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colectomy should be performed before the serum lactate level reaches 5 mmol/L. However, mortality and morbidity associated with colectomy may be reduced by performing instead a laparo scopic ileostomy followed by colon lavage with polyethylene glycol and vancomycin infusion into the colon via the ileostomy.

■ ■PROGNOSIS The mortality rate attributed to CDI, previously found to be 0.6–3.5%, has reached 6.9% in recent outbreaks and is progressively higher with increasing age. Most patients recover, but recurrences are common. ■ ■PREVENTION AND CONTROL Strategies for the prevention of CDI are of two types: those aimed at preventing transmission of the organism to the patient and those aimed at reducing the risk of CDI if the organism is transmitted. Transmission of C. difficile in clinical practice has been prevented by gloving of personnel, elimination of the use of contaminated electronic thermometers, and use of hypochlorite (bleach) solution for environ mental decontamination of patients' rooms. Hand hygiene is critical; hand washing is recommended in CDI outbreaks because alcohol hand gels are not sporicidal. CDI outbreaks have been best controlled by restricting the use of specific antibiotics, such as clindamycin, second- and third-generation cephalosporins, and fluoroquinolones. Outbreaks of CDI due to antibiotic-resistant strains have resolved promptly when specific antibiotic use is restricted. Future primary prevention strate gies include use of monoclonal antibodies, as well as biotherapeutics with live organisms to prevent colonization. Vaccines have to date been unsuccessful. PART 5 Infectious Diseases ■ ■FURTHER READING Dingle KE et al: Effects of control interventions on Clostridium difficile infection in England: An observational study. Lancet Infect Dis 17:411, 2017. Feuerstadt P et al: SER-109, an oral microbiome therapy for recur rent Clostridioides difficile infection. N Engl J Med 386:220, 2022. Guh AY et al: Trends in U.S. burden of Clostridioides difficile infection and

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Urinary Tract Infections:

Cystitis, Prostatitis, and Pyelonephritis Barbara W. Trautner, Prathit A. Kulkarni,

Nicolás W. Cortés-Penfield, Kalpana Gupta In the preantibiotic era, urinary tract infection (UTI) caused significant morbidity. Hippocrates described acute cystitis as sometimes lasting for a year before either resolving or worsening to involve the kidneys. Early twentieth-century chemotherapeutics for UTI were ineffective, and persistent infection was common. Nitrofurantoin, which became available during the 1950s, was the first tolerable and effective agent for UTI treatment. Today, UTI remains common, being one of the leading reasons for which antibiotics are used within and outside the hospital. Patients typically favorably and quickly to appropriately chosen mod ern antimicrobials. Since the most common manifestation of UTI is acute cystitis, which is far more prevalent among women than among men, most clinical research on UTI has involved healthy young adult women recruited from college campuses or large U.S. health maintenance organizations. Therefore, clinicians must understand that UTI remains relatively under studied in other patient populations, and they must use expert judgment to decide when and to what extent UTI clinical trial data and treatment guidelines can be generalized to other groups of patients. ■ ■DEFINITIONS The term urinary tract infection refers to an infection somewhere along the urinary tract that produces clinical symptoms. Infection can be caused either by bladder invasion by a new urinary pathogen or by a shift in the existing urinary bacteria’s dynamic equilibrium with the host; both causes result in local tissue injury and inflammation. Thus, while UTI encompasses a broad range of clinical presentations, from acute simple cystitis to bacteremic emphysematous pyelonephritis, importantly, the presence alone of bacteria in the urinary tract in a patient without related symptoms does not constitute UTI. The pres ence of bacteria in the urine

without associated symptoms is instead termed asymptomatic bacteriuria (ASB). This distinction between UTI and ASB has major clinical impli cations. Both UTI and ASB connote the presence of bacteria in the urinary tract and are usually accompanied by white blood cells in the urine (termed pyuria). However, while antibiotic treatment of UTI is almost always indicated to relieve the symptoms attributable to urinary bacterial infection and to prevent progression of the infection, ASB typically poses no threat for most patients and usually does not require treatment. Limited data suggest inappropriate treatment of ASB might in fact increase risk for future UTI, perhaps by facilitating bladder colo nization with more virulent and potentially more resistant pathogens. Two exceptions to the general rule that ASB should not be treated are patients who are pregnant or who are about to undergo certain urologic procedures. In pregnant patients, untreated ASB is associated with pyelonephritis, preterm delivery, and low birth weight, which justifies use of routine ASB screening and treatment. In patients undergoing procedures that cause urologic mucosal injury (e.g., lithotripsy or transurethral resection of the prostate), bacterial translocation from urine to blood can occur; therefore, screening for, and periprocedural treatment of, ASB is recommended in this setting. In this chapter, the term urinary tract infection denotes symptom atic disease; cystitis, symptomatic infection of the bladder; prostatitis, symptomatic infection of the prostate; and pyelonephritis, symptomatic infection of the kidneys. Uncomplicated urinary tract infection refers to an infection confined to the bladder in a woman or man without a urinary catheter, whereas complicated urinary tract infection refers to infection that extends beyond the bladder (e.g., prostatitis, pyelone phritis, bacteremia, or UTI in the setting of intermittent or indwelling

urinary catheterization, termed catheter-associated UTI [CAUTI]). Recurrent urinary tract infection is not necessarily complicated; indi vidual episodes can be uncomplicated and treated as such. This approach to UTI categorization differs from the classic approach, in which UTI in men and other populations perceived to be at higher risk for poor outcome (e.g., patients with diabetes, anatomic abnormali ties of the urinary tract, or immunocompromise) was automatically considered complicated. The new updated approach more closely reflects actual clinical practice. For the frontline clinician, the key con siderations in diagnostic workup and therapy for UTI include whether the patient is stable for outpatient management, whether a source of recalcitrant and/or recurrent infection (e.g., obstructing renal calculi) needs to be identified, and whether the prescribed antimicrobial agents must achieve adequate levels in the blood and renal tissue in addition to the urine. Prostatitis, usually categorized as either acute bacterial prostatitis (ABP) or chronic bacterial prostatitis (CBP), can complicate cystitis or arise hematogenously (e.g., as a metastatic focus of Staphylococcus aureus bacteremia) in men and transgender women. While prostatitis is certainly an infection of the genitourinary tract, it is largely unrepre sented in UTI clinical trial data, and earlier ABP literature suggests that prolonged therapy with antimicrobials penetrating the prostate might be required. Therefore, clinical practice guidelines for complicated UTI cannot be assumed to be generalizable to patients with prostatitis. Urethritis is occasionally caused by Escherichia coli and other urinary pathogens but is predominantly due to Neisseria gonorrhea, Chlamydia trachomatis, and Mycoplasma genitalium. Hence, symptoms such as urethral pain, pruritus, or discharge should prompt evaluation for sexually transmitted infections (STIs), which are covered in Chap. 141. ■ ■EPIDEMIOLOGY AND RISK FACTORS During the neonatal period, the incidence of UTI is slightly higher among males than among females because male infants more com monly have congenital urinary tract anomalies. After 50 years of age, obstruction from prostatic hypertrophy becomes common in men, and incidence of UTI is almost as high among men as among women. Between 1 year and ~50 years of age, however, UTI and recurrent UTI are predominantly

conditions of females, with most true male UTI occurring in the context of urinary catheterization or anatomic abnormalities. The prevalence of ASB is ~5% among women between ages 20 and 40 and might be as high as 40–50% among elderly women and men. Up to 80% of women develop at least one UTI during their lifetime, predominantly acute simple cystitis. The lifetime prevalence of UTI in men in the United States is estimated to be 14%. 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 might indicate the need to evaluate the patient for a sequestered focus of ongoing infection. The rate of UTI recurrence ranges from 0.3 to 7.6 infections per patient per year, with an average of 2.6 reinfections per year. It is not uncom mon for multiple recurrences to follow an initial infection, resulting in clustering of episodes. Clustering may be related to the presence of a new risk factor, sloughing of the protective outer bladder epithelial layer in response to bacterial attachment during acute cystitis, or possibly

antibiotic-related alteration of the normal bacterial flora. The likelihood of recurrence decreases with increasing time since the last infection. Risk factors for recurrent UTI include frequent sexual intercourse, use of spermicide, a new sexual partner, first UTI before 15 years of age, and maternal history of UTI; of these, frequent sexual intercourse and sper micide use are the most consistently documented risk factors. Some component of UTI susceptibility is likely hereditary, as family and maternal history of UTI has been identified as a risk factor for cys titis, pyelonephritis, and recurrent UTI. In addition, colonization with specific bacterial strains predisposed to cause infection might also be an important factor, as suggested by studies indicating that new sexual part ners are a risk factor for UTI in women and that uropathogenic E. coli are shared between partners via vaginal and oral sex. Beyond this, risk factors for UTI can be grouped broadly into three categories: (1) factors that impede the normal outflow of urine, (2) factors that introduce new

bacteria into the genitourinary tract or serve as a nidus of infection, and (3) factors that disrupt or impair local mucosal defenses.

The flushing action of normal urination is a key mechanism by which the host controls urinary bacterial populations and mitigates bacterial ascent from the urethra to the bladder and kidneys. Ana tomic factors that result in urinary obstruction or retention have been associated with cystitis, pyelonephritis, and recurrent UTI. These risk factors include congenital urinary tract abnormalities, cystoceles, pelvic-organ prolapse, bladder dysfunction leading to overflow urinary incontinence, and benign prostatic hypertrophy. Importantly, not all men with UTI have detectable urinary tract abnormalities; this point is particularly relevant for men ≤45 years of age. Factors that promote bacterial entry into the urinary tract predis pose to UTI. Sexual activity is likely the most common among these and is temporally associated with cystitis, with an increased relative risk in one study ranging from 1.4 with weekly intercourse to 4.8 with intercourse five times weekly. For men, insertive rectal intercourse and lack of circumcision are associated with increased UTI risk, the latter likely because E. coli is tends to colonize the glans and prepuce and subsequently migrate into the urinary tract. For men and women, urinary instrumentation (e.g., intermittent or chronic catheterization or existence of a draining nephrostomy tube) dramatically increases bacterial entry into the urinary tract and risk of UTI. In addition, for eign bodies in the urinary tract (e.g., stents and kidney stones) also can become colonized with bacteria and serve as niduses for recurrent UTI. Factors that disrupt or impair local mucosal defenses, usually either by irritating the urogenital mucosa or by disrupting the normal female urogenital microbiome (i.e., symbiotic lactobacilli),

predispose to UTI. Such factors include recent use of diaphragms or spermicide and menopause. Women with diabetes have two- to threefold higher rates of ASB and UTI than women without diabetes, and this risk increases further with a longer duration of having had diabetes and with the need for insulin rather than oral medications. The specific mechanisms for this risk are not clear, although impaired cytokine secretion or diabetes complications leading to bladder dysfunction likely contribute. Whether glycosuria is major contributor to UTI risk remains controversial. The U.S. Food and Drug Administration has issued a drug-safety warning for the observed association between use sodium–glucose cotransporter 2 (SGLT-2) inhibitors for treatment of diabetes and UTI. The postulated mechanism is that these drugs increase excretion of glucose in the urine. CHAPTER 140 Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis ■ ■ETIOLOGY E. coli is the predominant pathogen across the spectra of UTI clinical syndromes and patient populations. In cases of acute cystitis in the United States, E. coli accounts for 75–90% of isolates, Staphylococcus saprophyticus for 5–15% (with more frequent isolation from younger women), and other Enterobacterales species (i.e., Klebsiella, Proteus, Enterobacter, and Citrobacter) for the majority of the remainder. The microbiology of pyelonephritis is similar to that of acute cystitis, as would be expected since pyelonephritis usually develops as ascend ing infection from the bladder. The microbiology of CAUTI is more diverse, but E. coli remains the predominant organism. Other impor tant pathogens in CAUTI are Pseudomonas aeruginosa, enterococci, Staphylococcus aureus, and Candida. Genetic sequencing of the bladder microbiome has consistently demonstrated that more bacterial spe cies are present than can be identified by routine culture methods, in both symptomatic and asymptomatic states. The clinical significance of these noncultivable organisms is unknown, but such work demon strates that the healthy bladder is often not a sterile site. Antimicrobial resistance among Enterobacterales species that cause UTI is increasing. One recent surveillance study of isolates from the United States demonstrated resistance rates of >20% to trimethoprimsulfamethoxazole (TMP-SMX), fluroquinolones, and nitrofurantoin among ambulatory patients in many regions of the country. In addi tion, approximately 6% of isolates were resistant to three or more antibiotic classes, and approximately 9% of isolates had production of extended-spectrum β-lactamase. Surveillance studies conducted in South America and Europe have yielded similar findings. The increased

prevalence of multidrug-resistant uropathogens has left few oral options for therapy in some cases and no single agent or agents that can confidently be recommended for empirical ambulatory treatment of UTI without regard to geographic region. Since resistance rates vary in different areas, local antibiogram data can help inform which drugs should be used as preferred empirical therapy in UTI, with the caveat that organisms are identified only in cases in which urine is sent for culture—typically, when complicated or recurrent UTI is suspected— and so may overestimate antimicrobial resistance in healthy ambula tory patients with a primary episode of UTI.

■ ■PATHOGENESIS The urinary tract can be viewed as an anatomic unit linked by a con tinuous column of urine extending from the kidneys to the urethra. 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. The other main route of entry into the genitourinary tract is hematogenous in cases where bacteremia precedes UTI. Importantly, 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. 140-1). For example, bacteria often enter the

bladder after sexual intercourse, but normal voiding and innate host defense mecha nisms 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. Additionally, abnormal micturition and/or significant residual urine volume promotes infection. In the simplest terms, anything that increases the likelihood of bacteria enter ing the bladder and staying there increases risk of developing UTI. 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. PART 5 Infectious Diseases Bacteria can also gain access to the urinary tract through the blood stream. However, hematogenous spread only accounts for less than 2% of documented UTIs and usually results from bacteremia caused by relatively virulent organisms, such as S. aureus and Salmonella. The isolation of either of these pathogens from a urine culture warrants consideration of concomitant bacteremia. Hematogenous infections can also produce focal renal abscesses or pyelonephritis. The pathogenesis of candiduria in particular is distinct because the hematogenous route is more common in that situation. The presence of Candida in the urine of a non-instrumented immunocompetent patient implies either genital contamination or potentially widespread visceral dissemination. By contrast, candiduria is common in catheter ized patients, particularly following antimicrobial therapy for CAUTI or inappropriate treatment of ASB. Host

Genetic background

Behavioral factors

Underlying disease

Tissue-specific receptors Organism

Type of organism

Presence of virulence factors

Expression of virulence factors Organism Host Infection, colonization, or elimination Environment Environment

Vaginal ecology

Anatomy/urinary retention

Medical devices FIGURE 140-1 Pathogenesis of urinary tract infection. The relationship among specific host, pathogen, and environmental factors determines the clinical outcome.

Environmental Factors • VAGINAL ECOLOGY Vaginal ecology is an important environmental factor affecting risk of UTI in women. Colonization of the vaginal introitus and periurethral area with organ isms 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 risk of UTI. Nonoxynol-9 in spermicide is toxic to normal vaginal lactobacilli and thus is likewise associated with an increased risk of vaginal colonization and bacteriuria due to E.

coli. In postmenopausal women, the previously predominant vaginal lactobacilli are replaced with colonizing Gram-negative bacteria because of vaginal atrophy. Topical estrogens have been demonstrated to reduce frequency of recurrent UTIs in postmenopausal women without altering systemic hormone levels. Given the side effects of systemic hormone replace ment, oral estrogens should not be used to prevent UTI. ANATOMIC AND FUNCTIONAL ABNORMALITIES Any condition that permits urinary stasis or obstruction predisposes the patient to devel opment of 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 urinarydiversion surgery all create an environment that can lead to UTI. Inhibition of ureteral peristalsis and decreased ureteral tone leading to vesicoureteral reflux are important in the pathogenesis of pyelonephri tis in pregnant patients. Anatomic factors—in particular, the length of the urethra—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. In women, famil ial disposition to UTI is well documented. Additionally, 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 recur rent UTI might be persistent vaginal colonization with E. coli, even during asymptomatic periods. Vaginal and periurethral mucosal cells from women with recurrent UTI bind uropathogenic bacteria three fold more than do mucosal cells from women without recurrent infec tion. This difference appears to be at least partly mediated by not expressing certain blood group antigens, facilitating adherence of E. coli to the urothelium. 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. Microbial Factors Strains of E. coli that cause invasive symp tomatic infection of the urinary tract in otherwise normal hosts often possess and express genetic virulence factors, including bacterial-surface adhesins that mediate microbial binding to specific receptors on the surface of uroepithelial cells. The best-studied adhes ins are the P fimbriae, hairlike protein structures that interact with a specific receptor on renal epithelial cells. (The letter P denotes the abil ity 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 which is not always expressed. 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 uroepi thelial cells. Toxins, metal (iron)-acquisition systems, biofilm forma tion, and bacterial capsules also can contribute to the ability of pathogenic E. coli to thrive in the bladder. APPROACH TO THE PATIENT Clinical Syndromes and Diagnostic Approaches The key questions to be addressed when UTI is suspected are: • Does the patient actually have UTI (rather than ASB or uri nary symptoms not related to infection)?

• If the patient does have UTI, is it confined to the bladder (cystitis), or is there evidence that infection might be present beyond the bladder? • If the diagnosis is uncertain, would it be safe to delay empiri cal antimicrobial therapy while attempting to achieve more diagnostic certainty? The answers to these immediate clinical questions will shape the diagnostic and therapeutic approach. ASYMPTOMATIC BACTERIURIA A diagnosis of ASB should be strongly suspected when a patient with a positive urine culture does not have either localizing urinary symptoms or systemic symptoms that are unexplained. The clinical presentation is typically bacteriuria that is detected incidentally

when a patient undergoes a screening urine culture. Accordingly, diagnostic stewardship (i.e., not sending urine cultures in patients who lack clinical signs and symptoms that suggest UTI except when screening patients who are pregnant or about to undergo urologic procedures) is the key intervention in reducing misdiagnosis of UTI and inappropriate treatment of ASB. In the setting of pyuria (presence of white blood cells in the urine) and bacteriuria in a patient without symptoms localizing to the urinary tract, systemic symptoms and signs such as fever, altered mental status, and leukocytosis could be features of UTI but do not on their own merit a diagnosis of UTI unless other potential etiologic causes for such findings have been adequately explored and ruled out. Critically, the degree of pyuria in an asymptomatic patient should not influence the diagnosis of ASB versus true UTI. Very high levels of pyuria are common in urinary stasis, such as in patients with end-stage renal disease or obstructed urinary catheters. In practice, one of the most challenging clinical scenarios to dif ferentiate ASB from true UTI occurs when an older patient presents with isolated altered mentation, often superimposed on chronic cognitive deficits and potentially with little prior documentation. Accurately diagnosing the cause of such a patient's acute encepha lopathy is challenging both because the patient might not be able to reliably report localizing urinary symptoms and because true UTI is an important diagnostic consideration on a long list of possible causes of the patient's symptoms. In such a patient, the treating clinician should first establish whether there is evidence of sepsis. If not, the next consideration is whether empirical therapy for poten tially serious bacterial infection can be safely withheld while the diagnostic process is ongoing and symptomatic treatment for other noninfectious causes of delirium is given. The clinician should seek out collateral history, such as by calling the patient's caregivers if none are present at the bedside, to elicit information about what occurred prior to the patient's development of acute encephalopa thy. A history of prior recurrent UTIs is might not be accurate and instead reflects a history of persistent ASB. The clinician must be vigilant to avoid premature diagnostic closure. Specifically, the clinician should rule out other potential causes of delirium, particu larly those whose treatment is time-sensitive or that may worsen with if the diagnosis is not considered and addressed. CYSTITIS The typical symptoms of cystitis are dysuria, urinary frequency, and urinary urgency. Other common symptoms include supra pubic discomfort or tenderness and new nocturia, hesitancy, or gross hematuria. Fever, rigors, and unilateral back or flank pain are all inconsistent with uncomplicated cystitis and should provoke investigation for infection beyond the bladder (i.e., involving the kidneys, prostate, or bloodstream). 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 (or, if rapidly available, urine microscopy) should be performed. In the scenario of a woman with symptoms potentially suggestive of cystitis, a negative dipstick result does not fully rule out UTI, and appropriate next

steps would include formal urine microscopy with reflex to culture, possibly a pelvic examination or STI testing, and close clinical follow-up. In pregnant patients, in patients suspected to have a resistant organism, or in cases of recurrent UTI, a urine culture is specifically warranted to guide appropriate therapy. Urine dipstick and/or urine microscopy alone are not sufficient. The signs and symptoms of cystitis in men are similar to those in women, but this diagnosis should be approached cautiously, as cys titis in men is less common, except in the setting of urinary cathe terization/instrumentation or obstructive uropathy due to prostatic hypertrophy. Urine cultures should be obtained for all cases of male UTI, as the documentation of bacteriuria can differentiate the less common syndromes of acute and chronic bacterial prostatitis from the more common entity of chronic pelvic pain syndrome, which is not associated with bacteriuria and not improved

by antibiotics. PROSTATITIS Prostatitis includes both infectious and noninfectious abnormali ties 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). ABP presents as dysuria, frequency, and pain in the prostatic pelvic or perineal area. It is typically a severe illness that can be accompanied by fever, rigors, and/or bladder outlet obstruction. CBP presents more insidiously as recurrent episodes of cystitis, sometimes with associated pelvic and perineal pain. Systemic signs of infection are typically absent, and many patients are evaluated for CBP in the ambulatory setting. Males with recur rent cystitis should be evaluated for a prostatic focus as well as for urinary retention. CHAPTER 140 Men with febrile UTI can have an elevated serum level of prostate-specific antigen and an enlarged prostate and enlarged seminal vesicles on ultrasound—findings suggestive 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 febrile UTI, including at the first episode, should have imaging performed (CT or ultrasound) if it has not been performed previ ously. The purpose of such investigation is specifically to evaluate for urinary tract abnormalities or obstruction. If the diagnosis of UTI is unclear or if UTI is recurrent, referral for urologic consulta tion is appropriate. Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis PYELONEPHRITIS Fever is one of the main features distinguishing cystitis from pyelo nephritis, and while “febrile UTI” is sometimes used as a diagnos tic category in UTI research, practically speaking, many of these patients have pyelonephritis or other infection that has extended beyond the bladder (hence the inclusion of fever as a criterion for complicated UTI). Mild pyelonephritis can present with low-grade fever with or without lower back or costovertebral angle pain, whereas severe pyelonephritis often manifests with high fever, rigors, nausea, vom iting, and flank pain. Symptoms are generally acute in onset and may or may not be preceded by symptomatic cystitis. Obstructive uropathy related to acute papillary necrosis (i.e., when the sloughed papillae obstruct the ureter) can complicate pyelonephritis. Acute papillary necrosis can also occur in sickle cell disease and analge sic nephropathy. In the rare cases of bilateral papillary necrosis, a rapid rise in the serum creatinine level might be the first indication of the condition. Emphysematous pyelonephritis is a particularly severe form of pyelonephritis associated with production of gas in the renal and perinephric tissues. It occurs almost exclusively in patients with poorly controlled diabetes (Fig. 140-2). Xanthogranu lomatous pyelonephritis occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, leads to suppurative destruction of renal tissue (Fig. 140-3). On pathologic

FIGURE 140-2 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). PART 5 Infectious Diseases examination, the residual renal tissue frequently has a yellow color ation, with infiltration by lipid-laden macrophages (hence the term xanthogranulomatous). 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. CATHETER-ASSOCIATED URINARY TRACT INFECTION (CAUTI) Clinically, CAUTI can be defined by the presence of symptoms along with presence of bacteriuria and pyuria. CAUTI may cause localizing urinary symptoms or otherwise unexplained systemic manifestations, such as fever. The accepted threshold for bacteriuria to meet the definition of CAUTI is ≥103 colony-forming units per milliliter

of urine. The central diagnostic difficulty of CAUTI is that, because cathe ters provide a conduit for bacteria to enter the bladder, bacteriuria is inevitable with urinary catheterization. The typical signs and symp toms of UTI, including pain, urgency, dysuria, fever, and peripheral leukocytosis, also have less predictive value for diagnosis of UTI in catheterized patients. Since bacteriuria and pyuria are expected in this population, the diagnostic evaluation of a febrile patient with a urinary catheter should not end with an abnormal urinalysis. To make a diagnosis of CAUTI, first, signs and symptoms of UTI (localizing and/or systemic) should be present along with pyuria and bacteriuria. Additionally, other infectious and noninfectious causes of the patient's symptoms should be systematically ruled out before settling on the diagnosis of CAUTI. ■ ■DIAGNOSTIC TOOLS History The diagnosis of any of the UTI syndromes or ASB begins with a detailed history (Fig. 140-4). Patient-reported symptoms have high positive predictive value in uncomplicated cystitis, at least among adult women; data are lacking for other populations. Self-diagnoses among women with recurrent UTI are particularly accurate and account for the success of patient-initiated treatment for recurrent cystitis. A meta-analysis of the diagnostic utility of history and physical findings for UTI concluded that, in women presenting with at least one localizing urinary symptom (dysuria, frequency, hematuria, or back

A B FIGURE 140-3 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.) pain) and no complicating factors, the probability of acute cystitis or pyelonephritis is 50%. If vaginal discharge and complicating factors are absent and risk factors for UTI are present, then the probability of UTI is close to 90%. Further laboratory evaluation with dipstick testing or urine culture prior to antimicrobial treatment is not necessary in such patients unless there is concern for resistant pathogens (e.g., in patients presenting with recurrent UTI, prior treatment failure, known coloni zation with extensively resistant pathogens, or high local prevalence of resistance to the empirical antibiotic being given). In applying the patient's history as a diagnostic tool, one significant con cern is that STIs—caused by C. trachomatis in particular—might be inap propriately treated as UTI. Importantly, women with multiple sexual partners and inconsistent use of condoms are at increased risk for both UTI and STIs, and symptoms alone do not always distinguish between these conditions. Dysuria might instead be due to cervicitis (C. trachomatis, N. gonorrhoeae), vaginitis (Candida albicans, Trichomonas vaginalis), herpetic urethritis, interstitial cystitis, or noninfectious vaginal or vul var irritation. Vaginal discharge in particular should prompt consider ation of STI. In this particular patient population, consideration should

Clinical Presentation Patient Characteristics Diagnostic and Management Considerations Otherwise healthy woman who is not pregnant, low risk for multidrug resistance Woman with a history of or risk factors for STI Acute onset of urinary symptoms Dysuria Frequency Urgency Male with perineal, pelvic, or prostatic pain Patient with indwelling urinary catheter All other patients Otherwise healthy woman who is not pregnant Acute onset of back pain, nausea/vomiting, or fever with or without cystitis symptoms All other patients Systemic symptoms Elderly patients; patients with spinal cord injury, immunocompromise, no alternate diagnosis Fever Altered mental status

Leukocytosis Consider complicated UTI Consider other etiologies Urine culture Blood cultures Positive urine culture in patient who is pregnant, or patient undergoing invasive urologic procedure No urinary symptoms Positive urine culture in all other patients Positive urine culture in patient with indwelling catheter Otherwise healthy woman who is not pregnant Recurrent acute urinary symptoms Male patient FIGURE 140-4 Diagnostic approach to urinary tract infection (UTI). NTF, nitrofurantoin; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection. be given to STI screening either at the time of empirical treatment for UTI or if symptoms do not resolve with treatment. Urine Dipstick Test, Urinalysis, and Urine Culture Useful tools in the diagnosis of UTI include the urine dipstick test (for nitrite and leukocyte esterase) and microscopic urinalysis (for counts of red and white blood cells), both of which provide point-of-care informa tion that can primarily be used for ruling out UTI in patients who do not have a clear clinical diagnosis. Urine culture, another diagnostic tool, can retrospectively provide proof that bacteria were present in the urinary tract and can provide information on susceptibilities of the

Consider uncomplicated cystitis No urine culture needed Consider telephone management Consider uncomplicated cystitis or STI Urinalysis, culture STI evaluation, pelvic exam Consider acute prostatitis Urinalysis and culture Consider urology evaluation Consider CAUTI Exchange or remove catheter Urinalysis and culture Blood cultures if fever Consider complicated UTI Urinalysis and culture Address any modifiable anatomic or functional abnormalities Consider pyelonephritis Urinalysis and culture Consider outpatient management Consider pyelonephritis or acute prostatitis (male) CHAPTER 140 Urine culture Blood cultures Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis Consider ASB Screening and treatment warranted Consider ASB No additional workup or treatment needed Consider CA-ASB No additional workup or treatment needed Remove unnecessary catheters Consider recurrent cystitis Urine culture to establish diagnosis Consider prophylaxis or patient-initiated management (see text) Consider chronic bacterial prostatitis Consider urology consult isolated organism(s). A key point is that patients with urinary catheter ization will almost always have both pyuria and bacteriuria. Therefore, presence of pyuria and bacteriuria alone in the absence of symptoms do not indicate a diagnosis of UTI. Understanding the parameters of the dipstick test is important in interpreting its results. Only members of the Enterobacterales family convert nitrate to nitrite, and enough nitrite must accumulate in the urine to reach the threshold of detection. This poses three problems limiting nitrites' sensitivity and specificity. First, nitrites could be posi tive in a patient with Enterobacterales ASB. Second, nitrites would be negative in a patient with UTI due to non-Enterobacterales organisms.

Third, nitrites might also be falsely negative in a woman with acute cys titis who is voiding frequently because of significant oral fluid intake.

The leukocyte esterase test detects this enzyme in neutrophils present in the host's urine, whether the cells are intact or lysed. Practi cally speaking, it is a less sensitive and specific surrogate for pyuria as measured by urine microscopy. Many reviews have attempted to describe the diagnostic accuracy of dipstick testing for UTI. The most important point for practicing clinicians is that a dipstick test negative for both nitrite and leukocyte esterase should prompt consideration of diagnoses other than UTI to explain the patient's symptoms, keeping in mind that the dipstick results can be falsely negative in a small per centage of cases. Importantly, a negative urine dipstick test is not suf ficiently sensitive to rule out bacteriuria in pregnant women, for whom ASB screening should be performed via urine culture. Urine microscopy reveals pyuria in nearly all

cases of cystitis and hematuria in approximately 30% of cases. Pyuria has historically been defined as >10 leukocytes per high-powered microscopy field (HPF). Modern data indicate that, at least for older women, median urine white blood cells (WBCs) per HPF are far higher in UTI. As such, the cutoff of >10 WBCs/HPF has poor specificity (36%) for UTI, and a cutoff closer to 250 WBCs/HPF might better correlate with presence of urinary symptoms. However, at present, >10 WBCs/HPF remains the generally accepted standard for what defines presence of pyuria. Detection of bacteria in a urine culture from a patient with symptoms of cystitis can confirm the diagnosis of UTI. However, culture results often do not become available until at least 24 h after a patient presents for care, with identification of individual organisms and their suscepti bilities usually requiring an additional 24–48 h. Furthermore, identify ing the presence of bacteria in the urine does not necessarily imply the presence of symptoms; therefore, a positive urine culture is consistent with both UTI and ASB. This issue is a perennial source of inaccuracy for retrospective studies of UTI, which are often flawed by defining UTI as the combination of pyuria and bacteriuria without requiring clinical documentation of symptoms. Studies of women with symptoms of cysti tis have found that a colony count threshold of >102 bacteria/mL is more sensitive (95%) than a threshold of 105/mL for the diagnosis of acute cystitis in women. Fewer data are available in men about the threshold of bacteriuria to establish cystitis. When interpreting urine culture results, the clinician should consider that contamination with the normal microbial flora of the distal urethra, vagina, or skin is common and that these contaminants can grow to high numbers when 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. PART 5 Infectious Diseases TREATMENT Urinary Tract Infections The approach to diagnosis and treatment is influenced by which of the UTI clinical syndromes is suspected and presence of risk factors for resistant pathogens (Fig. 140-4). GENERAL CONSIDERATIONS FOR ANTIMICROBIAL THERAPY Studies indicate that treatment of UTI is usually the first or second most common indication for antimicrobials in ambulatory, inpa tient, and long-term-care settings. Responsible use of antimicrobi als for this common infection has broad implications for preserving antibiotic effectiveness into the future. Importantly, antimicrobial therapy is warranted for any true (symptomatic) UTI. Studies of nonantibiotic treatment for UTI (e.g., with nonsteroidal anti-inflammatory drugs alone) suggest that this approach delays clinical response and predisposes patients to more invasive infections. Delayed therapy, in which a patient 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 patients who do not have cysti tis to begin with; however, this approach has the downsides of

prolonging discomfort and a small increased risk of progression to pyelonephritis in patients who do have true UTI. Potentially higheryield antimicrobial stewardship interventions in UTI management include encouraging clinicians to avoid unnecessary treatment of ASB, to avoid ordering urine cultures in patients who lack urinary or systemic symptoms suggestive of UTI, and to avoid prescribing overly long antibiotic durations for UTI. In 1999, trimethoprim-sulfamethoxazole (TMP-SMX) was rec ommended as the treatment of choice for uncomplicated cystitis in the first published UTI guidelines of the Infectious Diseases Society of America. However, local uropathogen resistance patterns and national differences in the availability of certain antimicrobial agents are such that providing a global or even national recom mendation for a single preferred empirical antibiotic for UTI is challenging. Instead, clinicians must use their knowledge of local resistance

patterns and individual patient factors (e.g., allergies and potential for drug–drug interactions) to select from groups of antimicrobials based on their efficacy, toxicity risks, and potential for collateral damage (defined below). The choice of antimicrobial agent, the dose, and the duration of therapy also depend on the clinical syndrome (that is, which type of UTI specifically is being treated) and the rapidity of clinical improvement. Collateral damage refers to the adverse ecologic effects of anti microbial therapy, including killing of the patient's normal flora (predisposing to Clostridioides difficile infection) and selection of drug-resistant organisms. The implication of collateral damage for UTI management is that a drug that is highly efficacious for treat ment 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 significantly adversely affect resistance patterns. Drugs used for UTI that have a minimal effect on fecal flora include pivmecil linam, fosfomycin, and nitrofurantoin. In contrast, TMP-SMX, quinolones, and β-lactams (particularly the late-generation cepha losporins) affect the fecal flora more significantly and are notably the agents for which rising resistance has been documented. Choosing judiciously whether to initiate antibiotic therapy and then selecting the agent with the least potential for collateral dam age to be given for the shortest effective duration are important factors in global efforts to stem the rise of antimicrobial-resistant organisms. Common risk factors for resistance to specific anti microbials in UTI include prior urine or blood cultures with an organism resistant to that antimicrobial, recent exposure to that antimicrobial, or travel to an area where resistance to that antimi crobial is especially prevalent. For each of these factors, the magni tude of risk is greater with more recent exposures in the preceding year; the greatest increase in risk occurs with fluoroquinolones. More data is available documenting this risk of resistance with prior exposure to the antibiotic for fluoroquinolones than for other antibiotics. Other general risk factors for antimicrobial resistance in UTI include urinary catheterization, prior exposure to antibiotics of any class, and residence in a healthcare facility. ASYMPTOMATIC BACTERIURIA Critically, treatment of ASB does not decrease frequency of subse quent true UTIs. Clinical trial data from renal transplant recipients suggest that ASB treatment might even increase future risk of infec tion. Importantly, though, treatment of ASB in pregnant patients and patients undergoing high-risk urologic procedures is recom mended to reduce risk of complications (see discussion above) and should be guided by urine culture results. In all other populations, screening for and treating ASB are discouraged. Specifically, a urine culture does not need to be obtained at the time of placement or removal of a urinary catheter if the patient is asymptomatic. The majority of cases of catheter-associated bacteriuria are asymptom atic and do not warrant antimicrobial therapy. CYSTITIS Many episodes of uncomplicated cystitis in women (i.e., cystitis without systemic symptoms, symptoms of pyelonephritis, or urinary

TABLE 140-1 Treatment Strategies for Acute Uncomplicated Cystitis DRUG DOSE DURATION COMMON SIDE EFFECTS Nitrofurantoin 100 mg bid Women or men: 5–7 days Nausea, headache TMP-SMX 1 DS tablet bid Women: 3 days Men: 7 days Rash, urticaria, nausea, vomiting, hematologic abnormalities Fosfomycin 3-g sachet Women: 1 day Men: qod × 3 doses Pivmecillinam 400 mg bid Women: 3–7 days Nausea, vomiting, diarrhea Fluoroquinolones Dose varies by agent Women: 3 days Men: 7 days β-Lactams Dose varies by agent Women or men: 5–7 days Diarrhea, nausea, vomiting, rash, urticaria Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole; bid, twice a day; qod every other day. catheterization) can be managed remotely (Fig. 140-4). Studies of telephone-management algorithms for UTI indicate low risk of serious complications, with the important caveat that such algo rithms have generally involved otherwise healthy women who are at low risk of complications of UTI; thus, patients with other UTI

syndromes or more complicated prior histories require further diag nostic evaluation and might not be as adequately managed remotely. As described above, cystitis in men is unusual except in the setting of urinary catheterization or obstructive uropathy. Before settling on this diagnosis in men, however, the clinician should be confident that ABP, CBP, and pyelonephritis with or without uri nary obstruction have been excluded. True uncomplicated cystitis in afebrile men can be treated with only 7 days of antimicrobial therapy; the durations shorter than 7 days used for uncomplicated cystitis in women have not been adequately studied in men. Several effective therapeutic regimens are available for acute uncomplicated cystitis in women; data are very limited on therapy for cystitis in men (Table 140-1). Preferred agents for treatment of acute uncomplicated cystitis include TMP-SMX, nitrofuran toin, fosfomycin, and pivmecillinam. Fosfomycin is somewhat less studied than TMP-SMX and nitrofurantoin, but it is also effective and is preferred in cystitis because of its selective concentration in urine, low risk for collateral damage, and potential to retain efficacy against MDR E. coli. Pivmecillinam was approved for treatment of cystitis in the United States in 2024. It also often retains activity against MDR E. coli, including some expressing extended-spectrum β-lactamases. Alternative agents for treatment of cystitis include fluoroquino lones and β-lactams. β-lactams require longer durations of therapy (5–7 days) even in uncomplicated cystitis and are associated with higher clinical failure rates (compared with either fluoroquinolones or TMP-SMX) in some randomized controlled trials. Despite these limitations, β-lactams are favored over fluoroquinolones as an alternative agent for treatment of uncomplicated cystitis because of the bacterial resistance and side effects associated with fluoroqui nolones. Fluoroquinolones are highly effective for treating UTI but cause high collateral damage as well as numerous rare but serious drug toxicities (e.g., collagen vascular pathology such as tendon rupture, retinal detachment, and aortic aneurysm), leading the U.S. Food and Drug Administration (FDA) to advise against using fluoroquinolones for uncomplicated cystitis in women unless no alternatives are available. Importantly, in men, if there is concern for prostatic involvement, fluoroquinolones or TMP-SMX are pre ferred over β-lactams because fluoroquinolones have superior pen etration into the prostate. The pros and cons of each specific agent are discussed in more detail below. TMP-SMX remains an excellent option for treatment of cys titis in areas where local uropathogen antibiogram data do not clearly favor other preferred agents or when the patient has recent microbiology demonstrating a TMP-SMX–susceptible uropatho gen. Otherwise, the optimal setting for empirical use of TMP-SMX is uncomplicated cystitis in a patient who has an established rela tionship with the practitioner and has no barriers to seeking further care if their symptoms do not respond promptly.

Diarrhea, nausea, headache Nausea, vomiting, diarrhea, headache, drowsiness, insomnia Resistance to nitrofurantoin remains low despite >70 years of use, probably because several mutational steps are required for bacterial resistance to this drug. Nitrofurantoin remains highly active against E. coli. However, importantly, most Proteus, Provi dencia, Morganella, Pseudomonas, and Serratia and some Klebsiella and Enterobacter strains are intrinsically resistant to this drug. A 5-day course of nitrofurantoin is as effective as a 3-day course of TMP-SMX for treatment of acute uncomplicated cystitis in women. Nitrofurantoin should not be used in patients with a creatinine clearance <30 mL/min. It does not reach significant levels in tissue and so cannot be used to treat pyelonephritis or prostatitis. Addi tionally, we advise against long-term (i.e., multiple years) prescrip tion of nitrofurantoin as prophylaxis for recurrent UTIs because of the risk of sometimes irreversible pulmonary toxicities. CHAPTER 140 Guidelines also recommend fosfomycin, which interferes with bacterial cell-wall formation, as an option for uncomplicated cysti tis, given its easy dosing and low collateral damage. While fosfomy cin is active against E. coli, its activity against

other Enterobacterales species is less reliable. Moreover, fosfomycin susceptibility testing is difficult to perform, and the results of such testing are not typi cally included in standard automated microbiologic susceptibility reports. Oral fosfomycin is given as a single 3-g dose sachet (pow der) that is dissolved in a glass of water and swallowed. Similar to nitrofurantoin, renal tissue levels of fosfomycin are low, and a dif ferent antibiotic should be used if treating pyelonephritis. While not extensively studied for this indication, fosfomycin has been used in the treatment of prostatitis to manage pathogens resistant to other oral agents. Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis Despite their often high rates of urinary secretion, β-lactams as a class have not performed as well as TMP-SMX or fluoroquinolones for treatment of acute cystitis. Rates of pathogen eradication are lower, and relapse rates are higher with β-lactam drugs compared with other agents. The generally accepted explanation for this observation is that β-lactams fail to eradicate uropathogens from the vaginal reservoir, which is specific to female patients with UTI. Supporting this hypothesis are limited indirect data indicating that treatment success with cephalexin is as good as or better than success with other classes in male UTI. Amoxicillin resistance has become widespread in E. coli, and many strains resistant to TMPSMX are also resistant to some or all of the other oral β-lactams. Thus, as described for TMP-SMX above, β-lactams such as cef podoxime or cefixime are optimally used for patients known to have susceptible uropathogens or in areas where local antibiograms demonstrate that resistance remains uncommon. The fluoroquinolones ciprofloxacin and levofloxacin are highly effective as short-course therapy for cystitis due to susceptible flora. By contrast, moxifloxacin in particular might not reach adequate urinary levels. The two main concerns about using fluoroquino lones 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 fluoroquinolones' rare but potentially serious adverse effects (increased risk of Achilles' tendon rupture, neuropa thy, and aortic dissection). In light of these potential detrimental

effects, the FDA issued an advisory against using fluoroquinolones to treat acute cystitis in patients who have other effective therapeu tic options.

Urinary analgesics are appropriate in certain situations to help the patient with resolution of bladder discomfort in cystitis. The urinary tract analgesic phenazopyridine is widely used but can cause significant nausea. Combination analgesics containing uri nary antiseptics (such as methenamine and methylene blue), a urine-acidifying agent (sodium phosphate), and an antispasmodic agent (hyoscyamine) also are available. There are no well-established criteria for when to use these agents, although as mentioned above, multiple clinical trials demonstrate that symptomatic treat ments alone are not an adequate substitute for antimicrobials when patients have true UTI. PROSTATITIS The prostate is involved in the majority of cases of febrile UTI in men and can also be a source of recurrent cystitis. ABP should specifically be suspected in men presenting with UTI with systemic symptoms without another clear anatomic location of UTI, such as pyelonephritis. CBP should be suspected when patients have recurrent UTI, especially if not in the context of urinary catheter ization). Both ABP and CBP should be suspected when patients have prostatic symptoms. If ABP is suspected, antimicrobial therapy should be promptly initiated after urine and blood cultures are obtained. For ABP, at least 2 weeks and potentially up to 4 weeks of a fluoroquinolone or TMP-SMX is recommended for susceptible uropathogens. Identification of a prostatic abscess should prompt consultation to urologic specialists. For CBP, a 4- to 6-week course of antibiotics is typically given, and recurrences (not uncommon) may warrant up to a 12-week

course of therapy. These durations are based on older observational studies and historic norms of practice and need be to clarified with modern randomized controlled trials. PART 5 Infectious Diseases PYELONEPHRITIS Patients with pyelonephritis have tissue-invasive disease and are often systemically ill. Therefore, empirical therapy should be reli able and rapidly reach therapeutic levels in both renal parenchyma and blood. In years past, increasing TMP-SMX resistance made fluoroquinolones the empirical treatment of choice for pyelone phritis, and quinolones remain among the best-studied agents for acute pyelonephritis. However, quinolone resistance is now also increasingly prevalent. For hospitalized patients, we recommend empirical therapy with an IV β-lactam for pyelonephritis, with attention to choosing an agent to which the patient has not recently had a resistant uro pathogen in urine or blood and appears highly reliable based on the local antibiogram. For patients with pyelonephritis who are not and do not need to be hospitalized, we recommend empirical therapy with TMP-SMX, ciprofloxacin, or levofloxacin based on local anti biogram data, along with urine culture collection and short-term follow-up. Optimally, an initial dose of IV or IM β-lactam or an aminoglycoside to ensure effective empirical therapy can be pre scribed, where this is practical and feasible. Ambulatory patients with pyelonephritis should be hospitalized if they are unable to tolerate oral medications (e.g., due to nausea and vomiting) or are unlikely to adhere to short-term follow-up. For susceptible isolates, clinical trial data indicate that 5–7 days of an oral fluroquinolone or 7–14 days of oral TMP-SMX (depend ing on rapidity of clinical improvement) are highly effective options for pyelonephritis. Oral β-lactam agents are less effective and should be used with caution and close follow-up. Nitrofurantoin, pivmecillinam, and fosfomycin should not be used for pyelonephri tis. Options for parenteral therapy for uncomplicated pyelonephri tis include late-generation cephalosporins (such as ceftriaxone or cefepime), piperacillin-tazobactam, a carbapenem, or fluoroqui nolones (although the high bioavailability of this class makes IV administration superfluous for patients with who can tolerate and absorb oral medications). Alternative parenteral antibiotics include

novel β-lactam/β-lactamase inhibitors (e.g., meropenem-vaborbactam) and aminoglycosides, which are considered alternative due to cost and toxicity profiles, respectively. In general, the treatment of pyelonephritis should be guided by urine culture results and clinical resolution of symptoms. Pyelone phritis due to drug-resistant uropathogens requiring nonpreferred antibiotics should be treated in consultation with infectious disease specialists. Once the patient has responded clinically, oral therapy can be substituted for parenteral therapy. Treatment can be con cluded at 7 days for patients who have clinically responded (i.e., res olution of fever and return to hemodynamic stability with adequate source control) within that timeframe and who can be treated with a fluoroquinolone or TMP-SMX. Oral β-lactams may necessitate a longer course of treatment for pyelonephritis. Patients with pyelonephritis who have not had a clinical response within 72 h should undergo further evaluation for an uncontrolled source of infection. Pyelonephritis can be complicated by acute papillary necrosis causing urinary obstruction, which requires intervention to relieve the obstruction, overcome the infection, and preserve renal function. Perinephric and renal cortical abscesses may require drainage percutaneous drainage. Percutaneous drain age can also be used as the initial therapy in emphysematous pyelo nephritis and can be followed by elective nephrectomy as needed depending upon the patient’s clinical status in consultation with urologic specialists. Xanthogranulomatous pyelonephritis (XGP) is treated with close collaboration with urologic colleagues and often requires nephrectomy; antibiotic treatment duration should be individualized in cases of XGP. CATHETER-ASSOCIATED UTI The bacteriology of CAUTI is diverse, and urine culture results are essential to guide treatment. The

catheter should be exchanged (or, if possible, removed entirely) during treatment for CAUTI, the purpose of which is to remove biofilm-associated organisms that could serve as a nidus for reinfection. When possible, this should be done prior to sending urine cultures to ensure that the culture results reflect the microbiology of the bladder rather than the cath eter walls. Most clinicians treat CAUTI for 7–14 days based on clinical response; the need for longer therapy than is used in uncomplicated cystitis is supported by a randomized controlled trial that identified more relapses after 3 versus 14 days of antimicrobials. Further stud ies on the optimal duration of therapy in CAUTI 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 avoid ance of inappropriate catheterization) and team-communication strategies have shown the benefit of such approaches in decreasing rates of CAUTI in both acute- and long-term-care settings. Anti microbial catheters impregnated with silver or nitrofurazone have not been shown to provide significant clinical benefit with regard to reducing CAUTI rates and should not be used routinely. Evidence is insufficient to systematically recommend suprapubic catheters and condom urinary catheters as alternatives to indwelling urinary catheters as a way to prevent bacteriuria. Intermittent catheteriza tion may be preferable to long-term indwelling urethral catheteriza tion in certain populations (e.g., patients with spinal cord injury) to prevent both infectious and anatomic complications. UTI IN PREGNANT PATIENTS Aminopenicillins (ampicillin and amoxicillin) and cephalosporins have been used extensively in pregnancy and are the drugs of choice for treatment of ASB or UTI in pregnant patients. Importantly, though, widespread resistance to aminopenicillins precludes their use for pregnant patients with UTI if urine culture results are not already available. One retrospective case-control study suggested an association between nitrofurantoin use in the first trimester and birth defects, but this association has not been confirmed, and the

American College of Obstetrics and Gynecology (ACOG) suggests that nitrofurantoin can be used during all trimesters if β-lactam agents are not an option. Sulfonamides (including TMP-SMX) should be avoided both in the first trimester (because of possible teratogenic effects) and near term (because of a possible role in the development of neonatal kernicterus), although ACOG suggests TMP-SMX can be used as a potential treatment option at both times if no alternatives are available. Fluoroquinolones are avoided dur ing pregnancy because of possible adverse effects on fetal cartilage development. Pregnant patients with ASB or cystitis are generally treated for 5–7 days because of the absence of evidence to support shorter durations of therapy in this patient population. For preg nant patients with pyelonephritis, guidelines recommend parenteral β-lactam therapy with or without aminoglycosides based on limited observational data and historic norms of practice. 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 antimicro bial drugs, and those with underlying diabetes mellitus. In many studies, >50% of urinary Candida isolates have been found to be non–C. albicans species. The clinical presentation of candiduria varies widely—from asymptomatic colonization to pyelonephritis and sepsis—thereby making management challenging in some instances, particularly for patients with multiple other ongoing medical conditions. Removal of the urinary catheter results in reso lution of candiduria in more than one-third of asymptomatic cases. As with ASB, treatment of asymptomatic patients with candiduria has not been found to reduce recurrence of candiduria or subse quent infection. Therefore, treatment of asymptomatic patients is not routinely recommended for most patients. By contrast, candiduria should be treated in patients who have

symptomatic cystitis or pyelonephritis or those who are asymptom atic but are at high risk for disseminated disease (e.g., patients with neutropenia, patients who will undergo urologic manipulation, and low-birth-weight infants). Fluconazole (200–400 mg/d for 7–14 days) reaches high levels in the urine and is the first-line regi men 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 relatively unstudied and are not recommended as first-line agents but can be considered in certain cases. For Candida isolates with high levels of resistance to fluconazole, oral flucytosine and/or parenteral ampho tericin B are additional options. Bladder irrigation with amphotericin B is generally not recommended. ■ ■PREVENTION OF RECURRENT UTI IN WOMEN Recurrence of uncomplicated cystitis in women is common, and a preventive strategy is indicated if recurrent UTIs are interfering with a patient's lifestyle. The threshold of three or more symptomatic episodes per year to intervene or develop a specific preventive strategy is not absolute; clinicians are recommended to engage in shared decisionmaking with each individual patient to make determinations about a UTI preventive strategy. Initial evaluation of a patient with recurrent cystitis should include confirmation of the diagnosis of recurrent UTI, imaging to identify renal calculi or another potential nidus of infection, and assessment for urinary retention. Referrals to urology, urogynecology, and/or pelvic physical therapy might be helpful when the diagnosis is unclear or an anatomic abnormality is suspected. Nonantimicrobial prophylactic approaches to recurrent UTI are increasingly being studied. Observational data indicate that increasing fluid intake might reduce recurrent UTIs, and such an approach is gen erally well tolerated by healthy adults. Two recent clinical trials found that methenamine hippurate (converted to the antiseptic formaldehyde in the bladder) is well tolerated and might reduce recurrent UTIs as much as antibiotic prophylaxis. A recent Cochrane review of random ized clinical trials of cranberry products also found a significant benefit

for adult women and children with recurrent UTI. Less is known about which products and what precise dosing are optimal. Lactobacillus probiotics are under investigation for UTI prevention, with one recent factorial trial suggesting that intravaginal but not oral lactobacilli products reduce recurrent UTIs. We advise caution, however, in rec ommending probiotics to immunocompromised patients, in whom probiotic-associated invasive infections have been described. Studies of mannose products for UTI prevention have produced mixed results.

Three antibiotic prophylactic strategies are available: continu ous (using daily or thrice-weekly dosing), postcoital (one dose after intercourse), and patient-initiated therapy. For the continuous and postcoital strategies, low doses of TMP-SMX or nitrofurantoin are typi cally utilized. Such approaches are usually highly effective during the period of active antibiotic intake. A prophylactic regimen is typically prescribed for 6 months and then discontinued. If bothersome infec tions recur, the prophylactic program can be reinstituted for the same duration or for a longer period. Selection of resistant strains in the fecal flora has been documented in studies of patients taking prophylactic antibiotics. An approach of alternating antibiotic prophylaxis with periods of nonantimicrobial prevention could hypothetically allow for intermittent recovery of the gut microbiome. The choice between methenamine and cranberry products should be based on shared decision-making and individual patient response. Some studies suggest that although the rate of UTI will be decreased when using nonantimicrobial prophylaxis compared with no prophylaxis, the rate of UTI might be slightly higher than dur ing the antibiotic-suppression period. Patient-initiated therapy involves supplying the patient with materi als 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. CHAPTER 140 Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis ■ ■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 risk of infection or death. The relationships among recurrent UTI, chronic pyelonephritis, and renal insufficiency have been widely studied. In the absence of anatomic abnormalities such as reflux, recur rent infections in children and adults do not lead to chronic pyelone phritis or renal failure. Additionally, infection does not play a primary role in chronic interstitial nephritis; the primary etiologic factors in this condition are analgesic overuse, obstruction, reflux, and toxin exposure. By contrast, in the presence of underlying renal abnormali ties (particularly obstructing stones), infection as a secondary factor can accelerate renal parenchymal damage. ■ ■FURTHER READING Bilsen M et al: Current pyuria cutoffs promote inappropriate urinary tract infection diagnosis in older women. Clin Infect Dis 76:2070, 2023. Brehm TJ et al: Acute and chronic infectious prostatitis in older adults. Infect Dis Clin North Am 37:175, 2023. Christmas MM et al: Menopause hormone therapy and urinary symptoms: A systematic review Menopause 30:672, 2023. Drekonja DM et al: Effect of 7 vs 14 days of antibiotic therapy on reso lution of symptoms among afebrile men with urinary tract infection: A randomized clinical trial. JAMA 326:324, 2021. Gupta V et al: Effectiveness of prophylactic oral and/or vaginal pro biotic supplementation in the prevention of recurrent urinary tract infections: A randomized, double-blind, placebo-controlled trial. Clin Infect Dis 78:1154, 2024. Hooton TM et al: Asymptomatic bacteriuria and pyuria in premeno pausal women. Clin Infect Dis 72:1332, 2021. Lafaurie M et al: Antimicrobial for 7 or 14 days for febrile urinary tract Infection in men: A multicenter noninferiority double-blind,

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Revision #1
Created 2026-01-06 16:32:55 UTC by Omar Ayman
Updated 2026-01-06 16:32:55 UTC by Omar Ayman