

XXIII URINARY TRACT INFECTIONS

Kalpana Gupta, MD, MPH, and Walter E. Stamm, MD, FACP

Definitions

Urinary tract infection (UTI) is the most common of all bacterial infections; it affects persons throughout their life span. The term UTI encompasses a variety of clinical entities, ranging from asymptomatic bacteriuria to cystitis, prostatitis, and pyelonephritis. UTIs may be further characterized as uncomplicated (occurring without an anatomic or other predisposing reason) or complicated (associated with structural or functional abnormalities of the urinary tract and kidney) and as community acquired or nosocomial (generally, catheter associated).

Epidemiology and Risk Factors

UTI occurs far more commonly in females than in males, except at the extremes of age [see Table 1]. During the neonatal period, the incidence of UTI is slightly higher in males than in females because of the greater frequency of congenital anomalies of the urinary tract in male infants. After 50 years of age, the incidence of UTI is almost as high in men as in women, presumably because of obstruction from prostatic hypertrophy. In persons between 1 and about 50 years of age, UTI is predominantly a disease of females. Recurrent UTI, as with the initial infection, occurs more frequently in women than in men.

WOMEN

As many as 50% to 80% of women in the general population acquire at least one UTI during their lifetime; most of these infections are uncomplicated cystitis.¹ In a prospective cohort study of sexually active healthy women, the incidence of acute cystitis was 50 to 70 episodes per 100 person-years.² Recent use of a diaphragm with spermicide, frequency of sexual intercourse, and a history of UTI were identified as independent risk factors for cystitis in this study.² Cystitis has also been temporally related to recent sexual intercourse.

The incidence of acute uncomplicated pyelonephritis is difficult to ascertain because this infection is less common than cystitis and because most episodes are treated in the outpatient setting. In a recent population-based analysis of over 4,887 persons, the annual incidence of pyelonephritis in females was 12 to 13 cases per 10,000 outpatients and three to four per 10,000 inpatients³; in males, the incidence was much lower, occurring at a rate of two to three cases per 10,000 outpatients and one to two cases per 10,000 inpatients. Factors independently associated with pyelonephritis in young healthy women include frequency of sexual intercourse, having a new sexual partner, UTI in the past 12 months, maternal history of UTI, diabetes, and incontinence.⁴ Thus, many of the factors predisposing women to cystitis also increase the risk of pyelonephritis.

YOUNG MEN

UTI is rare in young men and has traditionally been attributed to the presence of urologic abnormalities.

However, it is apparent that uncomplicated UTI can occur in men who acquire uropathogens through direct sexual contact, in the form of unprotected anal intercourse with a man or a woman, or unprotected vaginal intercourse with a woman whose vagina is colonized with uropathogens.⁵ Lack of circumcision is also associated with an increased risk of UTI because of an increased incidence of *Escherichia coli* colonization of the glans and prepuce and the subsequent migration of *E. coli* to the urinary tract.^{6,7}

RECURRENT UTI

About 20% to 30% of women who have had one episode of UTI will have recurrent episodes.⁵ Recurrence may result from relapse or reinfection. Relapse in either sex is caused by the reappearance of an organism from a sequestered focus, usually within the kidney or prostate, shortly after completion of therapy. Sequestration of infecting organisms in the bladder epithelium has been demonstrated in animal models of UTI, but the importance of this phenomenon in humans is not yet clear.⁸ The recent demonstration of intracellular bacterial communities and filamentous bacteria in the urine samples of women with gram-negative acute cystitis and the absence of such findings in the urine samples of asymptomatic women and women with gram-positive uropathogens suggests that bladder invasion may play a role in the pathogenesis of recurrent UTI in a subset of women.⁹ In reinfection, the course of therapy has successfully eradicated the infection and there is no sequestered focus, but organisms are reintroduced from the fecal reservoir. The majority of recurrences are thought to be reinfections.⁵ Studies of the natural history of recurrent UTI in women have found that the rate of recurrence ranges from 0.3 to 7.6 infections per patient per year, with an average rate of 2.6 infections per year.¹⁰ Clustering of episodes occurs; it is not uncommon for multiple recurrences to follow an initial infection. The likelihood of a recurrence decreases with increasing time since the last infection. A case-control study of women with recurrent UTI identified frequency of sexual intercourse, use of spermicide, having a new sexual partner, a history of first UTI occurring before 15 years of age, and a maternal history of UTI as independent risk factors for recurrent UTI.¹¹

PREGNANCY

The incidence of asymptomatic bacteriuria in pregnant women is approximately 4% to 10%, which is similar to the rate reported in sexually active nonpregnant women of childbearing age.¹²⁻¹⁴ If not treated, 20% to 40% of pregnant women with bacteriuria in the first trimester will acquire acute pyelonephritis later in pregnancy. A meta-analysis estimated that treatment of asymptomatic bacteriuria would lead to approximately a 75% reduction in the incidence of pyelonephritis.¹⁴ Premature births and perinatal mortality are increased in pregnancies complicated by UTI.^{13,14} There

Table 1 Incidence of Urinary Tract Infection According to Age and Sex

Age Group	Incidence (%)	Approximate Sex Ratio (Male:Female)
Neonatal	1.0	1.5:1.0
Preschool age	1.5–3.0	1:10
School age	1.2	1:30
Reproductive age	3–5	1:50
Geriatric	10–30	1:1.5

is little evidence that the infections that develop during pregnancy have long-term effects.

DIABETES

The rates of asymptomatic bacteriuria and UTI in diabetic women are twofold to threefold higher than those in non-diabetic women; these differences have not been observed in men.^{15,16} A longitudinal cohort study found that the risk of UTI in diabetic women increased as the duration of diabetes increased; UTI was also more prevalent in patients who were treated with insulin as compared with oral medication.¹⁶ In hospitalized diabetic patients, particularly those with multiple-organ complications, the incidence of infection and true pyelonephritis also appears to be increased, partly because of poor bladder function and urinary catheterization. Other clinical conditions causing obstruction in urinary flow or incomplete voiding also predispose diabetic patients to infection. In addition, impaired cytokine secretion may contribute to asymptomatic bacteriuria in diabetic women.¹⁷

Etiology

The spectrum of organisms causing UTI varies by clinical syndrome. In acute uncomplicated cystitis, the etiologic agents are highly predictable: *E. coli* accounts for 75% to 90% of isolates; *Staphylococcus saprophyticus* accounts for 5% to 15% of isolates (particularly in younger women); and *Klebsiella* species, *Proteus* species, enterococci, *Citrobacter* species, and other organisms account for 5% to 10% of isolates. The spectrum of agents that cause uncomplicated pyelonephritis is less well studied than, but is similar to, that which causes acute cystitis. In complicated UTIs, *E. coli* remains the predominant organism, but other aerobic gram-negative rods, such as *Klebsiella* species, *Proteus* species, *Citrobacter* species, *Acinetobacter* species, *Morganella* species, and *Pseudomonas aeruginosa* are also frequently isolated. Gram-positive bacteria, such as enterococci, *S. aureus*, and *S. epidermidis*, as well as yeast, are also important pathogens in complicated UTI.

Pathogenesis

Bacteria can establish infection in the urinary tract by traveling from the urethra to the bladder and then up the ureter to the kidney. However, introduction of bacteria into the bladder does not inevitably lead to sustained infection. For example, bacteria often enter the bladder after sexual intercourse, but normal micturition and innate host defense mechanisms in the bladder eliminate these organisms. The

bladder mucosal surface has antibacterial properties that eliminate some organisms, presumably through mucus trapping and a polymorphonuclear leukocyte response. In addition, urine that has a low pH, high or very low osmolarity, high urea concentration, or high organic acid content inhibits bacterial growth. Abnormal micturition, a significant residual urine volume, or both will promote true infection. There are also acquired and intrinsic host factors, as well as bacterial virulence factors, which increase the likelihood of development of UTI (see below).

Bacteria can also gain access to the urinary tract through the bloodstream. However, hematogenous spread accounts for fewer than 2% of documented UTIs and usually results from bacteremia caused by relatively virulent organisms, such as *Salmonella* and *S. aureus*. Hematogenous infections may produce focal abscesses or areas of pyelonephritis within a kidney and result in positive urine cultures.

VAGINAL ECOLOGY AND UTI

In women, colonization of the vaginal introitus with organisms from the fecal flora, usually *E. coli*, is the critical initial step in the pathogenesis of UTI. Sexual intercourse and the use of a diaphragm with spermicide or of spermicide alone are strongly associated with an increased risk of *E. coli* vaginal colonization and bacteriuria, probably because of alterations in the normal vaginal microflora.¹⁸

In postmenopausal women, there is an increased incidence of gram-negative vaginal colonization and bacteriuria. These trends correlate with the changes in the vaginal environment that occur with menopause: disappearance of the previously predominant lactobacilli from the vaginal microflora and a rise in pH. A case-control study of community-dwelling postmenopausal women found significantly lower rates of vaginal colonization with lactobacilli in those women who were not taking hormone replacement therapy than in those who were using systemic or topical estrogen.¹⁹ In a randomized, placebo-controlled trial in postmenopausal women with a history of recurrent UTI, topical estrogen therapy resulted in restoration of the premenopausal vaginal flora and a decrease in both the prevalence of vaginal *E. coli* colonization and the incidence of UTI.²⁰

GENETIC FACTORS

There is increasing evidence that genetically determined factors may influence susceptibility to recurrent UTI. Women with recurrent UTI demonstrate a propensity for 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. These observations suggest that epithelial cells from susceptible women may possess specific types or greater numbers of receptors to which *E. coli* can bind, thereby facilitating colonization. This increased susceptibility is determined in part by Lewis blood group type and whether the woman secretes blood group antigens into bodily fluids. Vaginal epithelial cells from nonsecretors of blood group antigens bind significantly greater numbers of bacteria, and nonsecretors are particularly at risk for recurrent UTI.^{21,22} Mutations in host-response genes (e.g., those coding for Toll receptors and the

interleukin-8 receptor) have been linked to severity of UTIs in animals.²³ There is now evidence to suggest that an increase in susceptibility to pyelonephritis in humans is associated with polymorphisms in the IL-8 specific receptor gene *CXCR1*, the low expression of which results in incapacitation of neutrophil-dependent host defense.²⁴

BACTERIAL VIRULENCE

Certain strains of *E. coli* possess chromosomally encoded virulence determinants that confer the ability to infect the anatomically normal urinary tract and produce acute inflammatory disease (e.g., cystitis and pyelonephritis). Characteristics that have been associated with uropathogenicity are the presence of certain O and K surface antigens (the O antigen is the outer polysaccharide portion of the bacterial envelope, and the K antigen is the antiphagocytic capsular antigen), the presence of the siderophore aerobactin, resistance to the bactericidal activity of serum, the ability to produce toxins such as hemolysin and cytotoxic necrotizing factor, and certain intracellular metabolic capabilities.²⁵

Also important is the presence of adhesins on the surface of uropathogenic bacteria that mediate binding to specific receptors on the surface of uroepithelial cells. The best-studied adhesion structure is the P fimbriae, which are hairlike protein structures found on the surface of certain pathogenic strains of *E. coli*. P fimbriae interact with a specific receptor on epithelial cells. This epithelial cell receptor contains the carbohydrate moiety α -D-galactopyranosyl-(1→4)- β -D-galactopyranoside, which is found in the P blood group antigens. The prevalence of P-fimbriated *E. coli* correlates with the severity of disease the strain is likely to cause: there is a low prevalence (10% to 20%) in *E. coli* strains from the fecal flora of asymptomatic persons; there is a higher prevalence (50% to 60%) in strains that cause cystitis; and the highest prevalence (70% to 100%) is found in strains that cause pyelonephritis.^{25,26} P fimbriae also appear to be important in the pathogenesis of bloodstream invasion from the kidney. From 75% to 100% of *E. coli* strains isolated from the blood of otherwise healthy patients with pyelonephritis express P fimbriae. In contrast, *E. coli* strains that cause urosepsis in persons with compromising medical conditions are much less likely to have P fimbriae.²⁶

Another adhesion structure is the type 1 pilus (fimbria), which all *E. coli* strains possess. Type 1 pili are also thought to play a key role in initiating *E. coli* bladder infection; they mediate binding to uroplakins, which are mannosylated glycoproteins on the surface of bladder uroepithelial cells.²⁵ In addition to P fimbriae and type 1 pili, other adhesins may play a role in mediating attachment of uropathogenic strains of *E. coli* to the uroepithelium in selected circumstances.

The binding of uropathogenic *E. coli* to receptors on uroepithelial cells initiates a complex series of intracellular signaling events that alters epithelial cell function [see Figure 1].¹⁰ Chemokines and cytokines are synthesized and secreted, inflammatory cells are attracted into the bladder epithelium, and epithelial cells undergo apoptosis and exfoliation, carrying attached *E. coli* away in the urine.

ANATOMIC AND FUNCTIONAL ABNORMALITIES

Persons who have major anatomic and functional abnormalities of the urinary tract, including vesicoureteral reflux, ureteral obstruction, or a foreign body (e.g., a stone, a catheter,

or a tumor), are markedly predisposed to UTI, particularly infections involving the kidney. In such persons, UTI can develop as a result of infection with bacteria, including *E. coli* strains, that are not normally uropathogenic.²⁵ Not surprisingly, infection with nonuropathogenic strains of bacteria is also common in hospitalized patients, presumably because they have anatomic and functional abnormalities. Bacterial invasion of the prostate and incomplete bladder emptying caused by bladder outlet obstruction are the primary predisposing factors in men with UTI. Instrumentation and incomplete bladder emptying are important predisposing factors for UTI in patients with spinal cord injury or diabetes. Inhibition of ureteral peristalsis leading to vesicoureteral reflux is important in the pathogenesis of pyelonephritis in pregnant women.

Vesicoureteral reflux plays a key role in the pathogenesis of renal infection and, more important, in the evolution of chronic renal damage. It is commonly associated with UTI in children but also occurs because of anatomic abnormalities in children without UTI. Reflux provides a direct route for infection to reach the pelvicalyceal system of the kidney; severe reflux may occur intrarenally. Renal scars caused by chronic pyelonephritis are often associated with such reflux. Most reflux-associated renal damage occurs in infancy, because with growth there is a tendency for self-correction of at least mild degrees of reflux. The long-term effects of reflux on kidney structure and function are a major justification for an aggressive radiologic approach in infants and young children with UTI [see Management, below].²⁷

Diagnosis

CLINICAL PRESENTATIONS AND LABORATORY FINDINGS

The clinical presentation of UTI is quite variable, ranging from asymptomatic bacteriuria to typical symptomatic cystitis to acute pyelonephritis. In addition, clinical symptoms do not always correlate with the site of infection (bladder versus kidney) or with the degree of bacteriuria. Approximately 30% of patients with lower urinary tract symptoms also have silent infection of the kidney.⁵ Despite considerable effort, researchers have been unable to develop a noninvasive technique for differentiating renal infections from bladder infections. The best noninvasive test to delineate the anatomic site of infection appears to be the response to short-course antibiotic therapy [see Management, below].

Cystitis

The typical symptoms of cystitis are dysuria, urinary frequency, and urgency. Nocturia and suprapubic or back discomfort are also often present. In addition, the urine may be cloudy, malodorous, or bloody.

A meta-analysis evaluating the probability of UTI on the basis of history and physical findings concluded that the probability of UTI was at least 50% in a woman presenting with one or more symptoms of UTI. 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. Similarly, a combination of dysuria and frequency—the most common symptoms—in the absence of vaginal discharge increases the probability of UTI to 96%. Further laboratory evaluation with dipstick or

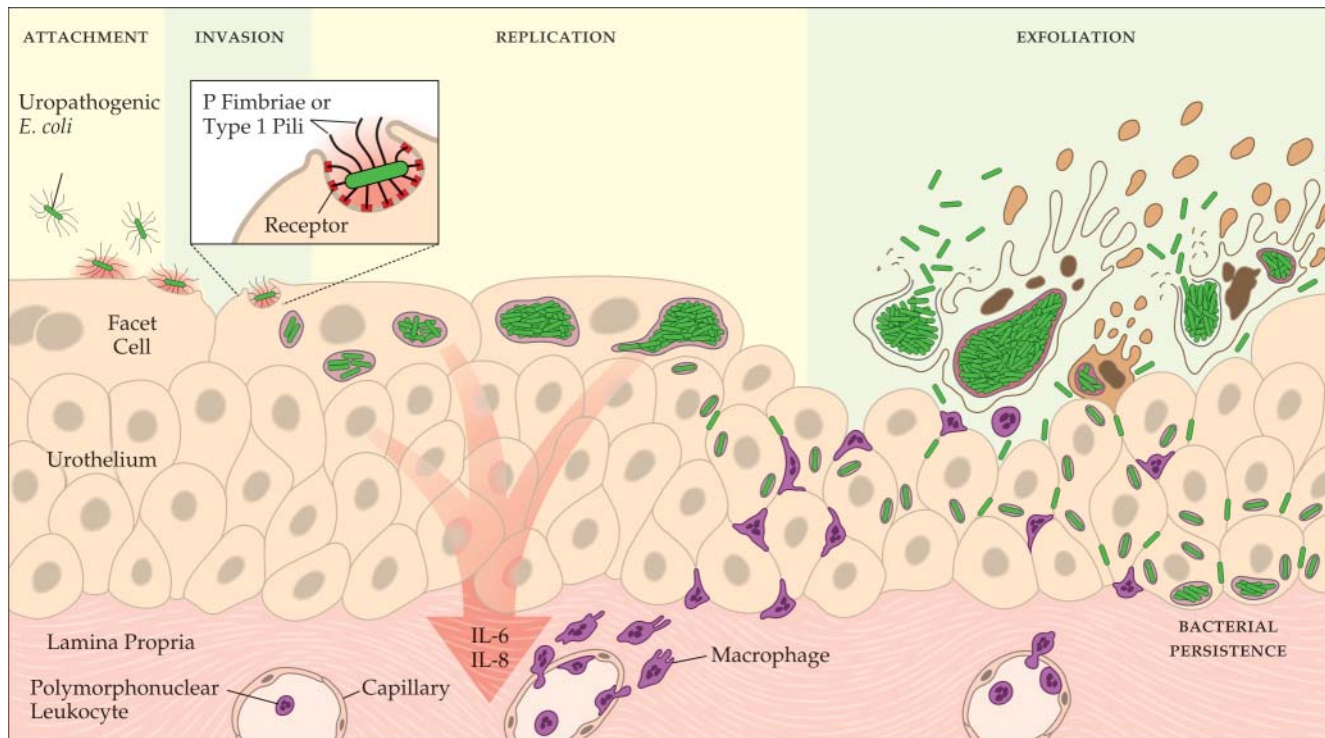


Figure 1 The pathophysiology of infection by uropathogenic *Escherichia coli* in bladder epithelial cells.²³ Uropathogenic *E. coli* organisms attach to receptors on superficial bladder cells with P fimbriae or type 1 pili. Once contact is established, the bacteria are internalized into the cells, where they can replicate to high levels. However, attachment or invasion can result in the activation of apoptotic pathways within the cells, leading to the eventual exfoliation and clearance of infected host cells. Interactions between *E. coli* and the cells can also result in the induction of inflammatory cytokines, leading to the influx of polymorphonuclear leukocytes into the bladder epithelium. *E. coli* can escape from dying cells, thereby avoiding clearance by exfoliation, and infect surrounding and underlying epithelial cells. Within the bladder epithelium, *E. coli* can escape immune surveillance and persist at subclinical levels. (IL-6—interleukin-6; IL-8—interleukin-8)

urine culture can be omitted in such patients, and empirical therapy can be considered. If the history is not clear, then a urine dipstick should be performed. A positive nitrite or leukocyte esterase result makes the probability of UTI about 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 and close clinical follow-up are recommended. Interestingly, the only physical examination finding that increased the probability of UTI was costovertebral angle tenderness (suggesting pyelonephritis), and the authors recommended that the physical examination could be omitted in patients with typical symptoms of acute uncomplicated cystitis.²⁸

On dipstick testing, the presence of leukocyte esterase, nitrite, or both has about 75% to 90% sensitivity and 70% to 82% specificity.⁵ The pH is typically elevated, and blood may be present. Depending on the clinical circumstances, it may be appropriate to follow dipstick testing with urine culture and antimicrobial-sensitivity testing [see Management, below].

Urine microscopy reveals pyuria in nearly all cases of cystitis and hematuria in about 30% of cases. Bacteriuria is demonstrable on Gram stain of unspun urine in over 90% of cases with 10^5 bacteria/ml or higher. Approximately two thirds of women presenting with clinical cystitis will have urinary colony counts of 10^5 bacteria/ml or higher. Studies

in women with symptoms of cystitis have found that a colony count threshold of greater than 10^2 bacteria/ml has greater sensitivity (95%) and specificity (85%) than a threshold of 10^5 bacteria/ml for the diagnosis of acute cystitis in women⁴ [see Bacterial Count on Urine Culture, below].

Pyelonephritis

Patients with pyelonephritis can present with clinical manifestations that range from mild to relatively severe—from low-grade fever with lower back or costovertebral angle pain to fever, shaking chills, nausea, vomiting, and loin pain. Symptoms are generally acute in onset and may or may not be associated with symptoms of cystitis.^{5,29} The primary finding on physical examination is costovertebral angle tenderness on deep palpation. Tachycardia may accompany fever. Pyuria and bacteriuria are usually demonstrable on urine microscopy and Gram stain. Bacteremia may complicate the course of pyelonephritis; but in patients with pyelonephritis, bacteremia is seldom associated with the more serious sequelae of gram-negative infection (i.e., triggering of the complement, clotting, and kinin systems), which may lead to septic shock, disseminated intravascular coagulation, or both. When shock or disseminated intravascular coagulation occurs, the possibility of obstruction must be considered. In a particularly serious form of obstructive uropathy associated with acute papillary necrosis, the

sloughed papillae may obstruct the ureter. This should be suspected in diabetic patients who have severe pyelonephritis and persistent bacteremia despite antibiotic therapy. Papillary necrosis may also be evident in some cases of pyelonephritis complicated by obstruction, sickle cell disease, analgesic nephropathy, or combinations of these conditions. Emphysematous pyelonephritis, which is a particularly severe form of pyelonephritis associated with production of gas in renal and perinephric tissues, occurs almost entirely in diabetic patients.

Renal and Perirenal Abscesses

Two unusual forms of UTI are macroscopic renal and perirenal abscesses. In the past, most of these abscesses were secondary to hematogenous infection with *S. aureus*. Currently, most of them are secondary to ascending UTI with the usual Enterobacteriaceae organisms. Such infections are often complicated by renal calculi and obstruction of urinary flow from either the kidney or the ureter. Less commonly, preexisting renal cysts become infected and develop into abscesses. In rare instances, there is contiguous spread from a neighboring site of suppuration, such as the colon or overlying rib. The usual presentation of such infections is insidious, with chronic fever, weight loss, night sweats, and anorexia, and is often associated with flank or back pain. When the abscess is under pressure, usually because of obstruction, a more acute presentation with associated bacteremia may occur. Symptoms specific to the urinary tract, such as dysuria, hematuria, and urinary retention, are sometimes noted but are often absent. On physical examination, costovertebral angle tenderness or even a palpable mass may be found; in 30% to 50% of patients, however, this finding is absent.

Routine laboratory tests are of variable value in patients with renal or perirenal abscesses: leukocytosis may be present, anemia is not unusual, and signs of inflammation (e.g., pyuria or proteinuria) may be evident on urinalysis. In more than half of patients with renal or perirenal abscesses, the organism in the abscess may be isolated on urine culture. Definitive diagnosis, however, depends on radiographic detection of a mass lesion. Gallium and ultrasound scans may be helpful, but a computed tomographic or magnetic resonance imaging scan is considered the diagnostic test of choice.³⁰ If prompt drainage and antibiotic therapy are not provided, renal or perirenal abscesses may extend to the peritoneal cavity, chest, or skin.

Prostatitis

A common complication of UTI in men is prostatitis. Bacterial prostatitis is usually caused by the same gram-negative bacilli that cause UTI in females; 80% or more of such infections are caused by *E. coli*. The pathogenesis of this condition is poorly understood. Antibacterial substances in prostatic secretions probably protect against such infections.

A National Institutes of Health expert consensus panel has recommended classifying prostatitis into three syndromes: acute bacterial prostatitis, chronic bacterial prostatitis, and chronic pelvic pain syndrome (CPPS). Acute bacterial prostatitis is a febrile illness characterized by chills; dysuria; urinary frequency and urgency; and perineal, back,

or pelvic pain. Bladder outlet obstruction may occur. On physical examination, the prostate is found to be enlarged, tender, and indurated. Pyuria is present, and urine cultures generally grow *E. coli* or another typical uropathogen. Chronic bacterial prostatitis is a clinically more occult disease and may be manifested only as recurrent bacteriuria or variable low-grade fever with back or pelvic discomfort. Urinary symptoms usually relate to the reintroduction of infection into the bladder, with both pyuria and bacteriuria being present; a chronic prostatic focus is the most common cause of recurrent UTI in men.

CPPS describes the large group of men who present with minimal signs on physical examination but have a variety of irritative or obstructive voiding symptoms; perineal, pelvic, or back pain; and sexual dysfunction. These men can be divided into those with and those without inflammation (defined as > 10 white blood cells per high-power field in expressed prostatic secretions). The etiology and appropriate management in these patients, regardless of inflammatory status, are unknown.³¹ In a placebo-controlled trial, ciprofloxacin, tamsulosin, or both did not show a significant benefit in the symptom scores of men who had had symptoms of CPPS for at least 3 of the previous 6 months; for this reason, antibiotics are not recommended in the management of men with long-standing CPPS that has proved unresponsive to an initial course of antimicrobial therapy. The potential benefit of antimicrobial therapy in patients who have not received a course of antimicrobials is under study.^{32,33}

INTERPRETATION OF URINE CULTURES

The correlation between clinical symptoms and the presence of infection is imprecise. In addition, it is frequently difficult to obtain a urine specimen that is uncontaminated by the normal microbial flora of the distal urethra, vagina, or skin. When evaluating urine cultures, therefore, the physician should consider both the species and the number of bacteria found.⁵

Species Found on Urine Culture

More than 95% of UTIs result from a single bacterial species. Thus, in most instances, a culture that grows out mixed bacterial species is contaminated and needs to be repeated. Polymicrobial infection may occur in certain settings, however, including long-term catheterization, incomplete bladder emptying because of neurologic dysfunction, and the presence of a fistula between the urinary tract and the GI or genital tract. Organisms that are commonly found in the vaginal introitus and distal urethra, such as *S. epidermidis*, diphtheroids, and lactobacilli, seldom cause UTI except in complicated settings. Another marker of contamination is the presence of squamous epithelial cells in a urine specimen. On the other hand, pyuria is highly associated with inflammation of the urinary tract, which is most commonly caused by infection.

Bacterial Count on Urine Culture

The number of organisms per milliliter of a clean-voided urine specimen is a useful indicator.⁵ The growth of 10⁵ or more colonies of a single bacterial species per milliliter of urine in two consecutive urine cultures is the diagnostic

criterion for asymptomatic bacteriuria in women. In women with acute dysuria, the presence of at least 10^2 organisms/ml of a single coliform species appears to be a more accurate criterion for infection than a threshold of 10^5 organisms/ml. Women with dysuria and pyuria who have less than 10^2 bacteria/ml may have urethritis caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or herpes simplex virus or vulvovaginitis caused by *Trichomonas vaginalis* or *Candida* species. Clinical and laboratory criteria can help differentiate these conditions [see Table 2]. In men, the minimal level indicating infection appears to be 10^3 organisms/ml. In general, probably 70% of persons with true bacterial UTI will have more than 10^5 organisms/ml; 30% will have lower concentrations of bacteria.

The presence of organisms on a Gram stain of unspun urine is highly suggestive of significant bacteriuria; however, a negative Gram stain does not rule out infection. The Gram stain has excellent sensitivity for demonstrating bacteriuria when the urine colony count exceeds 10^5 organisms/ml but has poor sensitivity at lower colony counts.

Management

ANTIMICROBIAL THERAPY

In general, antimicrobial therapy is warranted for any symptomatic infection of the urinary tract. The choice of antimicrobial agent, dose, and duration of therapy depends on the site of infection and the presence or absence of complicating conditions. Therefore, each category of UTI merits a different approach on the basis of the particular clinical syndrome that is present.

Treatment of Women with Acute Uncomplicated Cystitis

Antimicrobial therapy for healthy reproductive-age women with uncomplicated UTI should have the dual objective of eradicating the infection and eliminating uropathogenic clones of bacteria from the vaginal and GI reservoirs to prevent early recurrences. In general, the species and antimicrobial susceptibilities of the bacteria that

cause acute uncomplicated cystitis are highly predictable. Thus, in otherwise healthy women presenting with typical symptoms of acute cystitis (dysuria and frequency without signs or symptoms of vaginitis), it is safe and cost-effective to omit the urine culture and use empirical short-course therapy. Three-day therapy seems to be optimal; single-dose therapy results in higher relapse rates (probably because of failure to eradicate the uropathogen from the vaginal reservoir), and 7-day therapy offers no additional benefit but costs more and causes more side effects. Therapy for 7 days, however, should be considered in women with a history of recent UTI, symptoms of more than 7 days' duration, or diabetes.³⁴

Several effective therapeutic regimens for acute uncomplicated cystitis in women are available [see Table 3]. Traditionally, trimethoprim-sulfamethoxazole (TMP-SMX) has been recommended as first-line treatment.^{35,36} However, resistance of uropathogens to TMP-SMX is increasing and now approaches 15% to 20% in some communities.^{37,38} Because in vitro TMP-SMX resistance has been correlated with clinical and bacteriologic failure of TMP-SMX therapy, factors other than the expected prevalence of TMP-SMX resistance should also be considered. These include a history of recent use of TMP-SMX or another antimicrobial and recent travel to an area with high TMP-SMX-resistance rates.³⁸ In a study of prospectively enrolled women who had acute uncomplicated cystitis, the strongest risk factor for having a TMP-SMX-resistant uropathogen was international travel in the previous 3 months; out-of-state travel also conferred an increased risk of resistance.³⁹

In such settings, an alternative first-line agent should be considered for empirical therapy.^{34,37,38} 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 in patients infected with susceptible strains. Other β -lactams, such as amoxicillin-clavulanate or cefpodoxime, can be used but are expensive and may be associated with higher relapse rates, probably because they fail to eradicate the uropathogen from the vaginal reservoir. Nitrofurantoin remains highly active against *E. coli* and most non-*E. coli* isolates

Table 2 Common Causes of Acute Dysuria in Women⁸²

Condition	Pathogen	Laboratory Findings			Symptoms, Onset, and Factors
		Pyuria	Hematuria	Urine Culture (cfu/ml)	
Cystitis	<i>Escherichia coli</i> (most common), <i>Staphylococcus saprophyticus</i> , <i>Proteus</i> species, <i>Klebsiella</i> species	Usual	Often	10^2 to $\geq 10^5$	Abrupt onset, multiple symptoms (dysuria, increased frequency, and urgency), suprapubic or low back pain, suprapubic tenderness on examination
Urethritis	<i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> ,	Usual	Rare	$< 10^2$	Gradual onset, mild symptoms, vaginal discharge or bleeding (caused by herpes simplex virus concomitant cervicitis), lower abdominal pain, new sexual partner, cervicitis or vulvovaginal herpetic lesions on examination
Vaginitis	<i>Candida</i> species, <i>Trichomonas vaginalis</i>	Rare	Rare	$< 10^2$	Vaginal discharge or odor, pruritus, dyspareunia, external dysuria, no increased frequency or urgency, vulvovaginitis on examination

Table 3 Treatment Regimens for Acute Uncomplicated Cystitis^{5*}

Host Considerations	Empirical Treatment Regimens
Otherwise healthy woman	<p>Three-Day Regimens TMP-SMX, 160/800 mg q. 12 hr Trimethoprim, 100 mg q. 12 hr Fluoroquinolones: Ciprofloxacin, 100–250 mg q. 12 hr Ciprofloxacin XR, 500 mg q.d. Levofloxacin, 250 mg q.d.</p> <p>Five- to Seven-Day Regimens Nitrofurantoin monohydrate/ macrocrystals, 100 mg q. 12 hr Nitrofurantoin macrocrystals, 50–100 mg q.i.d. Amoxicillin, 250 mg q. 8 hr or 500 mg q. 12 hr Cephalexin, 250 mg q. 6 hr, or other cephalosporin</p>
Male sex, diabetes, symptoms for 7 days, recent antimicrobial use, age > 65 yr	<p>Consider Seven-Day Regimen TMP-SMX, 160/800 mg q. 12 hr Fluoroquinolones, as per 3-day regimen Cephalexin, 250 mg q. 6 hr, or other cephalosporin</p>
Pregnancy	<p>Consider Seven-Day Regimen Amoxicillin, 250 mg q. 8 hr or 500 mg q. 12 hr Nitrofurantoin monohydrate/ macrocrystals, 100 mg q. 12 hr Nitrofurantoin macrocrystals, 50–100 mg q.i.d. Cephalexin, 250 mg q. 6 hr, or other cephalosporin TMP-SMX, 160/800 mg q. 12 hr[†]</p>

*Characteristic pathogens are *Escherichia coli* (85% to 90%) and *Staphylococcus saprophyticus* (5% to 15%); other organisms, which account for < 5% of cases, are *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Enterococcus* species.

[†]Treatments listed are those to be prescribed before the etiologic agent is known (Gram stain can be helpful); regimens can be modified once the agent has been identified. The recommendations are limited to drugs currently approved by the Food and Drug Administration, although not all the regimens listed are approved for these indications. Optimal empirical regimen may differ among settings because of differences in the antimicrobial susceptibility profiles of uropathogens. Fluoroquinolones should not be used in pregnancy.

[‡]Although TMP-SMX is classified as pregnancy category C, it is widely used; however, avoid use of this drug in the first and third trimesters of pregnancy. TMP-SMX—trimethoprim-sulfamethoxazole.

(except for *Proteus* species, which are intrinsically resistant to the drug). Although nitrofurantoin has traditionally been prescribed as a 7-day regimen, a recent randomized trial showed similar microbiological and clinical efficacies after a 5-day course of nitrofurantoin and after a 3-day course of TMP-SMX for treatment of women with acute cystitis; these findings suggest that shorter courses of nitrofurantoin may be considered.⁴⁰ Most fluoroquinolones are effective for short-course therapy of cystitis. There is no evidence that any one quinolone is more efficacious than another, although differences exist in the adverse effect profiles of these agents.⁴¹ In a randomized trial, 3-day regimens of ciprofloxacin (100 mg twice daily), double-strength TMP-SMX (160/800 mg twice daily), or ofloxacin (200 mg twice daily) were equally effective in the treatment of acute uncomplicated cystitis in women.⁴² In separate studies, 3-day regimens of TMP-SMX and ofloxacin were found to

be equally cost-effective.^{43,44} Higher costs were associated with 3-day regimens of ampicillin, cefadroxil, and nitrofurantoin because of lower efficacy and higher rates of side effects.^{43,44} However, increasing fluoroquinolone use has been correlated with increased rates of fluoroquinolone resistance, which suggests that patients with uncomplicated cystitis should be treated with an agent other than a fluoroquinolone, if possible.^{45,46}

If a patient is still symptomatic after therapy, both urinalysis and urine culture are necessary [see Figure 2]. If the urinalysis and culture are negative, a 2-day course of the urinary tract analgesic phenazopyridine, 200 mg three times daily after meals, can be prescribed.⁴⁷ A pelvic exam for evaluation of alternative diagnoses such as chlamydial, gonococcal, or herpetic infection should be considered, and close clinical follow-up is recommended.²⁸ If testing shows pyuria but not bacteriuria, pelvic examination for alternative diagnoses should be performed. If the patient has both pyuria and bacteriuria, the antimicrobial susceptibility of the infecting strain should be assessed for resistance and an alternative agent should be given. Finally, a patient who is symptomatic after a short-course regimen and has persistent infection with a uropathogen that is sensitive to the antibiotic used should be regarded as having covert renal infection. In this circumstance, a 14-day course of a fluoroquinolone or TMP-SMX is indicated.⁵

Treatment of postmenopausal women The antimicrobial approach for postmenopausal women with symptomatic cystitis is similar to that for younger women—namely, short-course therapy with TMP-SMX or a fluoroquinolone initially; longer courses of therapy should be reserved for patients who do not respond to short-course therapy. In a randomized clinical trial of the treatment of acute cystitis in postmenopausal women, 3-day therapy with ofloxacin was more cost-effective than 7-day therapy with cephalexin.⁴⁸ In another randomized trial, 3 days of ciprofloxacin for treatment of cystitis in women 65 years of age and older was equivalent to 7 days of ciprofloxacin and associated with fewer adverse effects.⁴⁹ The major difference in the management of older women with UTI is the recognition that topical estrogen replacement, in the form of vaginal estriol cream, may decrease the incidence of recurrent UTI in postmenopausal women.²⁰ Some studies of postmenopausal women have not found a protective effect with topical estrogen, particularly when it is delivered by pessary. The effects of systemic estrogen replacement on risk of UTI have not been studied in a randomized, controlled trial, but in general, a protective effect has not been demonstrated with this intervention.^{50–52}

Treatment of recurrent UTI Recurrence of uncomplicated cystitis in reproductive-age women is common, and some form of preventive strategy is indicated if three or more symptomatic episodes occur in 1 year. A variety of antimicrobial strategies are available, but before embarking on one of them, the patient should try such simple interventions as voiding immediately after sexual intercourse and using a contraceptive method other than a diaphragm and spermicide. There is little evidence to support the former approach, but it is still often recommended, given the difficulty in adequately studying this behavior and the low morbidity associated with implementing it. Ingestion of cranberry juice has been shown to be effective

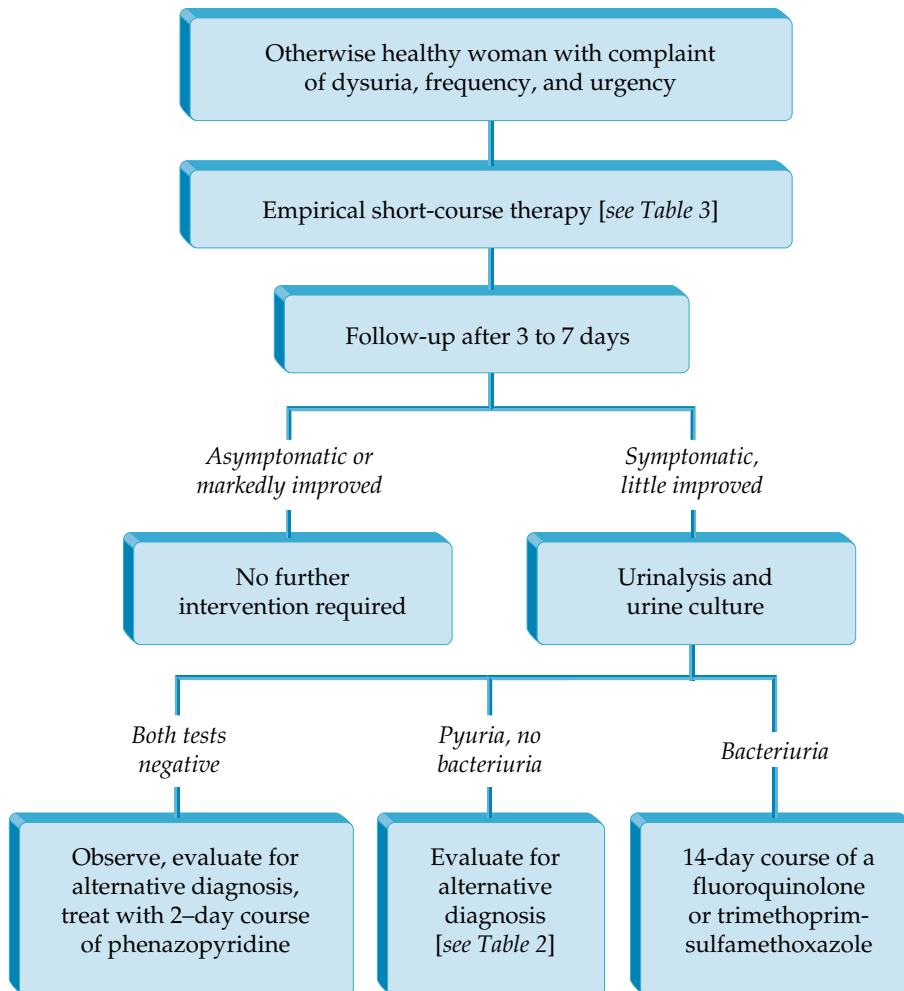


Figure 2 Clinical approach to acute uncomplicated cystitis in a woman.

in decreasing bacteriuria with pyuria, but not bacteriuria alone or symptomatic UTI, in an elderly population.⁵³ Cranberry juice was demonstrated to reduce the rate of recurrent UTI in younger women when combined with lingonberry.⁵⁴ A randomized trial comparing placebo, cranberry juice, and cranberry tablets also demonstrated a reduction in the UTI rate in young women from 32% in the placebo group to 20% with juice and 18% with tablets.⁵⁵ Thus, although the efficacy of cranberry juice for prevention of UTI needs further evaluation, there is mounting evidence that it may be effective in young otherwise healthy women.⁵⁶ This effect appears to be independent of any urinary acidification; rather, it is postulated that cranberry juice contains substances that inhibit the attachment of bacterial adhesins to the uroepithelium.⁵⁷

If simple nondrug measures are ineffective, continuous or postcoital (if the infections are temporally related to intercourse) low-dose antimicrobial prophylaxis with one of several regimens should be considered. A single dose of TMP-SMX (one half of a single-strength tablet, which amounts to 40 mg of trimethoprim and 200 mg of sulfamethoxazole), a fluoroquinolone (one tablet), or nitrofurantoin (50 mg; or 100 mg of nitrofurantoin macrocrystals) can safely and effectively decrease the rate of recurrent infections.²¹ Typically, a prophylactic regimen is initially

prescribed for 6 months and then discontinued. If the infections recur, the prophylactic program can be instituted for a longer period. Antimicrobial prophylaxis has been effectively used for as long as 5 years in preventing recurrence of infection.¹⁰

An alternative approach to antimicrobial prophylaxis for women with less frequent recurrences (fewer than four a year) is to supply the patient with TMP-SMX or a fluoroquinolone and allow her to self-medicate with short-course therapy at the first symptoms of infection. The patient is directed to keep track of the number of such episodes and to contact the physician if more than four episodes occur over a 12-month period or if symptoms persist on such therapy. This approach has been shown to be safe and effective in two separate studies of women with recurrent UTI.^{58,59}

Treatment of relapsing infection The approach to the minority of patients with relapsing infection, as evidenced by finding the same bacterial strain in a UTI that occurs within 2 weeks after completion of antimicrobial therapy, is very different from the management of reinfection. Two factors may contribute to the pathogenesis of relapsing infection in women: deep-tissue infection of the kidney that

is suppressed but not eradicated by a 14-day course of antibiotics, and structural abnormality of the urinary tract, particularly calculi. Patients with true relapsing UTIs should undergo radiologic or urologic evaluation and should be considered for longer-term therapy.

Acute Uncomplicated Pyelonephritis

Patients with clear-cut symptomatic pyelonephritis have deep-tissue infection, have (or are at risk for) bacteremia, and merit antimicrobial therapy. Two requirements guide the initial choice of antimicrobial regimens for pyelonephritis: the probability that the infecting organism is sensitive to the regimen should be at least 99%, and therapeutic blood levels should be quickly achievable. Depending on the severity of illness and the presence of comorbid conditions, pyelonephritis can be initially managed with oral outpatient therapy or with parenteral inpatient therapy. Patients with mild disease (i.e., those who have low-grade fever and no signs of sepsis) who are otherwise healthy and do not have significant nausea or vomiting can be managed as outpatients with an oral fluoroquinolone or TMP-SMX [see Figure 3 and Table 4].^{5,34,60} A randomized clinical trial

demonstrated that 7 days of therapy with oral ciprofloxacin (with or without an initial intravenous dose of the drug) was highly effective for the initial management of pyelonephritis in the outpatient setting.⁶⁰ A 5-day course of levofloxacin taken once daily has been shown to be highly effective; such a regimen is equivalent to a 10-day course of ciprofloxacin.⁶¹ Oral TMP-SMX is also very effective but should not be used unless the prevalence of TMP-SMX resistance in the area is very low or the strain is known to be susceptible.³⁴ An initial I.V. dose of ceftriaxone should be considered when oral TMP-SMX is being used, because in one study, patients receiving this combination regimen had high success rates even when the infecting strain was resistant to TMP-SMX.⁶² Amoxicillin-clavulanate should be considered if the Gram stain suggests enterococci. Regardless of which outpatient oral regimen is chosen, an initial I.V. dose of a fluoroquinolone or a third-generation cephalosporin in an observed setting may be of benefit.³⁸

Patients who are severely ill, cannot tolerate oral medication, or have complicating medical conditions should be hospitalized for parenteral therapy. Various regimens can be used, such as ampicillin plus gentamicin;

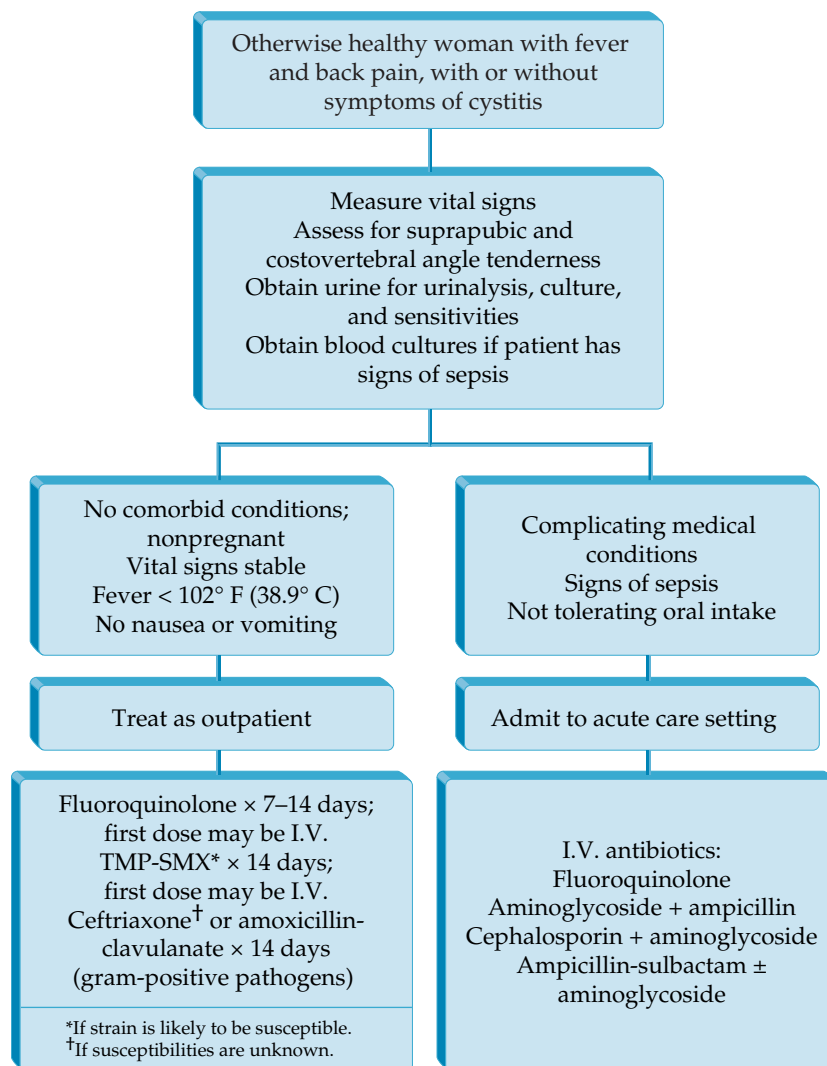


Figure 3 Clinical approach to acute uncomplicated pyelonephritis in a woman.

Table 4 Treatment Regimens for Acute Pyelonephritis⁵

Patient Status	Regimen	Comment
Outpatient	Fluoroquinolones × 5–14 days* Ciprofloxacin, 250–500 mg q. 12 hr Ciprofloxacin XR, 1,000 mg q.d. Levofloxacin, 250–750 mg q.d. TMP-SMX, 160/800 mg q. 12 hr × 14 days Amoxicillin, 500 mg q. 8 hr or 875 mg q. 12 hr Amoxicillin-clavulanate, 875/125 mg q. 12 hr × 14 days	Fluoroquinolones can be given orally throughout the entire course, if patient can tolerate oral intake If strain is likely to be susceptible If <i>Enterococcus</i> is suspected
Inpatient	I.V. fluoroquinolones × 14 days Ciprofloxacin, 200–400 mg q. 12 hr Gatifloxacin, 400 mg q.d. Levofloxacin, 250–500 mg q.d. Ceftriaxone,* 1–2 g I.V. q. 24 hr, or other third- or fourth-generation cephalosporin Ampicillin, 1 g I.V. q. 6 hr <i>plus</i> gentamicin, 1 mg/kg I.V. q. 8 hr or 3–5 mg/kg I.V. q. 24 hr Ampicillin-sulbactam Ticarcillin-clavulanate Piperacillin-tazobactam Imipenem-cilastatin	Patients can be switched to oral therapy after they have been afebrile for 24 hr Particularly useful if enterococcal infection is suspected Useful in complicated cases

*First dose of a fluoroquinolone or ceftriaxone may be given intravenously.
TMP-SMX—trimethoprim-sulfamethoxazole

fluoroquinolones; the third-generation cephalosporins (e.g., ceftriaxone); or, for susceptible strains, TMP-SMX. Combinations of a β -lactam and a β -lactamase inhibitor (e.g., ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam) or imipenem-cilastatin can be used in patients with more complicated histories, previous episodes of pyelonephritis, or recent urinary tract manipulations. After the patient has been afebrile for 24 hours (usually within 72 hours of initiating therapy), there is no benefit in maintaining parenteral therapy. Currently, prescription of oral TMP-SMX or a fluoroquinolone to complete a 14-day course of outpatient therapy appears to be the most effective means of eradicating both tissue infection and residual clones of uropathogens present in the GI tract that could cause early recurrence if allowed to remain.³⁴

UTI during Pregnancy

There are three major differences between the approach to UTI in pregnant women and that in nonpregnant women. First, in pregnant women, asymptomatic bacteriuria is actively sought and is as aggressively treated and followed as symptomatic infection; this is clearly not the case in nonpregnant women, for whom screening for asymptomatic bacteriuria is not recommended. Second, although short-course therapy is also the cornerstone of treatment during pregnancy for patients with uncomplicated cystitis (as well as those with asymptomatic bacteriuria), the drugs that can be safely used are far more limited for pregnant women. Third, follow-up of patients with bacteriuria during pregnancy is more intense, involving a more rapid deployment of prophylactic strategies in pregnant women with recurrent bacteriuria.¹³

Nitrofurantoin, ampicillin, and the cephalosporins have been considered relatively safe in early pregnancy. Sulfonamides should be avoided in the first trimester because

of possible teratogenic effects and avoided near term because of a possible role in the development of kernicterus. Trimethoprim is usually avoided because of evidence of fetal toxicity at high doses in animals, although it has been used successfully in humans during pregnancy without evidence of toxicity or teratogenicity. Fluoroquinolones are avoided because of possible adverse effects on fetal cartilage development. Nitrofurantoin, ampicillin, and the cephalosporins have been used most extensively in pregnancy and are the regimens of choice for the treatment of asymptomatic or minimally symptomatic UTI [see Table 3]. For pregnant women with overt pyelonephritis, admission to the hospital for parenteral therapy should be the standard of care; β -lactams with or without aminoglycosides are the cornerstone of therapy.^{13,62}

Prevention of UTI, including pyelonephritis, can be accomplished during pregnancy with nitrofurantoin or cephalexin taken prophylactically after coitus or at bedtime without relation to coitus. Such prophylaxis should be considered for patients who have had acute pyelonephritis during pregnancy, patients with bacteriuria during pregnancy who have had a recurrence after a course of treatment, and patients who had recurrent UTI before pregnancy that required prophylaxis.^{13,63}

Treatment of Men with UTI

It is uncommon for men to have UTI that is analogous to acute uncomplicated cystitis in women. Even when seemingly uncomplicated UTI does occur, men should never be treated with short-course therapy because of a high rate of early relapse. Instead, 7- to 14-day regimens of a fluoroquinolone should be prescribed. TMP-SMX is the best alternative drug, assuming susceptibility of the strain.⁶⁴

In men older than 50 years who have UTI, bacterial invasion of the prostate and possibly the kidneys should be

considered, even in the absence of overt signs of infection at these sites. Acute bacterial prostatitis should be treated with a fluoroquinolone for 2 weeks or with TMP-SMX for at least 4 weeks. Recurrence is common and usually connotes a sustained focus in the prostate that has not been eradicated. Several factors make eradication of prostatic foci difficult. Many antimicrobial agents do not diffuse well across the prostatic epithelium into the prostatic fluid, where the infection lies. The prostate may harbor calculi, which can block drainage of portions of the prostate gland or act as foreign bodies in which persistent infection can reside. An enlarged (and inflamed) prostate gland can cause bladder outlet obstruction, resulting in pools of stagnant urine in the bladder that are difficult to sterilize.³²

In view of these factors, intensive therapy for at least 4 to 6 weeks is recommended for chronic bacterial prostatitis. The drugs of choice for this purpose, assuming the organisms are susceptible, are the fluoroquinolones. The best alternative agent is TMP-SMX. Prolonged treatment with any of these drugs has a greater than 60% probability of eradicating infection. Most therapeutic failures result from either anatomic factors or infection by *Enterococcus faecalis* or *P. aeruginosa*; these two organisms are particularly likely to cause relapse after treatment with the antimicrobial agents currently recommended. Relapses should be treated for 12 weeks. If this therapy fails, long-term antimicrobial suppression or repeated treatment courses for each relapse are often needed.³²

Complicated UTI

Complicated UTI occurs in a heterogeneous group of patients with a wide variety of structural and functional abnormalities of the urinary tract and kidneys. The range of antimicrobial species and their susceptibility to antimicrobial agents are likewise heterogeneous. As a consequence, therapy for patients with complicated UTI requires individualization, although the following guidelines appear to be useful⁶⁵:

- As a rule, only symptomatic UTI requires therapy.
- If symptoms of UTI are present, a urine culture and susceptibilities should always be obtained.
- If the antimicrobial susceptibilities of the infecting organism are not known and symptomatic infection requires immediate therapy, consideration of previous microbiology or recent antimicrobial exposures can help guide initial empirical therapy.
- In patients with mild disease [see Pyelonephritis, above]), an oral regimen with a fluoroquinolone, or possibly TMP-SMX, is appropriate and can be given in the outpatient or inpatient setting depending on other patient factors.
- In patients who cannot take oral regimens or who have more severe disease, intravenous therapy with fluoroquinolones or broad-spectrum agents such as ampicillin plus gentamicin, imipenem-cilastatin, or piperacillin-tazobactam should be considered until the susceptibilities of the invading organism are identified [see Table 4].
- Whenever possible, every effort should be made to correct the underlying complicating factor in conjunction with the antimicrobial therapy.

Asymptomatic Bacteriuria

Bacteriuria detected in the absence of symptoms referable to the urinary tract does not warrant antimicrobial therapy except in specific settings. These include during pregnancy, before surgery or instrumentation of the urinary tract, and after renal transplantation. Treatment of asymptomatic bacteriuria in patients who are immunosuppressed because of transplantation other than renal (i.e., other solid organ or bone marrow) or because of neutropenia has not been well studied and is not currently recommended as standard practice.

In women with diabetes and asymptomatic bacteriuria, a large randomized trial of antimicrobial treatment versus no antimicrobials found no difference in the time to first symptomatic UTI between the groups. The authors conclude that there is no benefit to screening for asymptomatic bacteriuria or treating it in women with diabetes.⁶⁶

RADIOLOGIC EVALUATION TO RULE OUT FUNCTIONAL ABNORMALITIES

A final consideration in the management of UTI is the role of radiologic evaluation. Intravenous pyelography, ultrasonography, or CT should be carried out expeditiously to rule out obstruction in any patient with acute pyelonephritis who does not respond to an effective antimicrobial agent and in any patient in whom a persistent bacteremia has been demonstrated. Contrast-enhanced helical CT is the radiologic study of choice for imaging and evaluation of renal infections. The study should be performed without contrast when renal calculi are suspected.³⁰

For ambulatory patients who have UTI, guidelines are less clear. Radiographic evaluation, usually with intravenous pyelography and voiding cystourethrography, is carried out for delineation of surgically correctable lesions that might predispose patients to recurrent infection or progressive renal disease. Because congenital anatomic anomalies are particularly prevalent in young children who have a first or second UTI, such studies are obligatory for patients in this age group. In addition, careful prostatic examination and assessment of postvoiding residual urine volume should be considered in males with UTI at any stage of life because such infection is highly unlikely in this population unless anatomic anomalies or specific risk factors are present⁶⁶ [see Young Men, above]. In women with uncomplicated UTI, the incidence of correctable anatomic lesions is so low that radiologic and urologic evaluation should be restricted to patients who have rapid recurrence of infection or recurrent pyelonephritis despite adequate therapy.³⁰

Catheter-Associated UTI

UTIs are the most common nosocomial infections, representing 40% of all such infections. Most nosocomial UTIs are related to bladder catheterization. Catheter-associated UTIs are associated with increased mortality and costs.^{67,68} Multiple risk factors for catheter-associated UTIs have been identified, including the duration of catheterization, lack of systemic antibiotic therapy, female sex, age older than 50 years, and azotemia.⁶⁸ Risk factors for bacteremia related to catheter-associated UTI are not well established.

Several guidelines can be followed to minimize the occurrence of catheter-related infection [see Table 5]. Most important, the catheter should be inserted with strict aseptic technique by trained persons. In addition, a closed system should be used at all times. Even with optimal care, however, catheter use for 1 month or longer will eventually result in bladder infection. Apparently, little additional protection is provided by antibiotic rinses for the bladder, antibiotic ointments applied to the urethral meatus, and instillation of disinfectants such as hydrogen peroxide into the urinary collection bag. Although systemic antibiotics are of no value when the closed system is to be in place for an extended period, antibiotics may be protective when the catheter is in place for only a few days.⁶⁷ However, this advantage should be balanced against the risk of selecting for resistant flora if catheterization must be prolonged unexpectedly. In patients who require urethral catheterization for 2 to 10 days, use of a silver alloy-coated urinary catheter may offer some protection against infection.⁶⁹⁻⁷¹ In one randomized study of hospitalized patients, the use of a silver alloy-coated urinary catheter resulted in a lower rate of UTIs and a significant cost savings.⁷⁰ A nitrofurazone-impregnated catheter also has been shown to decrease the incidence of UTIs caused by gram-negative organisms.^{71,72}

Treatment of catheter-associated UTI depends on the clinical circumstances. Symptomatic patients (e.g., those with fever, chills, dyspnea, and hypotension) require immediate antibiotic therapy [see Complicated UTI, above]. In addition, it may be useful to remove and replace the urinary catheter if it has been in place for a week or longer. This eliminates difficult-to-eradicate organisms in the biofilm on the catheter. In an asymptomatic patient, therapy should be postponed until the catheter can be removed. Patients with persistent asymptomatic bacteriuria and those with lower urinary tract symptoms who have had the catheter removed respond well to short-course therapy.⁷³

Patients with long-term indwelling catheters seldom become symptomatic unless the catheter is obstructed or is eroding through the bladder mucosa. In patients who do

become symptomatic, appropriate antibiotics should be administered, and the catheter should be changed. Therapy for asymptomatic catheterized patients leads to the selection of increasingly antibiotic-resistant bacteria.^{67,68,71} Thus, although long-term bladder catheterization carries a significant risk of chronic pyelonephritis (10% or more if the catheter is in place for more than 90 days), there is no way to avoid this event other than by catheter removal.⁷⁴

The appearance of *Candida* in the urine is an increasingly common complication of indwelling catheterization, particularly for patients in the intensive care unit, on broad-spectrum antimicrobials, or with underlying diabetes mellitus.⁷⁵ *C. albicans* is still the most common isolate, although *C. glabrata* and other non-*albicans* species are also frequently isolated. The clinical presentation can vary from an asymptomatic laboratory finding to sepsis. In asymptomatic patients, removal of the urethral catheter results in resolution of the candiduria in as many as one third of cases. Treatment is recommended for patients with symptomatic candiduria (fever with or without cystitis symptoms), neutropenia, renal allografts; for patients who are undergoing urologic manipulation; and for low-birth-weight infants.⁷⁶ For adults who have candiduria, oral fluconazole, 200 mg/day for 7 to 14 days, is highly effective. It also has been shown to be effective for non-*albicans* species of *Candida* that have reduced susceptibility to fluconazole; the effectiveness of oral fluconazole against these organisms may be explained by the high concentrations that the drug achieves in the urine. Oral flucytosine, 25 mg/kg every 6 hours, may also be considered in patients who do not have renal insufficiency and are infected with non-*albicans* *Candida* species, although the development of resistance may occur rapidly when this agent is used alone.⁷⁶ For more severely ill patients, the possibility of pyelonephritis and candidemia should be evaluated, and systemic antifungal therapy with fluconazole, 6 mg/kg/day, or amphotericin, 0.6 mg/kg or more a day, should be instituted. The newer azoles and echinocandins have low urinary excretion and thus are not recommended for treatment of candiduria, although caspofungin has been reported to eradicate renal candidiasis and secondary candiduria in a case series.⁷⁷

Prognosis

Although earlier epidemiologic studies suggested that bacteriuria, whether symptomatic or asymptomatic, was associated with increased mortality, more recent findings suggest that bacteriuria does not itself cause an increase in mortality.⁷⁸ Rather, bacteriuria appears to be a marker for poor health, particularly in elderly patients. Not surprisingly, then, antimicrobial therapy for asymptomatic bacteriuria in the elderly is of no demonstrable clinical benefit.^{79,80}

The relationships between recurrent UTI, chronic pyelonephritis, and renal insufficiency have been widely studied. In the absence of anatomic abnormalities, recurrent infection in children and adults does not lead to chronic pyelonephritis or to renal failure. Also, 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

Table 5 Guidelines for Bladder Catheter Care

Use catheters only when absolutely necessary; remove as soon as possible.
Insert catheters aseptically and maintain by trained personnel only.
A sterile closed drainage system is mandatory. The catheter and drainage tube must never be disconnected except when irrigation is necessary to relieve obstruction. Strict aseptic technique is employed under these circumstances.
Obtain urine for culture by aspirating the catheter with a 21-gauge needle after the catheter is prepared with povidone-iodine.
Maintain downhill, nonobstructed flow, with the collection bag always below the level of the bladder and emptied at frequent intervals.
Replace indwelling catheters when obstruction or concretions are demonstrated.
Strict hand-washing precautions should be observed by staff caring for these patients.
Administer prophylactic antibiotics during catheter insertion and removal to patients with cardiac disease (particularly prosthetic valves) that predisposes to bacterial endocarditis.

underlying renal abnormalities, however, infection as a secondary factor can accelerate renal parenchymal damage. In children, the common combination of reflux, congenital anomalies, and infection appears to lead to significant renal parenchymal damage; moreover, kidneys in children appear to be more susceptible to damage than kidneys in adults.²⁷

A retrospective questionnaire study has found that men and women newly diagnosed with renal cell carcinoma were more likely to have a history of cystitis or pyelonephritis sometime in their lifetime and to be smokers than persons without renal cell carcinoma.⁸¹ The risk was greater for males than females. Although the study shows a possible association between UTI and renal cell cancer, data on causality, temporal relatedness, dose effect, and putative mechanisms are lacking.

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Figure 1 Seward Hung.