factors, number of episodes per year, and the person's preference. Factors commonly associated with recurrent infections include sexual intercourse and diaphragm or spermicide use for birth control. Therapeutic options include self-administered therapy, postcoital therapy, and continuous low-dose prophylaxis. In persons with infrequent infections (less than three infections per year), each episode may be treated as a separately occurring infection. Short-course therapy is appropriate in this setting. Many females have been treated successfully with self-administered short-course therapy at the onset of symptoms.[43,83]

In persons with more frequent symptomatic infections and no apparent precipitating event, long-term prophylactic antimicrobial therapy may be instituted. Prophylactic therapy reduces the frequency of symptomatic infections in older males and females, and children. In females, most studies show a reinfection rate of two to three per patient-year reduced to 0.1 to 0.2 per patient-year with treatment.[83] Before prophylaxis is initiated,

individuals should be treated conventionally with an appropriate agent. Trimethoprim–sulfamethoxazole (one-half of a single-strength tablet), trimethoprim (100 mg daily), fluoroquinolone (levofloxacin 500 mg daily), and nitrofurantoin (50 or 100 mg daily) all reduce the rate of reinfection as the single-agent therapy.[83] Full-dose therapy with these agents is unnecessary and single daily doses can be used. Therapy generally is prescribed for a period of 6 months, during which time urine cultures are followed monthly. If symptomatic episodes develop, the patient should receive a full course of therapy with an effective agent and then resume prophylactic therapy. Therapy with methenamine hippurate for short-term use may be beneficial, but its overall utility is not well documented, especially for long-term prophylaxis.[84] In females who experience symptomatic reinfections in association with sexual activity, voiding after intercourse may help prevent infection. Also, single-dose prophylactic therapy with trimethoprim–sulfamethoxazole taken after intercourse reduces the incidence of recurrent infection significantly.[83]

In postmenopausal females with recurrent infections, the lack of estrogen results in changes in the bacterial flora of the vagina, resulting in increased colonization with uropathogenic *E. coli*. Topically administered estrogen cream reduces the incidence of infections in this population.[18,19]

The remaining 20% of recurrent UTIs are relapses, that is, persistence of infection with the same organism after therapy for an isolated UTI. The recurrence of symptomatic or ASB after therapy usually indicates that the person has renal involvement, a structural abnormality of the urinary tract or chronic bacterial prostatitis. In the absence of structural abnormalities, relapse often is related to renal infection and requires a long duration of treatment. Females who relapse after short-course therapy should receive a 2-week course of therapy. In patients who relapse after 2 weeks of therapy, therapy should be continued for another 2 to 4 weeks. If relapse occurs after 6 weeks of therapy, urologic evaluation should be performed and any obstructive lesion should be corrected. If this is not possible, therapy for 6 months or longer may be considered. Asymptomatic adults who have no evidence of urinary obstruction should not receive long-term therapy.

In males, relapse usually indicates bacterial prostatitis, the most common cause of persistent bacteriuria. Although many agents have been used for long-term therapy of relapses, trimethoprim–sulfamethoxazole and the fluoroquinolones appear to be highly effective.

Special Conditions

Urinary Tract Infections in Pregnancy

During pregnancy, significant physiologic changes occur to the entire urinary tract that dramatically alter the prevalence of UTIs and pyelonephritis. Severe dilation of the renal pelvis and ureters, decreased ureteral peristalsis, and reduced bladder tone occur during pregnancy.[86] These changes result in urinary stasis and reduced defenses against reflux of bacteria to the kidneys. In addition, increased urine content of amino acids, vitamins, and nutrients encourages bacterial growth. All of these factors increase the incidence of bacteriuria resulting in symptomatic infections, especially during the third trimester.

ASB occurs in 4% to 7% of pregnant persons. Of whom, 20% to 40% will develop acute symptomatic pyelonephritis during pregnancy. If untreated, ASB has the potential to cause significant adverse effects, including prematurity, low birth weight, and stillbirth.[86,87] Because pyelonephritis is associated with significant adverse events during pregnancy, routine screening tests for bacteriuria should be performed at the initial prenatal visit and again at 28 weeks of gestation. In persons with significant bacteriuria, symptomatic or asymptomatic, treatment is recommended so as to avoid possible complications. Organisms associated with bacteriuria are the same as those seen in uncomplicated UTIs with *E. coli* isolated most frequently.

Therapy should consist of an agent administered for 7 days that has a relatively low adverse effect potential and is safe for the mother and baby. The administration of amoxicillin, amoxicillin–clavulanate, or cephalexin is effective in 70% to 80% of patients. Nitrofurantoin has been used in pregnancy; however, it must be used with caution as occurrences of birth defects have been reported. Tetracyclines should be avoided because of teratogenic effects and sulfonamides should not be administered during the third trimester because of the possible development of kernicterus and hyperbilirubinemia. In addition, fluoroquinolones should not be given because of their potential to inhibit cartilage and bone development in the newborn. A follow-up urine culture 1 to 2 weeks after completing therapy and then monthly until gestation is complete is recommended. Optimal treatment for preventing recurrent UTI and ASB has yet to be defined.[89]

Catheterized Patients

The use of an indwelling catheter frequently is associated with infection of the urinary tract and represents the most common cause of hospital-

acquired infection. The incidence of catheter-associated infection is related to a variety of factors, including method and duration of catheterization, the catheter system (open or closed), the care of the system, the susceptibility of the patient, and the technique of the healthcare personnel inserting the catheter. Catheter-related infections are reasonably preventable infections and are now considered one of the hospital-acquired complications chosen by the Centers for Medicare and Medicaid Services in which hospitals will no longer receive reimbursement for the treatment.[90,91]

Bacteria may enter the bladder in a number of ways. During the catheterization, bacteria may be introduced directly into the bladder from the urethra. Once the catheter is in place, bacteria may pass up the lumen of the catheter by the movement of air bubbles, motility of the bacteria, or capillary action. In addition, bacteria may reach the bladder from around the exudative sheath that surrounds the catheter in the urethra. Cleaning the periurethral area thoroughly and applying an antiseptic (povidone-iodine) can minimize infection occurring during insertion of the catheter. The use of closed drainage systems has reduced significantly the ability of bacteria to pass up the lumen of the catheter and cause infection. A bacterium passing around the catheter sheath in the urethra is probably the most important pathway for infection. Avoiding manipulation of the catheter and trauma to the urethra and urethral meatus can minimize this path of acquisition.

Persons with indwelling catheters acquire UTIs at a rate of 5% per day.[90-92] The closed systems are capable of preventing bacteriuria in most patients for up to 10 days with appropriate care. After 30 days of catheterization, however, there is a 78% to 95% incidence of bacteriuria, despite use of a closed system.[91,93] Unfortunately, UTI symptoms in a catheterized person are not clearly defined. Fever, peripheral leukocytosis, and urinary signs and symptoms may be of little predictive value.[90,91] When bacteriuria occurs in the asymptomatic, short-term catheterized person (less than 30 days), the use of systemic antibiotics should be withheld and the catheter should be removed as soon as possible. If the person becomes symptomatic, the catheter should be removed and treatment as described for complicated infections started. The optimal duration of therapy is unknown. In the long-term catheterized person (more than 30 days), bacteriuria is inevitable.[90,91] The administration of systemic antibiotics active against the infecting organism will sterilize the urine; however, reinfection occurs rapidly in more than 50% of persons. In addition, resistant organisms recolonize the urine. Symptomatic individuals must be treated because they are at the risk of developing pyelonephritis and bacteremia. Bacteria adhere to the catheter and produce a biofilm consisting of bacterial glycocalyces, Tamm–Horsfall protein, as well as apatite and struvite salts, that act to protect the bacteria from antibiotics.[92] Biofilm mechanisms and their treatment continue to be examined and more fully understood.[93,94] Recatheterization with a new sterile unit should be performed in symptomatic individuals, if the existing catheter has been in place for more than 2 weeks.

Various methods have been proposed to prevent the development of bacteriuria and infection in the patient with an indwelling catheter (see Table 139-4). The success of these methods depends on the type of catheter and the length of time it is in place. The use of constant bladder irrigation with antiseptic or antibacterial solutions reduces the incidence of infection in those with open drainage systems, but this approach has no advantage in those with closed systems. The use of prophylactic systemic antibiotics in persons with short-term catheterization reduces the incidence of infection over the first 4 to 7 days.[91,93] With long-term catheterization, however, antibiotics only postpone the development of bacteriuria and lead to the emergence of resistant organisms. Therefore, antibiotic prophylaxis should not be utilized in short-term or long-term catheterized patients.

PROSTATITIS

Bacterial prostatitis is an inflammation of the prostate gland and surrounding tissue as a result of infection. It is classified as either acute or chronic. By definition, pathogenic bacteria and significant inflammatory cells must be present in prostatic secretions and urine to make the diagnosis of bacterial prostatitis. Prostatitis occurs rarely in young males, but it is commonly associated with recurrent infections in persons older than 30 years. As many as 50% of all males develop some form of prostatitis at some period in their life.[95-97] The acute form typically is an acute infectious disease characterized by a sudden onset of fever, tenderness, and urinary and constitutional symptoms. Chronic prostatitis presents with few symptoms related to the prostate but rather symptoms of urinating difficulty, low back pain, perineal pressure, or a combination of these. It represents a recurring infection with the same organism that results from incomplete eradication of bacteria from the prostate gland.

Pathogenesis and Etiology

The exact mechanism of bacterial infection of the prostate is not well understood. The possible routes of infection are the same as those for UTIs. Reflux of infected urine into the prostate gland is thought to play an important role in causing infection. Intraprostatic reflux of urine occurs commonly and results in direct inoculation of infected urine into the prostate.[95-97] In addition, intraprostatic reflux of sterile urine can result in a chemical prostatitis and may be the cause of nonbacterial prostatitis. Sexual intercourse may contribute to infection of the prostate gland because prostatic

secretions from males with chronic prostatitis and vaginal cultures from their sexual partners grow identical organisms. Other known causes of bacterial prostatitis include indwelling urethral and condom catheterization, urethral instrumentation, and transurethral prostatectomy in patients with infected urine.

Physiologic factors are believed to contribute to the development of prostatitis. Functional abnormalities found in bacterial prostatitis include altered prostate secretory functions. Prostatic fluid obtained from normal males contains prostatic antibacterial factor. This heat-stable, low-molecular-weight cation is a zinc-complexed polypeptide that is bactericidal to most urinary tract pathogens.[98] The antibacterial activity of prostatic antibacterial factor is related directly to the zinc content of prostatic fluid. Prostate fluid zinc levels and prostatic antibacterial factor activity also appear diminished in persons with prostatitis, as well as in older males.[98] Whether these changes are a cause or effect of prostatitis remains to be determined.

The pH of prostatic secretions in patients with prostatitis is altered.[99] Normal prostatic secretions have a pH in the range of 6.6 to 7.6. With increasing age, the pH tends to become more alkaline. With inflammation of the prostate, prostatic secretions may have an alkaline pH in the range of 7 to 9. These changes suggest a generalized secretory dysfunction of the prostate that not only can affect the pathogenesis of prostatitis but also can influence the mode of therapy.

Gram-negative enteric organisms are the most frequent pathogens in acute bacterial prostatitis.[95-97] *E. coli* is the predominant organism, occurring in 75% of cases. Other gram-negative organisms frequently isolated include *K. pneumoniae*, *P. mirabilis*, and less frequently, *P. aeruginosa*, *Enterobacter* spp., and *Serratia* spp. Infrequently, cases of gonococcal and staphylococcal prostatitis occur. *E. coli* most commonly causes chronic bacterial prostatitis with other gram-negative organisms isolated less frequently. The importance of gram-positive organisms in chronic bacterial prostatitis remains controversial. *S. epidermidis*, *S. aureus*, and diphtheroids have been isolated.

Clinical Presentation

Acute bacterial prostatitis presents similarly to other acute infections with fever, chills, myalgias, and other typical signs and symptoms. Massage of the prostate will express a purulent discharge that will readily grow the pathogenic organism. Prostatic massage is contraindicated in acute bacterial prostatitis, however, because of the risk of inducing bacteremia and the associated local pain. The diagnosis of acute bacterial prostatitis can be made from the clinical presentation, abdominal, genital, and digital rectal examination, and the presence of significant bacteriuria. As with other UTIs, the infecting organism can be isolated from a midstream specimen.

CLINICAL PRESENTATION: Bacterial Prostatitis

Signs and Symptoms

- Acute bacterial prostatitis: High fever, chills, malaise, myalgia, localized pain (perineal, rectal, sacrococcygeal), frequency, urgency, dysuria, nocturia, and retention
- Chronic bacterial prostatitis: Voiding difficulties (frequency, urgency, dysuria), low back pain, and perineal and suprapubic discomfort

Physical Examination

- Acute bacterial prostatitis: Swollen, tender, tense, or indurated gland
- Chronic bacterial prostatitis: Boggy, indurated (enlarged) prostate in most patients

Laboratory Tests

- Bacteriuria
- Bacteria in EPSs

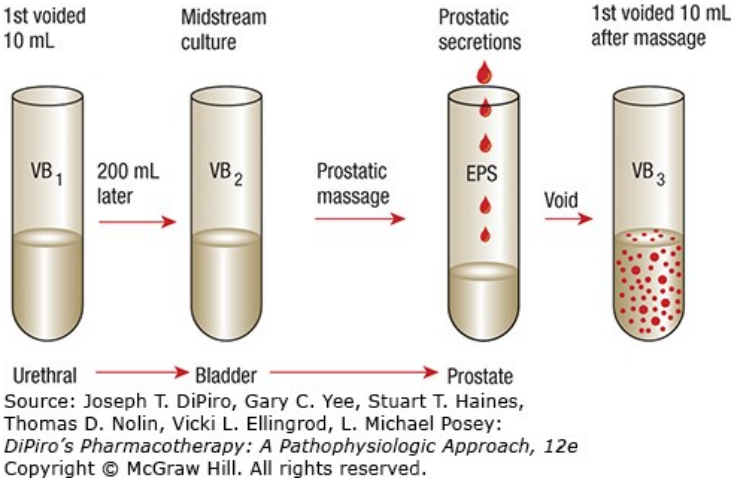
In contrast, chronic bacterial prostatitis is more difficult to diagnose and treat. Chronic bacterial prostatitis typically is characterized by recurrent UTIs

with the same pathogen and is the most common cause of recurrent UTI in males. The patient's clinical presentation can vary widely. Many adults, however, are asymptomatic.

Because physical examination of the prostate is often normal, urinary tract localization studies are critical to the diagnosis of chronic bacterial prostatitis. The method of quantitative localization culture, as described by Meares and Stamey,[15,100] remains the diagnostic standard (Fig. 139-3). The method compares the bacterial growth in sequential urine and prostatic fluid cultures obtained during micturition. The first 10 mL of voided urine is collected (voiding bladder 1, or VB_1) and constitutes urethral urine. After approximately 200 mL of urine has been voided, a 10-mL midstream sample is collected (VB_2). This specimen represents bladder urine. After the person voids, the prostate is massaged and expressed prostatic secretions (EPS) are collected. After prostatic massage, the patient voids again and 10 mL of urine is collected (VB_3.)

FIGURE 139-3

Segmented cultures of the lower tract in men. (EPS, expressed prostatic secretions; VB_1, voiding bladder 1; VB_2, voiding bladder 2; VB_3, voiding bladder 3)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The diagnosis of bacterial prostatitis is made when the number of bacteria in EPS is 10 times that of the urethral sample (VB_1) and midstream sample (VB_2). If no EPS is available, the urine sample following massage (VB_3) should contain a bacterial count 10-fold greater than that of VB_1 or VB_2. If significant bacteriuria is present, ampicillin, cephalexin, or nitrofurantoin should be given for 2 to 3 days to sterilize the urine prior to performing the localization study.

Treatment

9 The goals for the management of bacterial prostatitis are the same as those for UTIs. Acute bacterial prostatitis responds well to appropriate antimicrobial therapy that is directed at the most commonly isolated organisms. Prostatic penetration of antimicrobials occurs because the acute inflammatory reaction alters the cellular membrane barrier between the bloodstream and the prostate. Most patients can be managed with oral antimicrobial agents, such as trimethoprim–sulfamethoxazole and the fluoroquinolones (eg, ciprofloxacin, levofloxacin) (see Table 139-4). Other effective agents in this setting include cephalosporins and β-lactam–β-lactamase combinations. Although IV therapy is rarely necessary for total treatment, IV to oral sequential therapy with trimethoprim–sulfamethoxazole or the fluoroquinolones is appropriate. Most patients will become afebrile within 36 hours of antibiotic treatments.[96] The conversion to an oral antibiotic can be considered after the patient is afebrile for 48 hours or after 3 to 5 days of IV therapy. The total course of antibiotic therapy should be 4 weeks in order to reduce the risk of development of chronic prostatitis, although in some cases 2 weeks may be sufficient. Therapy may be prolonged with chronic prostatitis (6-12 weeks). Long-term suppressive therapy also may be initiated for recurrent infections, such as three times weekly ciprofloxacin, trimethoprim–sulfamethoxazole regular-strength tablet daily, or nitrofurantoin 100 mg daily.[100]

Chronic bacterial prostatitis often presents a more vexing situation because cures are obtained rarely. Despite high serum concentrations of

antibacterial drugs in excess of the minimal inhibitory concentrations of the infecting organisms, bacteria persist in prostatic fluid. Most likely the failure to eradicate sensitive bacteria is caused by the inability of antibiotics to reach sufficient concentrations in the prostatic fluid and cross the prostatic epithelium.

Several factors that determine antibiotic diffusion into prostatic secretions were delineated from the canine model. Lipid solubility is a major determinant in the ability of drugs to diffuse from plasma across epithelial membranes. The degree of ionization in plasma also affects the diffusion of drugs. Only unionized molecules can cross the lipid barrier of prostatic cells, and the drug's pK_a (negative logarithm of acid ionization constant) directly determines the fraction of unchanged drug.

The pH gradient across the membrane has an influence on tissue penetration, as well. A pH gradient of at least one pH unit between separate compartments allows for ion trapping. As the unionized drug crosses the epithelial barrier into prostatic fluid, it becomes ionized allowing less drug to diffuse back across the lipid barrier. In early studies with the canine model, the prostatic pH was acidic (6.4).[99] In humans, however, the pH of prostatic secretions from an inflamed prostate is actually basic (8.1-8.3).[99]

The choice of antibiotics in chronic bacterial prostatitis should include agents that are capable of reaching therapeutic concentrations in the prostatic fluid and which possess the spectrum of activity to be effective. Agents that achieve therapeutic prostatic concentrations include trimethoprim and the fluoroquinolones. Sulfamethoxazole penetrates poorly and probably contributes little to trimethoprim activity when used in combination. The fluoroquinolones appear to provide the best therapeutic options in the management of chronic bacterial prostatitis. Therapy should be continued for 4 to 6 weeks initially. Longer treatment periods may be necessary in some cases. If therapy fails with these regimens, chronic suppressive therapy may be used or surgery considered.

ANSWERS FOR BEYOND THE BOOK

1. **Correct answer:** Yes, pregnant females should be screened for ASB and treated if it is present. *(Reference: Asymptomatic Bacteriuria Guidelines)*

2. **Correct answer C:** Pyuria and leukocyte esterase can be found in the urinalysis of patients with or without a urinary tract infection but do not increase their risk for a complicated UTI. Age is not a specific risk factor associated with an increase in complicated UTI. Pregnancy does increase the risk of complicated UTI due to anatomical changes and host factors during pregnancy.

3. **Correct answer D:** Ciprofloxacin is not appropriate due to concerns about safety and risk to fetus during pregnancy. Not treating is inappropriate due to potential complications of urinary tract infections in pregnancy, specifically pyelonephritis, premature birth, and low birth weight. Trimethoprim/Sulfamethoxazole would be an appropriate choice, especially since she is in her second trimester, but the treatment would only be for 3 days. Nitrofurantoin has clinical experience and is relatively safe in pregnancy, especially after the first trimester.

4. **Correct answer A:** The patient is now showing signs of pyelonephritis with the fever and back pain, so longer treatment would be necessary. Therefore, longer treatment would be required than the 7 days of nitrofurantoin. In addition, pyelonephritis is not isolated in the bladder so you would need an agent that gets blood and tissue concentrations. Levofloxacin like ciprofloxacin is a fluoroquinolone and is therefore inappropriate due to concerns about safety and risk to fetus during pregnancy. The patient can be treated with oral therapy in an outpatient setting, so piperacillin/tazobactam intravenous would not be appropriate and is too broad spectrum for this sensitive *E. coli.* Trimethoprim/Sulfamethoxazole would be an appropriate choice, especially since she in in her second trimester, and is given orally for outpatient therapy. Fourteen days would be the appropriate length of treatment.

ABBREVIATIONS

ASB	asymptomatic bacteriuria
CFU	colony-forming unit
EPS	expressed prostatic secretions
GI	gastrointestinal
PMN	polymorphonuclear leukocyte
UTI	urinary tract infection
WBC	white blood cell

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SELF-ASSESSMENT QUESTIONS

1. Which of the following would be categorized as an uncomplicated urinary tract infection?
   A. An acute infection involving the lower urinary tract of a 17-year-old girl
   B. An acute infection with involvement of the kidneys of a 24-year-old male
   C. An acute recurrent infection involving the lower urinary tract of a 58-year-old female
   D. An acute infection with involvement of the kidneys of a 75-year-old male
2. When treating a community-acquired UTI in a treatment naive patient who has never had a UTI before, which of the following organisms should be most highly suspected and targeted when choosing antibiotic therapy?
   A. *Proteus mirabilis*
   B. *Staphylococcus saprophyticus*
   C. *Escherichia coli*
   D. *Enterococcus faecalis*
3. Which of the following patients is most likely to have a complicated UTI?
   A. A 40-year-old healthy woman with hypertension
   B. A 30-year-old healthy woman with GERD
   C. A 19-year-old healthy woman who has a urethral stricture
   D. A 10-year-old healthy girl with no medical issues
4. Which of the following host factors specifically inhibit bacterial growth in the urinary tract of male patients?
   A. Osmolality of the urine
   B. Prostatic secretions in the urine
   C. Urea concentration in the urine
   D. pH of the urine
5. JT is a 34-year-old woman who presents to her primary care clinic with fever, dysuria, flank pain, urgency, and vomiting. Which of her symptoms should make the healthcare provider caring for JT suspect that she has a urinary tract infection that has migrated to her upper genitourinary tract?

A. Fever, dysuria

B. Dysuria, urgency

C. Fever, urgency

D. Flank pain, vomiting

6. An 89-year-old male presents to the emergency department with altered mental status, dehydration, and acute kidney injury. His symptoms are attributed to an acute urinary tract infection and he is started on appropriate antibiotics. Which of the following symptoms would his family see the most drastic change in once antibiotics are started?

A. Mental status

B. Kidney function

C. Electrolyte levels

D. Urine amount

7. Altered mental status, change in eating habits, or gastrointestinal (GI) symptoms as opposed to typical manifestations of UTIs are frequently seen in which patient population?

A. Children

B. Elderly

C. Pregnant females

D. Males

8. Which of the following methods of urine collection is best for patients who are unable to void urine?

A. Midstream catch

B. Urine catch using the first 20 to 30 mL of urine flow

C. Catheterization

D. Suprapubic bladder aspiration

9. Which of the following results is most indicative that there is significant bacteria in the urine?

A. Hematuria

B. 10 white blood cell (WBC)/mm^3 (10×10^6/L)

C. More than 10^5 CFU/mL (10^8 CFU/L)

D. Leukocyte esterase positive

10. A 20-year-old woman is diagnosed with uncomplicated cystitis. She has no known drug allergies. Based on the 2010 IDSA Guidelines, which of the following regimens would be the most appropriate treatment for this patient?

A. Ciprofloxacin 500 mg orally twice daily for 3 days

B. Nitrofurantoin 100 mg orally twice daily for 5 days

C. Amoxicillin 500 mg orally four times daily for 3 days

D. Trimethoprim–sulfamethoxazole double strength, 1 tablet orally, 1 dose

11. A 50-year-old woman is admitted to the ICU with severe pyelonephritis. She has a history of anaphylaxis with penicillin. What would be the most appropriate empiric treatment?

A. Trimethoprim–sulfamethoxazole double strength, 1 tablet orally twice daily for 3 days

B. Nitrofurantoin 100 mg orally twice daily for 7 days

C. Cipofloxacin 400 mg IV twice daily for 3 days, followed by 500 mg orally twice daily for 11 days

D. Piperacillin/tazobactam 3.375 g IV q6 hours x 14 days

12. A 34-year-old woman is diagnosed with her third incidence of uncomplicated cystitis in the last 18 months. The trimethoprim–sulfamethoxazole resistance rate for *E.coli* is 10% in the community. Her last prescription filled was TMP/SMX and was completed 30 days ago. Which of the following would be the best choice treatment of an uncomplicated UTI for this patient?

A. Trimethoprim–sulfamethoxazole double strength, one tablet orally twice daily for 3 days

B. Amoxicillin 500 mg orally twice daily for 5 days

C. Fosfomycin 3 gm orally daily for 3 days

D. Ciprofloxacin 500 mg orally twice daily for 5 days

13. A 54-year-old man is diagnosed with acute bacterial prostatitis for the first time. He is an otherwise healthy male with a documented allergy to trimethoprim–sulfamethoxazole. Which of the following is the most appropriate therapy for this patient?

A. Ciprofloxacin 500 mg orally twice daily for 3 days

B. Trimethoprim–sulfamethoxazole double strength, one tablet orally twice daily for 4 weeks

C. Ciprofloxacin 500 mg orally twice daily for 4 weeks

D. Nitrofurantoin 100 mg orally twice daily for 5 days

14. Which of the following antibiotic agents should be avoided in all cases for the treatment of acute uncomplicated cystitis due to antimicrobial resistance?

A. Amoxicillin

B. Levofloxacin

C. Trimethoprim–sulfamethoxazole

D. Nitrofurantoin

15. A 24-year-old woman would like to know what she can do for her frequent UTIs. She notices that she mainly gets them after sexual intercourse. What would be the best recommendation to try first for this patient?

A. Drink cranberry juice daily

B. Levofloxacin 500 mg daily for 1 year

C. Topical estrogen cream

D. Urine voiding after intercourse

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Acute uncomplicated cystitis typically occurs in women of childbearing age and often typically involves the lower urinary tract

2. **C.** The most common cause of uncomplicated UTIs is Escherichia coli, which accounts for 80% to 90% of community-acquired infections. Additional causative organisms in uncomplicated infections include *Staphylococcus saprophyticus*, *Klebsiella* pneumoniae, *Proteus* spp., *Pseudomonas aeruginosa*, and *Enterococcus* spp.[11]

3. **C.** In this question because all patients are females, relatively young and have comorbidities unrelated to the urinary tract, the young woman with a urethral stricture is most likely to have a complicated UTI due to pre-disposing factors that increase her risk of infection of the urinary tract.

4. **B.** Although osmolality, urea concentration, and pH of the urine can help inhibit bacterial growth in the urine, prostatic secretions are specific to male patients and have been shown to inhibit bacterial growth in the urine.

5. **D.** Although patients with upper UTIs present with fever, dysuria, and urgency, the flank pain and vomiting are more specific to the upper GU tract involvement.

6. **A.** In the elderly population, patient's often present with unconventional symptoms when they have a UTI, including mental status change, GI issues (nausea/vomiting), etc. Patient's family members notice this most often, rather than changes in kidney function, electrolyte levels, and urine output which is best measured by a healthcare provider.

7. **B.** In the elderly, change in eating habits or gastrointestinal (GI) symptoms as opposed to typical manifestations of UTIs are frequently. In children, pregnant women, and men, common signs/symptoms include dysuria, urgency, frequency, nocturia, suprapubic heaviness, and gross hematuria.

8. **C.** Catheterization may be necessary for patients who are uncooperative or who are unable to void urine. If catheterization is performed carefully with aseptic technique, the method yields reliable results. Midstream catch is ideal for patients who are able to void on their own and the idea is to catch the urine after the first 20 to 30 mL have been voided to avoid contamination from bacteria that may adhere to the urethra. Suprapubic aspiration is invasive and not recommended as the first attempt to collect urine in those unable to void on their own.

9. **C.** The diagnosis of UTI is based on the isolation of significant numbers of bacteria from a urine specimen. Patients can have pyuria, hematuria, and test positive for leukocyte esterase without having a UTI.

10. **B.** The only viable option is the nitrofurantoin. The dosing and duration of therapy are not in accordance with the 2010 IDSA guidelines for neither TMP/SMX nor amoxicillin. Flouroquinolones would be reserved for the suspicion of more serious infections.

11. **C.** This infection is considered a complicated infection due to the fact that it is pyelonephritis and the patient has been admitted to the ICU. The patient needs 14 days of therapy which is why options A, B, and D are incorrect.

12. **A.** Because the resistance in the community of *E.coli* to trimethoprim-sulfamethoxazole is only 10% and although patient has had prior UTIs because it's been greater than 2 weeks and she has no risk factors. This is a new infection and we would treat it as such. Amoxicillin resistance with *E.coli* is known to be high and not recommended and fosfomycin and cipro would be reserved for patients with more severe infections.

13. **C.** The patient has a documented allergy to TMP/SMX and has never had prostatitis before. Typical therapy would include either a quinolone or TMP/SMX for 4 weeks. Therefore, options A and B are not appropriate for this patient. Patient has a documented serious penicillin allergy that makes D inappropriate as well.

14. **A.** The resistance rate of *E.Coli* to amoxicillin is close to 40% so it should never be used to treat UTI.

15. **D.** The utilization of both estrogen cream and cranberry juice is still somewhat controversial. With resistance increasing, levofloxacin should not be used for prophylaxis. Therefore, urine voiding after intercourse is the best option.