Chapter 135: Urinary Tract Infections, Pyelonephritis, and Prostatitis

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INTRODUCTION

Urinary tract infection (UTI) is a common and painful human illness that is rapidly responsive to modern antibiotic therapy, if the correct antibiotic is chosen for the particular urinary pathogen. In the preantibiotic era, UTI caused significant morbidity. Hippocrates, writing about a disease that appears to have been acute cystitis, said that the illness could last for a year before either resolving or worsening to involve the kidneys. When chemotherapeutic agents used to treat UTI were introduced in the early twentieth century, they were relatively ineffective, and persistence of infection after 3 weeks of therapy was common. Nitrofurantoin, which became available in the 1950s, was the first tolerable and effective agent for the treatment of UTI.

Since the most common manifestation of UTI is acute cystitis and since acute cystitis is far more prevalent among women than among men, most clinical research on UTI has involved women. Many studies have enrolled women from college campuses or large health maintenance organizations in the United States. Therefore, when reviewing the literature and recommendations concerning UTI, clinicians must consider whether the findings are applicable to their patient populations.

DEFINITIONS

UTI may be asymptomatic (subclinical infection) or symptomatic (disease). Thus, the term *urinary tract infection* encompasses a variety of clinical entities, including asymptomatic bacteriuria (ASB), cystitis, prostatitis, and pyelonephritis. The distinction between symptomatic UTI and ASB has major clinical implications. Both UTI and ASB connote the presence of bacteria in the urinary tract, usually accompanied by white blood cells and inflammatory cytokines in the urine. However, ASB occurs in the absence of symptoms attributable to the bacteria in the urinary tract and usually does not require treatment, while UTI has more typically been assumed to imply symptomatic disease that warrants antimicrobial therapy. Much of the literature concerning UTI, particularly catheter-associated infection, does not differentiate between UTI and ASB. In this chapter, the term *urinary tract infection* denotes symptomatic disease; *cystitis*, symptomatic infection of the bladder; and *pyelonephritis*, symptomatic infection of the kidneys. *Uncomplicated urinary tract infection* refers to an infection confined to the bladder, or acute cystitis. *Pyelonephritis* occurs when the infection involves the renal parenchyma. *Complicated urinary tract infection* is accompanied by symptoms that suggest the infection extends beyond the bladder, such as a fever or signs or symptoms of systemic illness. *Recurrent urinary tract infection* is not necessarily complicated; individual episodes can be uncomplicated and treated as such. *Catheter-associated bacteriuria* can be either symptomatic (CAUTI) or asymptomatic. This new approach to UTI categorization differs from the classical approach, in which men with UTI are automatically considered complicated. This updated categorization more closely reflects actual clinical practice. The key considerations in diagnostic workup and therapy for UTI are whether the patient is stable for outpatient management and whether the antimicrobial agents need to achieve adequate levels in blood and tissue.

EPIDEMIOLOGY AND RISK FACTORS

Except among infants and older adults, UTI occurs far more commonly in females than in males. During the neonatal period, the incidence of UTI is slightly higher among males than among females because male infants more commonly have congenital urinary tract anomalies. After 50 years of age, obstruction from prostatic hypertrophy becomes common in men, and the incidence of UTI is almost as high among men as among women. Between 1 year and ~50 years of age, UTI and recurrent UTI are predominantly diseases of females. The prevalence of ASB is ~5% among women between ages 20 and 40 and may be as high as 40–50% among elderly women and men.

As many as 50–80% of women in the general population acquire at least one UTI during their lifetime—uncomplicated cystitis in most cases. Recent use of a diaphragm with spermicide, frequent sexual intercourse, and a history of UTI are independent risk factors for acute cystitis. Cystitis is temporally related to recent sexual intercourse in a dose–response manner, with an increased relative risk ranging from 1.4 with one episode of intercourse in the

preceding week to 4.8 with five episodes. In healthy postmenopausal women, sexual activity, diabetes mellitus, and incontinence are risk factors for UTI.

Many factors predisposing women to cystitis also increase the risk of pyelonephritis. Factors independently associated with pyelonephritis in young healthy women include frequent sexual intercourse, a new sexual partner, a UTI in the previous 12 months, a maternal history of UTI, diabetes, and incontinence. The shared risk factors for cystitis and pyelonephritis are not surprising given that pyelonephritis typically arises through the ascent of bacteria from the bladder to the upper urinary tract. However, pyelonephritis can occur without symptomatic antecedent cystitis.

About 20–30% of women who have had one episode of UTI will have recurrent episodes. Early recurrence (within 2 weeks) is usually regarded as relapse rather than reinfection and may indicate the need to evaluate the patient for a sequestered focus. Intracellular bacterial communities of infecting organisms within the bladder epithelium have been demonstrated in animal models of UTI and in exfoliated human urothelial cells, but the clinical impact of this phenomenon in humans is not yet clear. The rate of recurrence ranges from 0.3 to 7.6 infections per patient per year, with an average of 2.6 infections per year. It is not uncommon for multiple recurrences to follow an initial infection, resulting in clustering of episodes. Clustering may be related temporally to the presence of a new risk factor, to the sloughing of the protective outer bladder epithelial layer in response to bacterial attachment during acute cystitis, or possibly to antibiotic-related alteration of the normal flora. The likelihood of a recurrence decreases with increasing time since the last infection. A case–control study of predominantly white premenopausal women with recurrent UTI identified frequent sexual intercourse, use of spermicide, a new sexual partner, a first UTI before 15 years of age, and a maternal history of UTI as independent risk factors for recurrent UTI. The only consistently documented behavioral risk factors for recurrent UTI include frequent sexual intercourse and spermicide use. In postmenopausal women, major risk factors for recurrent UTI include a history of premenopausal UTI and anatomic factors affecting bladder emptying, such as cystoceles, urinary incontinence, and residual urine.

In pregnant women, ASB has clinical consequences, and both screening for and treatment of this condition are indicated. Specifically, ASB during pregnancy is associated with maternal pyelonephritis, which in turn is associated with preterm delivery. Antibiotic treatment of ASB in pregnant women can reduce the risk of pyelonephritis, preterm delivery, and low-birth-weight babies.

The majority of men with UTI have a functional or anatomic abnormality of the urinary tract, most commonly urinary obstruction secondary to prostatic hypertrophy. That said, not all men with UTI have detectable urinary abnormalities; this point is particularly relevant for men ≤45 years of age. Lack of circumcision is associated with an increased risk of UTI because *Escherichia coli* is more likely to colonize the glans and prepuce and subsequently migrate into the urinary tract of uncircumcised men.

Women with diabetes have a two- to threefold higher rate of ASB and UTI than women without diabetes; there is insufficient evidence on which to base a corresponding statement about men. Increased duration of diabetes and the use of insulin rather than oral medication are associated with an elevated risk of UTI among women with diabetes. Poor bladder function, obstruction in urinary flow, and incomplete voiding are additional factors commonly found in patients with diabetes that increase the risk of UTI. Impaired cytokine secretion may contribute to ASB in diabetic women. The sodium–glucose co-transporter 2 (SGLT2) inhibitors used for treatment of diabetes result in glycosuria. Initial concerns that these drugs as a class increased the risk of UTI are not supported by data.

ETIOLOGY

The uropathogens causing UTI vary by clinical syndrome but are usually enteric gram-negative rods that have migrated to the urinary tract. The susceptibility patterns of these organisms vary by clinical syndrome and by geography. In acute uncomplicated cystitis in the United States, the etiologic agents are highly predictable: *E. coli* accounts for 75–90% of isolates; *Staphylococcus saprophyticus* for 5–15% (with particularly frequent isolation from younger women); and *Klebsiella*, *Proteus*, *Enterococcus*, and *Citrobacter* species, along with other organisms, for 5–10%. Similar etiologic agents are found in Canada, South America, and Europe. The spectrum of agents causing uncomplicated pyelonephritis is similar, with *E. coli* predominating. In complicated UTI (e.g., CAUTI), *E. coli* remains the predominant organism, but other aerobic gram-negative rods, such as *Pseudomonas aeruginosa* and *Klebsiella*, *Proteus*, *Citrobacter*, *Acinetobacter*, and *Morganella* species, also are frequently isolated. Gram-positive bacteria (e.g., enterococci and *Staphylococcus aureus*) and yeasts also are important pathogens in complicated UTI. Data on etiology and resistance are generally obtained from laboratory surveys and should be understood in the context that organisms are identified only in cases in which urine is sent for culture—typically, when complicated UTI or pyelonephritis is suspected. Genetic sequencing of the bladder microbiome or of all the bacteria that can be identified in the bladder has consistently demonstrated that more bacterial species are present than can be identified by routine culture methods, in both symptomatic and asymptomatic states. The clinical significance of these non-cultivatable organisms is unknown but has challenged

the assumption that the bladder is normally a sterile site.

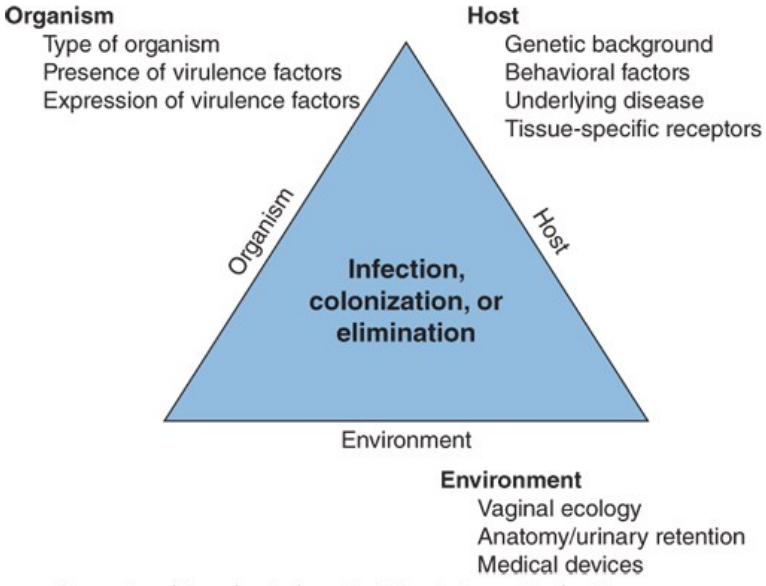
The available data demonstrate a worldwide increase in the resistance of *E. coli* to specific antibiotics commonly used to treat UTI. North American, South American, and European surveys from women with acute cystitis have documented resistance rates of >20% to trimethoprim-sulfamethoxazole (TMP-SMX) in many regions and >10% to ciprofloxacin in some regions. In community-acquired infections, the increased prevalence of multidrug-resistant uropathogens has left few oral options for therapy in some cases. Since resistance rates vary by local geographic region, with individual patient characteristics, and over time, it is important to use current and local data when choosing a treatment regimen.

PATHOGENESIS

The urinary tract can be viewed as an anatomic unit linked by a continuous column of urine extending from the urethra to the kidneys. In the majority of UTIs, bacteria establish infection by ascending from the urethra to the bladder. Continuing ascent up the ureter to the kidney is the pathway for most renal parenchymal infections. However, introduction of bacteria into the bladder does not inevitably lead to sustained and symptomatic infection. The interplay of host, pathogen, and environmental factors determines whether tissue invasion and symptomatic infection will ensue **(Fig. 135-1)**. For example, bacteria often enter the bladder after sexual intercourse, but normal voiding and innate host defense mechanisms in the bladder eliminate these organisms. Any foreign body in the urinary tract, such as a urinary catheter or stone, provides an inert surface for bacterial colonization. Abnormal micturition and/or significant residual urine volume promotes infection. In the simplest of terms, anything that increases the likelihood of bacteria entering the bladder and staying there increases the risk of UTI.

FIGURE 135-1

Pathogenesis of urinary tract infection. The relationship among specific host, pathogen, and environmental factors determines the clinical outcome.



Bacteria can gain access to the urinary tract through the bloodstream. However, hematogenous spread accounts for <2% of documented UTIs and usually results from bacteremia caused by relatively virulent organisms, such as *Salmonella* and *S. aureus.* Indeed, the isolation of either of these pathogens from a patient without a catheter or other instrumentation warrants a search for a bloodstream source. Hematogenous infections may produce focal abscesses or areas of pyelonephritis within a kidney and result in positive urine cultures. The pathogenesis of candiduria is distinct in that the hematogenous route is common. The presence of *Candida* in the urine of a non-instrumented immunocompetent patient implies either genital contamination or potentially widespread visceral dissemination.

Environmental Factors

VAGINAL ECOLOGY

Vaginal ecology is an important environmental factor affecting the risk of UTI in women. Colonization of the vaginal introitus and periurethral area with organisms from the intestinal flora (usually *E. coli*) is the critical initial step in the pathogenesis of UTI. Sexual intercourse is associated with an increased risk of vaginal colonization with *E. coli* and thereby increases the risk of UTI. Nonoxynol-9 in spermicide is toxic to the normal vaginal lactobacilli and thus is likewise associated with an increased risk of *E. coli* vaginal colonization and bacteriuria. In postmenopausal women, the previously predominant vaginal lactobacilli are replaced with colonizing gram-negative bacteria. The use of topical estrogens to prevent UTI in postmenopausal women is controversial; given the side effects of systemic hormone replacement, oral estrogens should not be used to prevent UTI.

ANATOMIC AND FUNCTIONAL ABNORMALITIES

Any condition that permits urinary stasis or obstruction predisposes the individual to UTI. Foreign bodies such as stones or urinary catheters provide an inert surface for bacterial colonization and formation of a persistent biofilm. Thus, vesicoureteral reflux, ureteral obstruction secondary to prostatic hypertrophy, neurogenic bladder, and urinary diversion surgery create an environment favorable to UTI. In persons with such conditions, *E. coli* strains lacking typical urinary virulence factors are often the cause of infection. Inhibition of ureteral peristalsis and decreased ureteral tone leading to vesicoureteral reflux are important in the pathogenesis of pyelonephritis in pregnant women. Anatomic factors—specifically, the distance of the urethra from the anus—are considered to be the primary reason why UTI is predominantly an illness of young women rather than of young men.

Host Factors

The genetic background of the host influences the individual's susceptibility to recurrent UTI, at least among women. A familial disposition to UTI and to pyelonephritis is well documented. Women with recurrent UTI are more likely to have had their first UTI before the age of 15 years and to have a maternal history of UTI. A component of the underlying pathogenesis of this familial predisposition to recurrent UTI may be persistent vaginal colonization with *E. coli*, even during asymptomatic periods. Vaginal and periurethral mucosal cells from women with recurrent UTI bind threefold more uropathogenic bacteria than do mucosal cells from women without recurrent infection. Epithelial cells from women who are non-secretors of certain blood group antigens may possess specific types of receptors to which *E. coli* can bind, thereby facilitating colonization and invasion. Mutations in host innate immune response genes (e.g., those coding for Toll-like receptors and the interleukin 8 receptor) also have been linked to recurrent UTI and pyelonephritis. The genetic patterns that predispose to cystitis and pyelonephritis appear to be distinct.

Microbial Factors

An anatomically normal urinary tract presents a stronger barrier to infection than a compromised urinary tract. Thus, strains of *E. coli* that cause invasive symptomatic infection of the urinary tract in otherwise normal hosts often possess and express genetic virulence factors, including surface adhesins that mediate binding to specific receptors on the surface of uroepithelial cells. The best-studied adhesins are the P fimbriae, hair-like protein structures that interact with a specific receptor on renal epithelial cells. (The letter *P* denotes the ability of these fimbriae to bind to blood group antigen P, which contains a D-galactose-D-galactose residue.) P fimbriae are important in the pathogenesis of pyelonephritis and subsequent bloodstream invasion from the kidney.

Another adhesin is the type 1 pilus (fimbria), which all *E. coli* strains possess but not all *E. coli* strains express. Type 1 pili are thought to play a key role in initiating *E. coli* bladder infection; they mediate binding to mannose on the luminal surface of bladder uroepithelial cells. Toxins, metal (iron) acquisition systems, biofilm formation, and capsules also can contribute to the ability of pathogenic *E. coli* to thrive in the bladder.

APPROACH TO THE PATIENT

Clinical Syndromes

The most important issue to be addressed when a UTI is suspected is the characterization of the clinical syndrome as ASB, uncomplicated cystitis, pyelonephritis, prostatitis, or complicated UTI. This information will shape the diagnostic and therapeutic approach.

ASYMPTOMATIC BACTERIURIA

A diagnosis of ASB can be considered only when the patient does not have local or systemic symptoms referable to the urinary tract. The clinical presentation is usually bacteriuria detected incidentally when a patient undergoes a screening urine culture for a reason unrelated to the genitourinary tract. Systemic signs or symptoms such as fever, altered mental status, and leukocytosis in the setting of a positive urine culture are nonspecific and do not merit a diagnosis of symptomatic UTI unless other potential etiologies have been considered.

CYSTITIS

The typical symptoms of cystitis are dysuria, urinary frequency, and urgency. Nocturia, hesitancy, suprapubic discomfort, and gross hematuria are often noted as well. Unilateral back or flank pain suggest that the upper urinary tract is involved, and are thus inconsistent with uncomplicated cystitis. Fever likewise suggests invasive infection beyond the bladder, involving kidney, prostate, or bloodstream.

PYELONEPHRITIS

Mild pyelonephritis can present as low-grade fever with or without lower-back or costovertebral-angle pain, whereas severe pyelonephritis can manifest as high fever, rigors, nausea, vomiting, and flank and/or loin pain. Symptoms are generally acute in onset, and symptoms of cystitis may not be present. Fever is the main feature distinguishing cystitis from pyelonephritis. The fever of pyelonephritis typically exhibits a high spiking "picket-fence" pattern and resolves over 72 h of therapy. Bacteremia develops in 20–30% of cases of pyelonephritis. Patients with diabetes may present with obstructive uropathy associated with acute papillary necrosis when the sloughed papillae obstruct the ureter. Papillary necrosis may also be evident in some cases of pyelonephritis complicated by obstruction, sickle cell disease, analgesic nephropathy, or combinations of these conditions. In the rare cases of bilateral papillary necrosis, a rapid rise in the serum creatinine level may be the first indication of the condition. *Emphysematous* pyelonephritis is a particularly severe form of the disease that is associated with the production of gas in renal and perinephric tissues and occurs almost exclusively in diabetic patients **(Fig. 135-2)**. *Xanthogranulomatous* pyelonephritis occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, leads to suppurative destruction of renal tissue **(Fig. 135-3)**. On pathologic examination, the residual renal tissue frequently has a yellow coloration, with infiltration by lipid-laden macrophages. Pyelonephritis can also be complicated by intraparenchymal abscess formation; this development should be suspected when a patient has continued fever and/or bacteremia despite antibacterial therapy.

PROSTATITIS

Prostatitis includes both infectious and noninfectious abnormalities of the prostate gland. Infections can be acute or chronic, are almost always bacterial in nature, and are far less common than the noninfectious entity *chronic pelvic pain syndrome* (formerly known as chronic prostatitis). Acute bacterial prostatitis presents as dysuria, frequency, and pain in the prostatic pelvic or perineal area. Fever and chills are usually present, and symptoms of bladder outlet obstruction are common. Chronic bacterial prostatitis presents more insidiously as recurrent episodes of cystitis, sometimes with associated pelvic and perineal pain. Men who present with recurrent cystitis should be evaluated for a prostatic focus as well as urinary retention.

COMPLICATED UTI

Complicated UTI presents as a systematic illness with an infectious focus in the urinary tract and frequently occurs in patients with an anatomic predisposition to infection, such as a foreign body in the urinary tract, or with factors predisposing to a delayed response to therapy.

FIGURE 135-2

Emphysematous pyelonephritis. Infection of the right kidney of a diabetic man by *Escherichia coli*, a gas-forming, facultative anaerobic uropathogen, has led to destruction of the renal parenchyma (*arrow*) and tracking of gas through the retroperitoneal space (*arrowhead*).

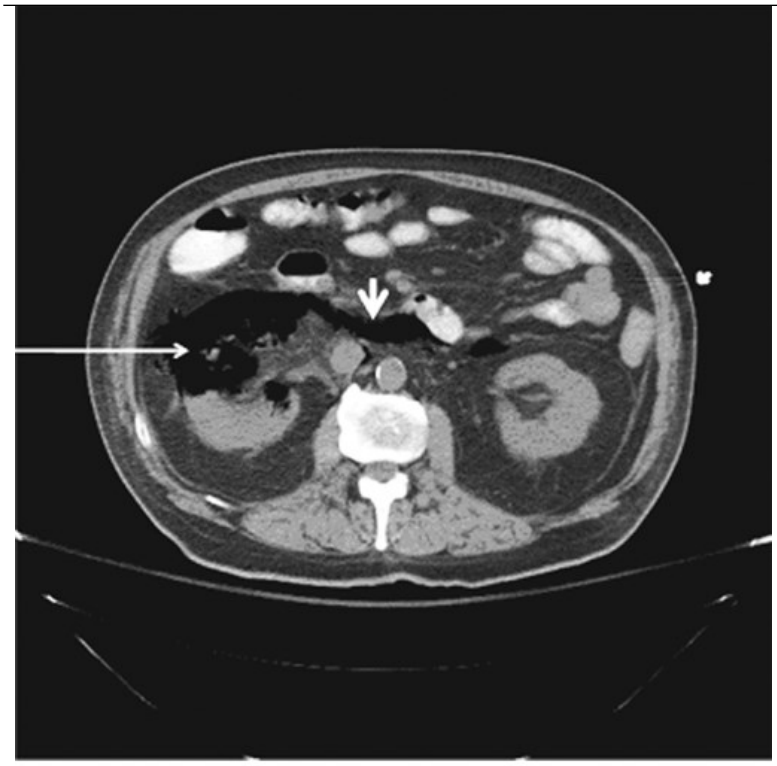
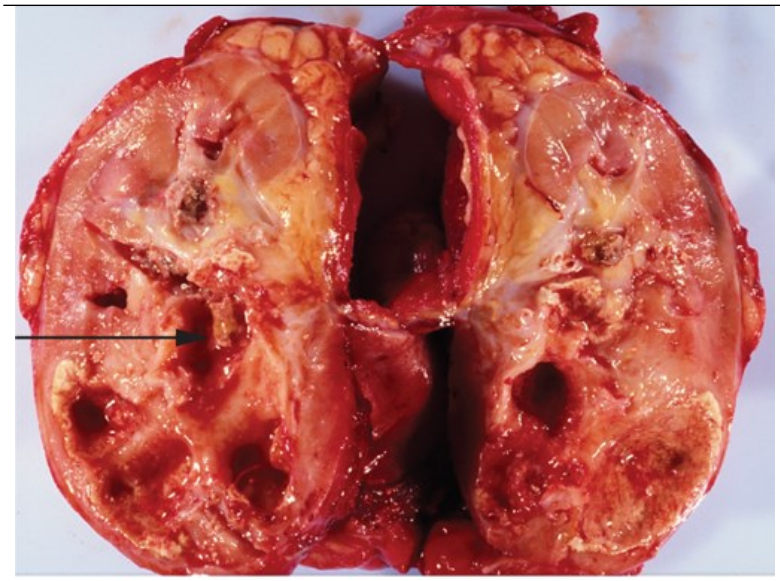


FIGURE 135-3

Xanthogranulomatous pyelonephritis. ***A.*** This photograph shows extensive destruction of renal parenchyma due to long-standing suppurative inflammation. The precipitating factor was obstruction by a staghorn calculus, which has been removed, leaving a depression (*arrow*). The mass effect of xanthogranulomatous pyelonephritis can mimic renal malignancy. ***B.*** A large staghorn calculus (*arrow*) is seen obstructing the renal pelvis and calyceal system. The lower pole of the kidney shows areas of hemorrhage and necrosis with collapse of cortical areas. *(Images courtesy of Dharam M. Ramnani, MD, Virginia Urology Pathology Laboratory, Richmond, VA.)*



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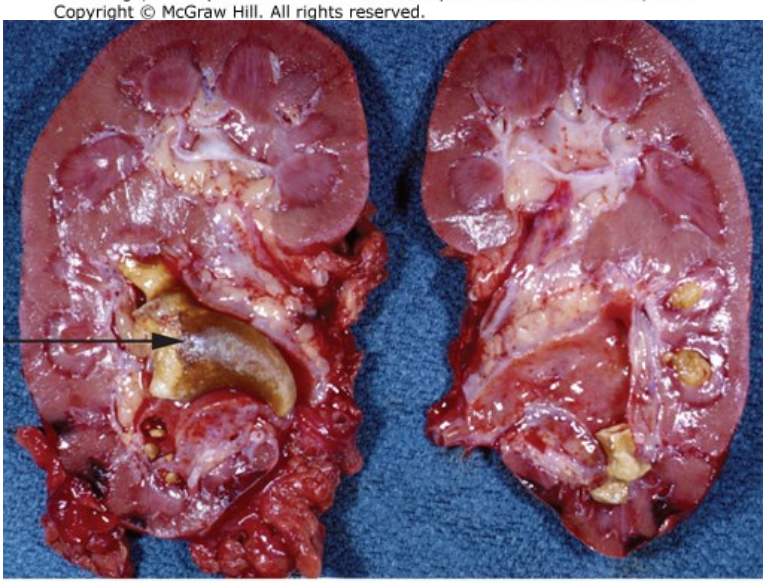


B

DIAGNOSTIC TOOLS

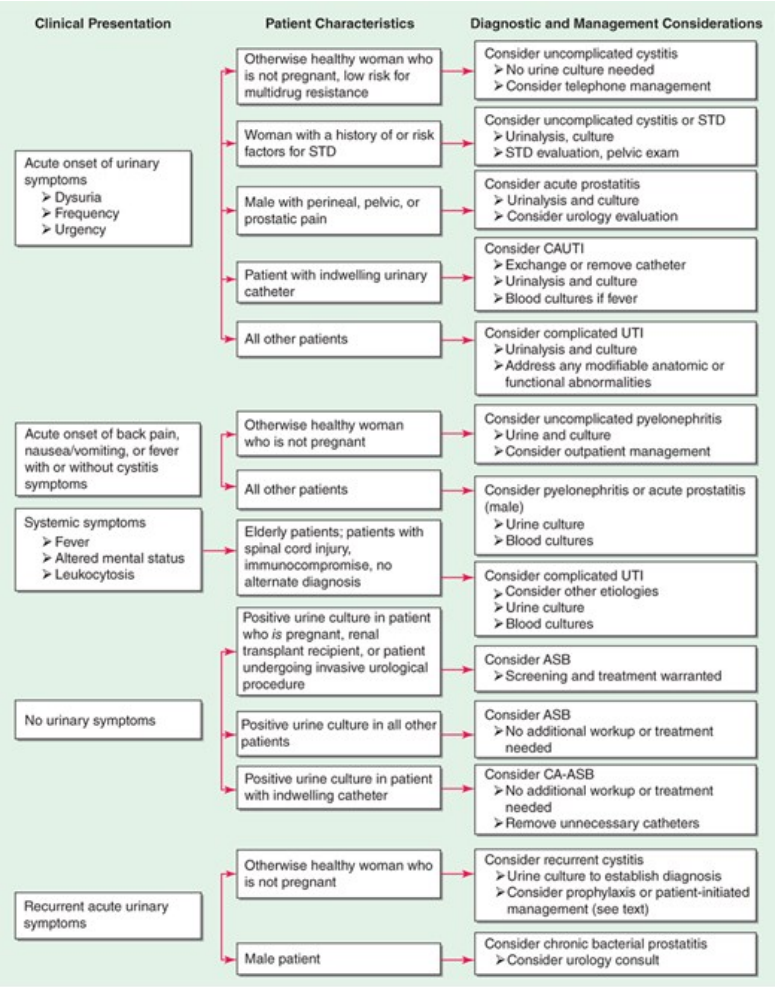
History

The diagnosis of any of the UTI syndromes or ASB begins with a detailed history **(Fig. 135-4)**. The history given by the patient has a high predictive value in uncomplicated cystitis. A meta-analysis evaluating the probability of acute UTI on the basis of history and physical findings concluded that, in women presenting with at least one symptom of UTI (dysuria, frequency, hematuria, or back pain) and without complicating factors, the probability of acute cystitis or pyelonephritis is 50%. The even higher rates of accuracy of self-diagnosis among women with recurrent UTI probably account for the success of patient-initiated treatment of recurrent cystitis. If vaginal discharge and complicating factors are absent and risk factors for UTI are present, then the probability of UTI is close to 90%, and no laboratory evaluation is needed. A combination of dysuria and urinary frequency in the absence of vaginal discharge increases the probability of UTI to 96%. Further laboratory evaluation with dipstick testing or urine culture is not necessary in such

patients before the initiation of definitive therapy, unless concern for resistant pathogens suggests a need for urine culture.

FIGURE 135-4

Diagnostic approach to urinary tract infection (UTI). ASB, asymptomatic bacteriuria; CA-ASB, catheter-associated ASB; CAUTI, catheter-associated UTI; STD, sexually transmitted disease.



In applying the patient's history as a diagnostic tool, the physician must remember that the studies included in the meta-analysis cited above did not enroll children, adolescents, pregnant women, men, or patients with complicated UTI. One significant concern is that sexually transmitted disease—that caused by *Chlamydia trachomatis* in particular—may be inappropriately treated as UTI. This concern is particularly relevant for female patients under the age of 25. The differential diagnosis to be considered when women present with dysuria includes cervicitis (*C. trachomatis*, *Neisseria gonorrhoeae*), vaginitis (*Candida albicans*, *Trichomonas vaginalis*), herpetic urethritis, interstitial cystitis, and noninfectious vaginal or vulvar irritation. Women with more than one sexual partner and inconsistent use of condoms are at high risk for both UTI and sexually transmitted disease, and symptoms alone do not always distinguish between these conditions.

Urine Dipstick Test, Urinalysis, and Urine Culture

Useful diagnostic tools include the urine dipstick test and urinalysis, both of which provide point-of-care information, and the urine culture, which can retrospectively confirm a prior diagnosis and provide organism susceptibility data for the patient's next UTI. Understanding the parameters of the dipstick test is important in interpreting its results. Only members of the family Enterobacteriaceae convert nitrate to nitrite, and enough nitrite must accumulate in the urine to reach the threshold of detection. If a woman with acute cystitis is forcing fluids and voiding frequently, the dipstick test for nitrite is less likely to be positive, even when *E. coli* is present. The leukocyte esterase test detects this enzyme in polymorphonuclear leukocytes in the

host's urine, whether the cells are intact or lysed. Many reviews have attempted to describe the diagnostic accuracy of dipstick testing. The bottom line for clinicians is that a urine dipstick test can confirm the diagnosis of uncomplicated cystitis in a patient with a reasonably high pretest probability of this disease; either nitrite or leukocyte esterase positivity can be interpreted as a positive result. Blood in the urine also may suggest a diagnosis of UTI. A dipstick test negative for both nitrite and leukocyte esterase in this type of patient should prompt consideration of other explanations for the patient's symptoms and collection of urine for culture. A negative dipstick test is not sufficiently sensitive to rule out bacteriuria in pregnant women, in whom it is important to detect all episodes of bacteriuria.

Urine microscopy reveals pyuria in nearly all cases of cystitis and hematuria in ~30% of cases. In current practice, most hospital laboratories use an automated system rather than manual examination for urine microscopy. A machine aspirates a sample of the urine and then classifies the particles in the urine by size, shape, contrast, light scatter, volume, and other properties. These automated systems can be overwhelmed by high numbers of dysmorphic red blood cells, white blood cells, or crystals; in general, counts of bacteria are less accurate than are counts of red and white blood cells. The authors' clinical recommendation is that the patient's symptoms and presentation should outweigh an incongruent result on automated urinalysis.

The detection of bacteria in a urine culture from a patient with symptoms of cystitis can confirm the diagnosis of UTI; unfortunately, however, culture results do not become available until 24 h after the patient's presentation. Furthermore, the presence of bacteriuria does not mean the patient has urinary symptoms, so a positive urine culture is consistent with both cystitis and ASB. Identifying specific organism(s) can require an additional 24 h. Studies of women with symptoms of cystitis have found that a colony count threshold of $\geq 10^2$ bacteria/mL is more sensitive (95%) and specific (85%) than a threshold of 10^5/mL for the diagnosis of acute cystitis in women. In men, the minimal level indicating infection appears to be 10^3/mL. Urine specimens frequently become contaminated with the normal microbial flora of the distal urethra, vagina, or skin. These contaminants can grow to high numbers if the collected urine is allowed to stand at room temperature. In most instances, a culture that yields mixed bacterial species is contaminated except in settings of long-term catheterization, chronic urinary retention, or the presence of a fistula between the urinary tract and the gastrointestinal or genital tract.

DIAGNOSTIC APPROACH

The approach to diagnosis is influenced by which of the clinical UTI syndromes is suspected and presence of risk factors for resistance (Fig. 135-4).

Uncomplicated Cystitis in Women

Uncomplicated cystitis in women can be treated on the basis of history alone. However, if the symptoms are not specific or if a reliable history cannot be obtained, then a urine dipstick test should be performed. A positive nitrite or leukocyte esterase result in a woman with one symptom of UTI increases the probability of UTI from 50% to ~80%, and empirical treatment can be considered without further testing. In this setting, a negative dipstick result does not rule out UTI, and a urine culture, close clinical follow-up, and possibly a pelvic examination are recommended. In women with pregnancy, suspected bacterial resistance, or recurrent UTI, a urine culture is warranted to guide appropriate therapy.

Cystitis in Men

The signs and symptoms of cystitis in men are similar to those in women, but this disease differs in several important ways in the male population. Collection of urine for culture is strongly recommended when a man has symptoms of UTI, as the documentation of bacteriuria can differentiate the less common syndromes of acute and chronic bacterial prostatitis from the very common entity of chronic pelvic pain syndrome, which is not associated with bacteriuria and thus is not usually responsive to antibacterial therapy. Men with febrile UTI often have an elevated serum level of prostate-specific antigen as well as an enlarged prostate and enlarged seminal vesicles on ultrasound—findings indicative of prostate involvement. In a study of 85 men with febrile UTI, symptoms of urinary retention, early recurrence of UTI, hematuria at follow-up, and voiding difficulties were predictive of surgically correctable disorders. Men with none of these symptoms had normal upper and lower urinary tracts on urologic workup. In general, men with a first febrile UTI should have imaging performed (CT or ultrasound); if the diagnosis is unclear or if UTI is recurrent, referral for urologic consultation is appropriate.

Asymptomatic Bacteriuria

The diagnosis of ASB involves both microbiologic and clinical criteria. The microbiologic criterion (including in urinary catheter–associated

asymptomatic bacteriuria) is ≥10^5 bacterial CFU/mL of urine. The clinical criterion is an absence of signs or symptoms referable to UTI.

TREATMENT

Urinary Tract Infections

Treatment of UTI accounts for a major proportion of antimicrobial use in ambulatory care, inpatient care, and long-term-care settings. Responsible use of antibiotics for this common infection has broad implications for preserving antibiotic effectiveness into the future. Nevertheless, antimicrobial therapy is warranted for any UTI that is truly symptomatic. The choice of antimicrobial agent, the dose, and the duration of therapy depend on the site of infection and the presence or absence of complicating conditions. Each category of UTI warrants a different approach based on the particular clinical syndrome.

Antimicrobial resistance among uropathogens varies from region to region and impacts the approach to empirical treatment of UTI. *E. coli* ST131 is the predominant multilocus sequence type found worldwide as the cause of multidrug-resistant UTI. Recommendations for treatment must be considered in the context of local resistance patterns and national differences in some agents' availability. For example, fosfomycin and pivmecillinam are not available in all countries but are considered first-line options where they are available because they retain activity against a majority of uropathogens that produce extended-spectrum β-lactamases. Thus, therapeutic choices should depend on local resistance, drug availability, and individual patient factors such as recent travel and antimicrobial use.

UNCOMPLICATED CYSTITIS IN WOMEN

Since the species and antimicrobial susceptibilities of the bacteria that cause acute uncomplicated cystitis are highly predictable, many episodes of uncomplicated cystitis can be managed over the telephone (Fig. 135-4). Most patients with other UTI syndromes require further diagnostic evaluation. Although the risk of serious complications with telephone management appears to be low, studies of telephone management algorithms generally have involved otherwise healthy women who are at low risk of complications of UTI.

In 1999, TMP-SMX was recommended as the first-line agent for treatment of uncomplicated UTI in the published guidelines of the Infectious Diseases Society of America. Since then, antibiotic resistance among uropathogens causing uncomplicated cystitis has increased, appreciation of the importance of collateral damage (as defined below) has increased, and newer agents have been studied. Unfortunately, there is no longer a single best agent for acute uncomplicated cystitis.

Collateral damage refers to the adverse ecologic effects of antimicrobial therapy, including killing of the normal flora and selection of drug-resistant organisms. The implication of collateral damage for UTI management is that a drug that is highly efficacious for the treatment of UTI is not necessarily the optimal first-line agent if it also has pronounced secondary effects on the normal flora or is likely to adversely affect resistance patterns. Drugs used for UTI that have a minimal effect on fecal flora include pivmecillinam, fosfomycin, and nitrofurantoin. In contrast, trimethoprim, TMP-SMX, quinolones, and ampicillin affect the fecal flora more significantly; these drugs are notably the agents for which rising resistance levels have been documented.

Choosing judiciously whether to initiate antibiotic therapy and then selecting the most urinary-focused agent for the shortest appropriate duration are important factors in global efforts to stem the rise of antimicrobial-resistant organisms. Several effective therapeutic regimens are available for acute uncomplicated cystitis in women **(Table 135-1)**. Well-studied first-line agents include TMP-SMX and nitrofurantoin. Second-line agents include β-lactams. There is increasing experience with the use of fosfomycin for UTIs (including complicated infections), particularly for infections caused by multidrug-resistant *E. coli*. According to an advisory from the U.S. Food and Drug Administration (FDA), fluoroquinolones should not be used for uncomplicated cystitis unless no alternatives are available. Pivmecillinam is not currently available in the United States or Canada but is a popular agent in some European countries. The pros and cons of specific agents are discussed briefly below.

Traditionally, TMP-SMX has been recommended as first-line treatment for acute cystitis, and it remains appropriate to consider the use of this drug in regions with resistance rates not exceeding 20%. In women with recurrent UTI, prior cultures can be used as a guide to TMP-SMX susceptibility, although interim acquisition of resistant bacteria can occur. TMP-SMX resistance has clinical significance: in TMP-SMX-treated patients with resistant isolates, the time to symptom resolution is longer and rates of both clinical and microbiologic failure are higher. Individual host factors associated with an elevated risk of UTI caused by a strain of *E. coli* resistant to TMP-SMX include recent use of TMP-SMX or another antimicrobial agent and recent travel to an area with high rates of TMP-SMX resistance. Prior urine cultures with an organism resistant to TMP-SMX also are a strong indication of risk of resistance in the current infection. The optimal setting for empirical use of TMP-SMX is uncomplicated UTI in a female

patient who has an established relationship with the practitioner and who can thus seek further care if her symptoms do not respond promptly.

Resistance to nitrofurantoin remains low despite >60 years of use, as several mutational steps are required for the development of bacterial resistance to this drug. Nitrofurantoin remains highly active against *E. coli* and most non–*E. coli* isolates. *Proteus*, *Pseudomonas*, *Serratia*, *Enterobacter*, and yeasts are all intrinsically resistant to this drug. Although nitrofurantoin has traditionally been prescribed as a 7-day regimen, guidelines now recommend a 5-day course, which is as effective as a 3-day course of TMP-SMX for treatment of acute cystitis; 3-day courses of nitrofurantoin are not recommended for acute cystitis. Nitrofurantoin does not reach significant levels in tissue and cannot be used to treat pyelonephritis.

Guidelines also recommend fosfomycin as a first-line agent to treat acute, uncomplicated cystitis in women. Oral fosfomycin is given as a single 3-g dose sachet (powder) that is dissolved in a glass of water and swallowed. Fosfomycin interferes with cell wall formation and is bactericidal. While fosfomycin susceptibility remains very high among *E. coli*, *Pseudomonas* is intrinsically resistant to fosfomycin, and its activity against *Klebsiella* species is unreliable. Fosfomycin susceptibility does not appear on standard, automated microbiological susceptibility reports.

Most fluoroquinolones are highly effective as short-course therapy for cystitis when the causative organism is susceptible to them; the exception is moxifloxacin, which may not reach adequate urinary levels. The fluoroquinolones commonly used for UTI include ciprofloxacin and levofloxacin. The two main concerns about fluoroquinolone use for acute cystitis are the propagation of fluoroquinolone resistance, not only among uropathogens but also among other organisms causing more serious and difficult-to-treat infections at other sites, and their rare but potentially serious adverse effects. For example, quinolone use in certain populations, including adults >60 years of age, has been associated with an increased risk of Achilles tendon rupture. Other potential side effects include irreversible neuropathy. An association with aortic dissection has been noted by both the FDA and the European Medicines Agency. In light of these detrimental effects, the FDA issued an advisory against using fluoroquinolones to treat acute cystitis in patients who have other therapeutic options.

β-Lactam agents generally have not performed as well as TMP-SMX or fluoroquinolones in acute cystitis. Rates of pathogen eradication are lower and relapse rates are higher with β-lactam drugs. The generally accepted explanation is that β-lactams fail to eradicate uropathogens from the vaginal reservoir. Many strains of *E. coli* that are resistant to TMP-SMX are also resistant to amoxicillin and cephalexin; thus, these drugs should be used only for patients infected with susceptible strains. However, given rising resistance to TMP-SMX and the goal of avoiding fluoroquinolones, oral cephalosporins (such as cefpodoxime and cefixime) are increasingly appearing in UTI treatment algorithms.

Urinary analgesics are appropriate in certain situations to speed resolution of bladder discomfort. The urinary tract analgesic phenazopyridine is widely used but can cause significant nausea. Combination analgesics containing urinary antiseptics (methenamine, methylene blue), a urine-acidifying agent (sodium phosphate), and an antispasmodic agent (hyoscyamine) also are available.

Interest in the responsible use of antibiotics has led to exploration of antibiotic-sparing approaches to the treatment of acute uncomplicated cystitis. Both placebo and analgesics alone have proved inferior to antibiotics for resolution of symptoms and prevention of pyelonephritis. Delayed therapy, in which a woman receives a prescription for antibiotics but fills it only if symptoms fail to resolve in a day or two, has the potential advantage of avoiding antibiotic use in those who either do not have cystitis to begin with or have a mild case that resolves spontaneously. The downside is that women who really do have cystitis endure discomfort for a longer period and may meanwhile progress to pyelonephritis. However, one certain measure for more responsible use of antibiotics in cystitis is to treat for the correct duration; in practice, many episodes of acute cystitis are treated longer than is recommended by evidence-based guidelines.

PYELONEPHRITIS

Since patients with pyelonephritis have tissue-invasive disease, the treatment regimen chosen should have a very high likelihood of eradicating the causative organism and should reach therapeutic blood levels quickly. High rates of TMP-SMX-resistant *E. coli* in patients with pyelonephritis have made fluoroquinolones the first-line therapy for acute uncomplicated pyelonephritis. Whether the fluoroquinolones are given orally or parenterally depends on the patient's tolerance for oral intake. A randomized clinical trial demonstrated that a 7-day course of therapy with oral ciprofloxacin (500 mg twice daily, with or without an initial IV 400-mg dose) was highly effective for the initial management of pyelonephritis in the outpatient setting. Oral TMP-SMX (one double-strength tablet twice daily for 14 days) also is effective for treatment of acute uncomplicated pyelonephritis if the uropathogen is known to be susceptible. If the pathogen's susceptibility is not known and TMP-SMX is used, an initial IV 1-g dose of ceftriaxone is recommended. Oral β-lactam agents are less effective than the fluoroquinolones and should be used with caution and close follow-up. Options for parenteral therapy for uncomplicated pyelonephritis include fluoroquinolones, an extended-spectrum cephalosporin with or without an

aminoglycoside, or a carbapenem. Combinations of a β-lactam and a β-lactamase inhibitor (e.g., ampicillin-sulbactam, piperacillin-tazobactam) or a carbapenem (imipenem-cilastatin, ertapenem, meropenem) can be used in patients with more complicated histories, previous episodes of pyelonephritis, anticipated antimicrobial resistance, or recent urinary tract manipulations; in general, the treatment of such patients should be guided by urine culture results. The treatment of very resistant organisms may require the use of newer, very broad-spectrum agents, in consultation with infectious disease specialists. Once the patient has responded clinically, oral therapy should be substituted for parenteral therapy.

UTI IN PREGNANT WOMEN

Nitrofurantoin, ampicillin, and the cephalosporins are considered relatively safe in early pregnancy. One retrospective case-control study suggesting an association between nitrofurantoin and birth defects has not been confirmed. Sulfonamides should clearly be avoided both in the first trimester (because of possible teratogenic effects) and near term (because of a possible role in the development of kernicterus). Fluoroquinolones are avoided because of possible adverse effects on fetal cartilage development. Ampicillin and the cephalosporins have been used extensively in pregnancy and are the drugs of choice for the treatment of asymptomatic or symptomatic UTI in this group of patients. Generally, pregnant women with ASB are treated for 4–7 days in the absence of evidence to support single-dose therapy. For pregnant women with overt pyelonephritis, parenteral β-lactam therapy with or without aminoglycosides is the standard of care.

UTI IN MEN

Since the prostate is involved in the majority of cases of febrile UTI in men, the goal in these patients is to eradicate the prostatic infection as well as the bladder infection. A 7- to 14-day course of a fluoroquinolone or TMP-SMX is recommended if the uropathogen is susceptible; clinical practice is tending toward the shorter, 7-day duration to reduce antibiotic exposure. If acute bacterial prostatitis is suspected, antimicrobial therapy should be initiated after urine and blood are obtained for cultures. Therapy can be tailored to urine culture results and should be continued for 2–4 weeks. For documented chronic bacterial prostatitis, a 4- to 6-week course of antibiotics is often necessary. Recurrences, which are not uncommon in chronic prostatitis, often warrant a 12-week course of treatment.

COMPLICATED UTI

Complicated UTI occurs in a heterogeneous group of patients, many with structural and functional abnormalities of the urinary tract and kidneys. The range of species and their susceptibility to antimicrobial agents are likewise heterogeneous. As a consequence, therapy for complicated UTI must be individualized and guided by urine culture results. Frequently, a patient with complicated UTI will have prior urine-culture data that can be used to guide empirical therapy while current culture results are pending. Xanthogranulomatous pyelonephritis is treated with nephrectomy. Percutaneous drainage can be used as the initial therapy in emphysematous pyelonephritis and can be followed by elective nephrectomy as needed. Papillary necrosis with obstruction requires intervention to relieve the obstruction and to preserve renal function.

ASYMPTOMATIC BACTERIURIA

Treatment of ASB does not decrease the frequency of symptomatic infections or complications except in pregnant women, persons undergoing urologic surgery, and perhaps neutropenic patients and renal transplant recipients. Treatment of ASB in pregnant women and patients undergoing urologic procedures should be directed by urine culture results. In all other populations, screening for and treatment of ASB are discouraged. The majority of cases of catheter-associated bacteriuria are asymptomatic and do not warrant antimicrobial therapy.

CATHETER-ASSOCIATED UTI

Multiple institutions have released guidelines for the treatment of CAUTI, which is defined by bacteriuria and symptoms in a catheterized patient. The signs and symptoms either are localized to the urinary tract or can include otherwise unexplained systemic manifestations, such as fever. The accepted threshold for bacteriuria to meet the definition of CAUTI is $\geq 10^3$ CFU/mL of urine, while the threshold for bacteriuria to meet the definition of ASB is $\geq 10^5$ CFU/mL.

As catheters provide a conduit for bacteria to enter the bladder, bacteriuria is inevitable with long-term catheter use. The typical signs and symptoms of UTI, including pain, urgency, dysuria, fever, peripheral leukocytosis, and pyuria, have less predictive value for the diagnosis of infection in catheterized patients. Furthermore, the presence of bacteria in the urine of a patient who is febrile and catheterized does not necessarily mean that the patient has CAUTI, and other explanations for the fever should be considered.

The etiology of CAUTI is diverse, and urine culture results are essential to guide treatment. Fairly good evidence supports the practice of catheter change during treatment for CAUTI. The goal is to remove biofilm-associated organisms that could serve as a nidus for reinfection. Pathology

studies reveal that many patients with long-term catheters have occult pyelonephritis. A randomized trial in persons with spinal cord injury who were undergoing intermittent catheterization found that relapse was more common after 3 days of therapy than after 14 days. In general, a 7- to 14-day course of antibiotics is recommended, but further studies on the optimal duration of therapy are needed.

The best strategy for prevention of CAUTI is to avoid insertion of unnecessary catheters and to remove catheters once they are no longer necessary. Quality-improvement collaboratives that have addressed technical aspects of CAUTI prevention (such as avoidance of inappropriate catheterization) as well as team communication strategies have shown the benefit of this approach in decreasing CAUTI in both acute- and long-term-care settings. Antimicrobial catheters impregnated with silver or nitrofurazone have not been shown to provide significant clinical benefit in terms of reducing rates of symptomatic UTI. Evidence is insufficient to recommend suprapubic catheters and condom catheters as alternatives to indwelling urinary catheters as a means to prevent bacteriuria. However, intermittent catheterization may be preferable to long-term indwelling urethral catheterization in certain populations (e.g., spinal cord–injured persons) to prevent both infectious and anatomic complications.

CANDIDURIA

The appearance of *Candida* in the urine is an increasingly common complication of indwelling catheterization, particularly for patients in the intensive care unit, those taking broad-spectrum antimicrobial drugs, and those with underlying diabetes mellitus. In many studies, >50% of urinary *Candida* isolates have been found to be non-*albicans* species. The clinical presentation varies from a laboratory finding without symptoms to pyelonephritis and even sepsis. Removal of the urethral catheter results in resolution of candiduria in more than one-third of asymptomatic cases. Treatment of asymptomatic patients does not appear to decrease the frequency of recurrence of candiduria. Therapy is recommended for patients who have symptomatic cystitis or pyelonephritis and for those who are at high risk for disseminated disease. High-risk patients include those with neutropenia, those who are undergoing urologic manipulation, those who are clinically unstable, and low-birth-weight infants. Fluconazole (200–400 mg/d for 7–14 days) reaches high levels in urine and is the first-line regimen for *Candida* infections of the urinary tract. Although instances of successful eradication of candiduria by some of the newer azoles and echinocandins have been reported, these agents are characterized by only low-level urinary excretion and thus are not recommended. For *Candida* isolates with high levels of resistance to fluconazole, oral flucytosine and/or parenteral amphotericin B are options. Bladder irrigation with amphotericin B generally is not recommended.

TABLE 135-1

Treatment Strategies for Acute Uncomplicated Cystitis

DRUG AND DOSE	ESTIMATED CLINICAL EFFICACY, %	ESTIMATED BACTERIAL EFFICACY,[a] %	COMMON SIDE EFFECTS
Nitrofurantoin, 100 mg bid × 5–7 d	87–95	82–92	Nausea, headache
TMP-SMX, 1 DS tablet bid × 3 d	86–100	85–100	Rash, urticaria, nausea, vomiting, hematologic abnormalities
Fosfomycin, 3-g single-dose sachet	83–95	78–98	Diarrhea, nausea, headache
Pivmecillinam, 400 mg bid × 3–7 d	55–82	74–84	Nausea, vomiting, diarrhea
Fluoroquinolones, dose varies by agent; 3-d regimen	81–98	78–96	Nausea, vomiting, diarrhea, headache, drowsiness, insomnia
β-Lactams, dose varies by agent; 5- to 7-d regimenb	79–98	74–98	Diarrhea, nausea, vomiting, rash, urticaria

[a]Microbial response as measured by reduction of bacterial counts in the urine. [b]Two trials tested cefpodoxime and one tested amoxicillin-clavulanate.

Note: Efficacy rates are averages or ranges calculated from the data and studies included in the 2010 Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases guideline for treatment of uncomplicated UTI and the 2014 *JAMA* systematic review on UTI in the outpatient setting. Ranges are estimates from published studies and may vary by specific agent and by rate of resistance.

Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

PREVENTION OF RECURRENT UTI IN WOMEN

Recurrence of uncomplicated cystitis in reproductive-age women is common, and a preventive strategy is indicated if recurrent UTIs are interfering with a patient's lifestyle. The threshold of two or more symptomatic episodes per year is not absolute; decisions about interventions should take the patient's preferences into account.

Three prophylactic strategies are available: continuous, postcoital, and patient-initiated therapy. Continuous prophylaxis and postcoital prophylaxis usually entail low doses of TMP-SMX or nitrofurantoin. These regimens are all highly effective during the period of active antibiotic intake. Typically, a prophylactic regimen is prescribed for 6 months and then discontinued, at which point the rate of recurrent UTI often returns to baseline. If bothersome infections recur, the prophylactic program can be reinstituted for a longer period. Selection of resistant strains in the fecal flora has been documented in studies of women taking prophylactic antibiotics for 12 months.

Patient-initiated therapy involves supplying the patient with materials for urine culture and with a course of antibiotics for self-medication at the first symptoms of infection. The urine culture is refrigerated and delivered to the physician's office for confirmation of the diagnosis. When an established and reliable patient–provider relationship exists, the urine culture can be omitted as long as the symptomatic episodes respond completely to short-course therapy and are not followed by relapse.

Non-antimicrobial prevention is increasingly being studied. Lactobacillus probiotics are one appealing approach to UTI prevention, but there is a paucity of data to support this strategy. Similarly, studies of cranberry products for UTI prevention have produced mixed results. Varied dosing and product composition between studies remain an issue for providing clinical guidance.

PROGNOSIS

Cystitis is a risk factor for recurrent cystitis and pyelonephritis. ASB is common among elderly and catheterized patients but does not in itself increase the risk of death. The relationships among recurrent UTI, chronic pyelonephritis, and renal insufficiency have been widely studied. In the absence of anatomic abnormalities such as reflux, recurrent infection in children and adults does not lead to chronic pyelonephritis or to renal failure. Moreover, infection does not play a primary role in chronic interstitial nephritis; the primary etiologic factors in this condition are analgesic abuse, obstruction, reflux, and toxin exposure. In the presence of underlying renal abnormalities (particularly obstructing stones), infection as a secondary factor can accelerate renal parenchymal damage.

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