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Urinary tract infections

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Urinary tract infections (UTIs) are a common infectious disease in primary care practice. Whereas young women make up most of the more than 7 million cases of infections per year, 2% of boys and 8% of girls will experience a UTI before the age of 10 [1] (National Ambulatory Medical Care Survey, National Center for Health Statistics. Unpublished data, 1995). Although UTIs were reported in 15% of men before the age of 35 during the Rand Health Insurance experiment, they are much more common later in life with disorders of the prostate [2]. Additionally, there are approximately 250,000 cases of pyelonephritis each year, resulting in more than 100,000 hospitalizations [3]. The annual cost of adult UTIs is estimated to be more than $1.5 billion annually [4].

Previous reviews of this topic have categorized adult patients into clinical groups that the primary care clinician is likely to encounter in practice: (1) young women with acute, uncomplicated cystitis; (2) recurrent cystitis; (3) uncomplicated pyelonephritis; (4) complicated UTI; and (5) asymptomatic bacteriuria [5]. In this article, the authors review these topics, highlighting recent research with the addition of UTIs in pregnancy and pediatric UTIs. Given the large number of hospitalized patients undergoing catheterization and residents of long-term care facilities in whom catheters are used frequently, the authors also discuss catheter-associated UTIs separately from complicated UTIs.

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Acute, uncomplicated cystitis in women

Uncomplicated UTIs are infections, either acute cystitis or acute pyelonephritis, occurring in patients without structural or metabolic abnormalities who are not immunosuppressed, respond quickly to antibiotics, and have a low incidence of complications. Table 1 lists risk factors and conditions associated with complicated UTI. Acute cystitis in women is generally an uncomplicated infection. Despite localization studies demonstrating that up to 30% of women presenting with cystitis-like symptoms may have upper tract involvement [6], rarely do these infections cause any cortical damage.

Risk factors among young women with UTIs include recent sexual intercourse, delayed postcoital micturition, and the use of an unlubricated condom [5,7,8]. There is, however, little evidence to support the commonly held beliefs that the direction of wiping after a bowel movement and use of tampons are associated with UTIs [9].

Table 1
Risk factors for and conditions associated with possible complicated urinary tract infections

Treatment
Failure to respond
Resistant organisms
Upper tract symptoms
Recent invasive instrumentation
Obstruction
Enlarged prostate
Nephrolithiasis
Increased postvoid residual
Neurogenic bladder
Immunosuppression
Diabetes mellitus
Sickle cell disease
Transplant patient
Human immunodeficiency virus
Steroid use
Metabolic
Nephrolithiasis
Gout
Hyperparathyroid
Anatomic or functional abnormality
Single kidney
Foreign body; eg, stent, catheter
Polycystic kidney
Vesicoureteral reflux (VER)
Other
Pregnancy
Second UTI in men

Local irritation of the bladder and urethra leads to the cardinal symptoms of acute cystitis: dysuria, frequency, and an absence of fever. Patients with acute cystitis usually experience a sudden onset of symptoms and may have suprapubic discomfort. Pyuria, bacteriuria, or hematuria are present variably on urinalysis. Although patients presenting with this triad of symptoms are likely to have acute cystitis, several other entities should be considered in patients presenting with acute dysuria.

Generally, patients presenting with dysuria in the ambulatory setting are diagnosed with cystitis, acute urethral syndrome, or vaginitis [10]. Patients with the acute urethral syndrome or vaginitis differ from those with cystitis in several ways. Patients with vaginitis due to *Candida*, *Trichomonas*, or nonspecific bacterial vaginosis usually do not have frequency or urgency but may present with a malodorous vaginal discharge, pruritus, dyspareunia, and a lack of pyuria or bacteriuria on urinalysis. Patients with acute urethral syndrome from *Chlamydia trachomatis* or *Neisseria gonnorrhoeae* may present with vaginal discharge or bleeding and more gradual symptom onset (compared with the abrupt onset of symptoms in acute cystitis) and may report a new sexual partner. Whereas pyuria usually is present on microscopic examination, bacteriuria is not present and the presence of hematuria is variable. Pelvic examination is indicated if the diagnosis of cystitis is not straightforward or if vaginitis or acute urethral syndrome is suspected.

The etiologic agents causing acute cystitis have remained relatively unchanged over time, but the resistance rates to common antibiotics have changed substantially. *Escherichia coli* causes most infections, with 5% to 15% caused by *Staphylococcus saprophyticus* and the remaining 5% to 10% caused by *Enterococci* and other aerobic gram-negative rods such as *Klebsiella*. In a recent study of isolates obtained from women diagnosed with acute cystitis between 1992 and 1996, resistance to trimethoprim-sulfamethoxazole (TMP-SMX) increased among *E. coli* isolates from 9% to 16% without any significant change in the incidence of *E. coli* as a uropathogen [11]. Although in vitro resistance to commonly used antibiotics is increasing, the clinical significance of this increased resistance is less clear. Few studies correlating in vitro resistance with clinical outcomes have been performed. Because urine cultures normally are obtained from patients suspected of having complications, this sample may not represent the true outpatient population. In a recent study, investigators determined that resistance among consecutive urine samples of women with acute, uncomplicated cystitis was significantly lower than that reported by a microbiologic laboratory [12]. Several studies report clinical cures among patients with resistant bacteria [13,14].

A great deal of uncertainty in the management of UTIs also occurs when attempting to make a diagnosis of UTI in the office setting. Although the diagnosis of UTIs was defined as greater than or equal to 10^5 organisms/mL by a quantitative culture in early studies, subsequent studies demonstrated that patients with lower colony counts had symptomatic UTIs [15]. Because

of the narrow spectrum of uropathogens and the relatively rare resistance to antimicrobials in the past, empiric therapy without a urine culture is the norm. Several other tests may aid the clinician in diagnosing UTI. Previous recommendations suggest empiric treatment for a symptomatic patient if the leukocyte esterase test result is positive [5]. Culture or microscopic examination would be obtained to ensure the presence of pyuria in the face of a negative test result. This step may be unnecessary, because one recent emergency department study found dipstick and urinalysis to be equivalent [16]. At equivalent cut-off points, however, both undertreatment and overtreatment occur at significant levels. The leukocyte esterase test is approximately 80% to 90% sensitive, whereas the nitrite test is only approximately 50% sensitive compared with a quantitative culture with greater than or equal to 10^5 colony-forming units as the gold standard [3]. Combining both tests improves the sensitivity into the 85% to 90% range. Both tests have high specificity, at approximately 95% [17]. Several recent studies, however, found decreased test characteristics when these tests were used in routine, daily practice [18,19]. Clinicians should be aware that false-negative nitrite test results may occur with low levels of bacteriuria, with patients taking diuretics, with patients on a low-nitrate diet, and with infections with bacteria that do not reduce nitrates such as *S. saprophyticus*. Although more costly and time-consuming, microscopic examination of the urine can detect significant pyuria or hematuria to aid in diagnosis. The microscopic examination is a specific but insensitive test for bacteriuria, however [3]. If the screening results are not conclusive or the clinical picture is unclear, a quantitative urine culture should be performed.

The treatment of acute cystitis has been studied extensively, and recent guidelines were issued by the Infectious Disease Society of America [20]. Several systematic reviews have concluded that 3-day regimens are more effective than single-dose therapy [20,21]. Several studies, however, have begun to reexamine single-dose therapy with fluoroquinolones having longer half-lives, such as pefloxacin and rufloxacin. Pefloxacin was found to be equivalent to 5 or 7 days of TMP-SMX, and rufloxacin and pefloxacin were found to be equivalent in single doses; however, adverse effects were significantly higher in the single-dosing groups [20].

Several authors recommend 3 days of TMP-SMX as standard therapy for acute cystitis [3,20]. Unfortunately, only a few studies have directly compared this treatment regimen to other efficacious regimens. One randomized trial compared 3-day regimens of four different antimicrobials for acute, uncomplicated cystitis [22]. Although TMP-SMX was most effective, cure rates for TMP-SMX (82%), amoxicillin (67%), and cefadroxil (66%) were not statistically different. Nitrofurantoin, on the other hand, was associated with significantly greater failure rates compared with TMP-SMX. Trimethoprim-sulfamethoxazole was, however, the most cost-effective treatment. Amoxicillin and first-generation cephalosporins

[23] are poor first-line agents unless treatment for more than 3 days is planned.

Several fluoroquinolones are believed to have efficacy similar to 3 days of TMP-SMX [20]; however, the use of these agents as first-line therapies may lead to resistance, decreasing their usefulness in other clinical situations as well as being more costly. The authors do not recommend the fluoroquinolones as a first-line agent in acute, uncomplicated cystitis. One exception, however, is when local resistance to TMP-SMX exceeds 20%. In this scenario, the Infectious Disease Society of America guideline recommends an alternative agent, and this recommendation is supported by a recent decision and cost analysis [20,24].

Health care system costs and patient convenience have led investigators to begin examining telephone-based clinical management of acute, uncomplicated cystitis [25]. A large-staff model health maintenance organization developed a telephone-based clinical practice guideline for women with presumed acute, uncomplicated UTIs. Women with dysuria between the ages of 18 and 55 were triaged to a primary care nurse. If the patients did not have evidence of pyelonephritis, risk factors for complicated UTI, or suspicion of a sexually transmitted disease, they were eligible for telephone management. Patients then were randomly assigned to either TMP-SMX or another agent if they were allergic to TMP-SMX. Investigators found that in this select population, they were able to decrease laboratory and utilization costs without increasing adverse outcomes and providing equal or improved quality of care.

Recurrent urinary tract infections

Recurrent UTIs are a common clinical problem. In one study of college-aged women who experienced a first UTI, 27% experienced a recurrence within 6 months [26]. Overwhelmingly, these recurrences are reinfections with a different organism rather than a persistent infection or relapse with the same organism [27]. Relapse with the same organism is a risk factor for complicated UTIs and may require longer duration of treatment and further work-up. Most recurrent UTIs are uncomplicated and not associated with any underlying anatomic abnormality requiring further work-up, however [28]. In a recent study of women having UTIs caused by *E. coli*, 40% (17 of 42) of women experienced a recurrence, with 75% being caused by a genetically different *E. coli* strain [29]. Patients with genetically identical isolates causing recurrent UTIs previously have been shown to have fecal flora reservoirs believed to be the source of the reinfection [30]. Demonstrable risk factors for recurrent UTIs are vaginal intercourse and the use of a diaphragm, cervical cap, or spermicide, whereas condom use decreased risk of a recurrent UTI [31]. A new sexual partner, a history of UTIs before age 15, and a maternal history of UTIs also have been shown to be risk factors for recurrent UTIs [32].

A pretreatment urine culture and susceptibility testing should be documented in patients with recurrent cystitis. Relapse should be considered if the reinfection occurs within 1 week of initial treatment, and it should be treated with a fluoroquinolone for 7 days [3]. Otherwise, the recurrent episode may be managed with short-course therapy. Given the lack of evidence that recurrent cystitis leads to hypertension or renal disease in the absence of urinary tract abnormalities, further work-up is recommended only if there is suspicion of complicated UTI [3].

Several management strategies for the prevention of recurrent cystitis have been recommended: (1) continuous prophylaxis, (2) patient-initiated therapy, and (3) postcoital prophylaxis [5,33]. Although no studies have examined which prophylactic regimen is superior, patient-initiated therapy has been recommended in patients experiencing less than two recurrent episodes per year, and postcoital prophylaxis has been recommended in patients experiencing more frequent episodes [5,34].

Two recent studies demonstrated that compliant women can accurately diagnose and safely treat a recurrent, uncomplicated UTI using self-initiated therapy in the outpatient setting [34,35]. Both studies used fluoroquinolones as therapy for recurrent infections regardless of when the recurrent event occurred. Few adverse effects specifically related to the protocols were noted, and the treatment regimens were economical. Importantly, patients overwhelmingly preferred self-initiated therapy to traditional treatment and were more satisfied with their health care.

Another recent study examined the use of oral cranberry juice and lactobacillus as agents to prevent UTIs [36]. Vaccinium berries and lactobacilli act against coliform bacteria causing UTIs. This study randomly assigned patients with cystitis caused by *E. coli* to receive either 50 mL of cranberry juice or a lactobacillus drink 5 days per week for 1 year. Compared with the open control group, there was a 20% absolute risk reduction in the group receiving cranberry juice in the first 6 months, and total infections at the end of 1 year were half that in the control group. There were no significant differences in the recurrence of UTIs in the lactobacillus group. Recurrent UTIs may be prevented by daily intake of cranberry juice.

Acute pyelonephritis

Although acute pyelonephritis has been studied less intensively than acute cystitis, there are several similarities and differences. With the exception of *S. saprophyticus* as a rare cause of pyelonephritis, the etiologic agents are almost identical to the causes of acute cystitis, with more than 80% attributable to *E. coli* [37]. Patients also generally present with more severe symptoms. In addition to the frequency and dysuria present in acute cystitis, patients are more likely to be febrile and may have flank pain, abdominal pain, nausea, or vomiting. The spectrum of acute pyelonephritis

is wide, however, ranging from a mild illness with symptoms of cystitis to the sepsis syndrome [5].

Laboratory analysis should include a urinalysis and urine culture to confirm the diagnosis. If the patient requires hospitalization, a blood culture may be obtained because 20% of patients may have positive culture results [5]. Gram's stain analysis of urine may aid in the choice of initial antibiotic therapy.

Although patients with acute pyelonephritis traditionally were hospitalized and treated with up to 6 weeks of therapy, safe and effective treatment has been demonstrated with 2 weeks of therapy [38]. A number of authors suggest that the entire course of antibiotics may be completed as an outpatient treatment in immunocompetent women without underlying illness [3,39]. A number of studies have demonstrated the safety and efficacy of oral therapy for patients with acute, uncomplicated pyelonephritis. In a retrospective chart review performed by Safrin et al [39], successful outcomes were noted in 90% of both the inpatient and outpatient groups, and no serious adverse events occurred in the outpatient group. In a prospective study, Bach et al [40] found that women with uncomplicated pyelonephritis could be treated with a fluoroquinolone on an outpatient basis with a high clinical cure rate and a low incidence of adverse events. It is reasonable to consider outpatient therapy for patients with acute, uncomplicated pyelonephritis. Indications for inpatient therapy are provided in the following list:

Indications for admission in pyelonephritis
Inability to maintain hydration or to tolerate oral medication
Severe pain or debilitation
Failure of outpatient treatment
Lack of follow-up or compliance
Diagnostic uncertainty
Risk factors for complicated UTI
Comorbid illness

Data demonstrating observable benefits of the common practice of administering a single dose of intravenous antibiotics before initiating oral therapy are lacking [20]; however, this conservative approach does ensure adequate initial therapy, especially if an agent with a long half-life, such as ceftriaxone, is used. Although a number of agents can be used, fluoroquinolones have been recommended by a number of authors as empiric therapy unless sensitivity to TMP-SMX is known [3]. If the Gram stain is suspicious for *Enterococcus*, these authors recommend the addition of amoxicillin until an organism is identified. If the patient requires hospitalization, the Infectious Disease Society of America guidelines recommend one of three initial intravenous therapies [20]: (1) fluoroquinolone, (2) aminoglycoside with or without ampicillin, and (3) extended-spectrum cephalosporin with or without an aminoglycoside. The guideline

goes on to recommend changing to culture-specific oral medication when defervescence occurs, usually at 48 to 72 hours. Failure to defervesce in this time frame should alert the clinician to a potential complicated infection, and further work-up should be initiated.

One recent study did examine a shorter course of antibiotics than the now accepted 10 days to 2 weeks of treatment for acute pyelonephritis [41]. Nonpregnant, premenopausal women without comorbid conditions were randomly assigned to receive 7 days of oral ciprofloxacin or 14 days of TMP-SMX. Greater clinical and bacteriologic cure rates were noted in the ciprofloxacin group, in addition to the occurrence of fewer adverse events. Whether the 7-day regimen is comparable to a 14-day regimen with ciprofloxacin was not studied, however.

Complicated urinary tract infections

Urinary tract infections are considered complicated if conditions exist that increase the likelihood of the patient having persistent or recurrent infection or treatment failure. These conditions include abnormal urinary tract anatomy, such as prostate gland enlargement leading to obstruction function; abnormal function, such as a neurogenic bladder; or abnormal metabolism, such as occurs in diabetic patients. The presence of multi-resistant organisms also is considered complicated. The authors discuss complicated UTIs in the elderly, UTIs in men, perinephric and renal abscess, and emphysematous pyelonephritis.

Elderly patients

There is no current evidence that asymptomatic bacteriuria increases the morbidity and mortality in elderly patients, as once was thought. Screening has shown that up to 40% of elderly patients have asymptomatic bacteriuria periodically [42]. Studies demonstrate that treatment of asymptomatic bacteriuria does not improve chronic genitourinary symptoms or mortality [43,44]. Although elderly patients presenting with nonspecific symptoms such as anorexia, fatigue, or weakness deserve work-up, these symptoms should not be attributed to a positive urine culture result obtained from an otherwise asymptomatic patient [45]. The practice of obtaining ''routine'' urine culture samples in patients without genitourinary symptoms should be discouraged.

> *Escherichia coli* is a less common cause of acute pyelonephritis in the elderly but is still responsible for approximately 60% of cases. The increased incidence of instrumentation and catheterization in these patients may lead to infections with organisms such as *Proteus, Klebsiella, Serratia*, or *Pseudomonas*. In more than 20% of patients, the predominant symptoms are not genitourinary but gastrointestinal or pulmonary. One third of patients do not show the usual febrile response and have no leukocytosis;

thus urinalysis and culture are as important in acutely ill elderly patients as they are in infants.

Although 60% of patients show bacteremia and up to 26% have septic shock, the mortality rate is not high when the patients are treated rapidly and properly. More than 95% of patients become afebrile within 48 hours. Radiologic evaluation should be performed early, and the examiner should look for obstructive disorders such as stones that lead to continuing sepsis. The elderly male patient will more frequently have acute prostatitis, often secondary to instrumentation of the urinary tract [46].

Urinary tract infections in men

Other than prostatitis, UTIs are rare in men, except at the extremes of age. The prevalence of UTIs increases in men older than 50 years, mainly through prostatic enlargement and instrumentation of the lower urinary tract. Prostatic involvement may occur in more than 80% of cases of febrile UTIs in men [47]. Acute bacterial prostatitis presents with fever, symptoms of UTI, and possibly rectal or perineal pain. A urine culture is usually adequate to identify the infecting organisms. Relapsing UTIs, despite adequate antimicrobial therapy, may indicate chronic bacterial prostatitis. Antibiotics with high tissue penetration into the prostate gland, such as doxycycline, trimethoprim, or a fluoroquinolone, should be used for treatment [48].

Young men have been found to be at risk for uncomplicated infection, such as cystitis or urethritis, if they are homosexual or uncircumcised or through heterosexual transmission of uropathogens [10]. *Escherichia coli* is the causative organism in almost half of the infections, whereas species of *Proteus*, *Providencia*, *Klebsiella*, *Enterobacter*, *Pseudomonas*, and *Citrobacter* are isolated less frequently [48]. Gram-positive cocci account for one fifth of the UTIs in men, primarily *Enterococcus faecalis* and occasionally *Staphylococcus epidermidis* or *S. aureus*. After obtaining a urine culture, treatment should consist of a 7-day course of therapy with either a fluoroquinolone or TMP-SMX. Rapid response to therapy is a good indicator that further urologic work-up is not indicated.

In the past, radiographic evaluation has been recommended for all initial male UTIs. Recent studies suggest this step may not be needed in all cases. Although most elderly men and approximately 30% of young men with a single episode of UTI have some anatomic abnormality revealed by excretory urography or intravenous pyelography, it may not be clinically relevant [48]. Ulleryd et al [49] prospectively evaluated 85 men aged 18 to 86 years with community-acquired, febrile UTIs. Surgically correctable disorders were found in 20 patients, all of whom were identified by a history of voiding difficulties, acute urinary retention at the time of the infection, microscopic hematuria at the 1-month follow-up, or through development of early recurrent symptoms. Urethral strictures and benign prostatic hypertrophy were the most common obstructing lesions. Microscopic

hematuria at the first follow-up appointment was found in cases of stone disease and bladder cancer.

Perinephric and renal abscess

Treatment failure is likely to occur when the infection of the kidney is more extensive. When the suppurative process is within the renal parenchyma, it is referred to as a *renal abscess* or as a *perinephric abscess* if the process is in the tissues surrounding the renal capsule. A perinephric abscess arises by direct extension from an infected kidney or by hematogenous spread, usually from sites of skin infection. Although in the past *Staphylococcus aureus* was the usual cause, currently the bacteria most frequently cultured are gram-negative enteric bacteria such as *E. coli, Proteus, Pseudomonas*, and *Klebsiella* [50].

In a retrospective review of 88 cases of patients with renal and perinephric abscesses, Yen et al [50] found that diabetes mellitus (47%), renal calculi (41%), and ureteral obstruction (20%) were the most common predisposing conditions. Fever and chills combined with flank pain or tenderness are the most common symptoms and signs, with some patients having abdominal pain and tenderness and possibly an abdominal or flank mass. Patients with perinephric or renal abscesses remain febrile longer, up to a week, despite antibiotic therapy, compared with less than 4 days for an acute UTI without abscess formation. Symptoms may be present up to 2 weeks before a diagnosis is made. Patients with extended duration of UTI signs and symptoms, renal insufficiency, or any of the predisposing systemic disorders should be considered for early ultrasound or CT evaluation. Initiation of antibiotic therapy and percutaneous drainage improves outcome.

Initial antibiotic therapy should be broad spectrum to cover the variety of organisms that can cause perinephric abscess. The antibacterial regimen can be more specific once a specimen has been obtained and can be altered further by culture results. In many cases, drainage of the abscess may be performed by percutaneous catheter insertion. Relief of any concomitant ureteral obstruction by ureteral catheterization or nephrostomy tube is necessary, with later definitive surgical therapy.

Emphysematous pyelonephritis

Emphysematous pyelonephritis can occur when infection is due to gas-producing organisms, such as *E. coli, Candida* spp, and *Clostridium septicum*, leading to extensive renal parenchymal gas formation and tissue necrosis with renal hematoma formation [46,51]. This rare and very serious condition can lead to septic shock and acute renal failure. Fewer than 100 case reports of emphysematous pyelonephritis are in the literature, occurring most commonly in middle-aged to elderly patients who are diabetic. Cases have been described in polycystic kidney disease and in renal allografts. In 10%

of the cases, bilateral renal involvement occurs. Successful treatment may result with relief of the obstruction, if present, by the use of antibiotics with high tissue penetration, such as quinolones. Nephrectomy must be strongly considered, however, because the mortality rate for emphysematous pyelonephritis approaches 75% in patients with the disorder.

Asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as the presence of at least 10^5 colony-forming units of urinary tract pathogens per milliliter, typically on two successive cultures. Patients at risk for serious sequelae from asymptomatic bacteriuria include the immunocompromised, those with abnormal urinary tract anatomy or function, and pregnant women. Men or women undergoing genitourinary procedures and renal transplant recipients are also at increased risk. Screening for asymptomatic bacteriuria preoperatively, with appropriate treatment, has been shown to reduce postoperative complications, including bacteremia [52].

The prevalence of asymptomatic bacteriuria varies among different populations studied; 100% in patients with long-term indwelling catheters, 50% in patients with intermittent catheterization, and 15% to 50% in institutionalized elderly patients [53]. In healthy women 18 to 40 years of age, the prevalence of asymptomatic bacteriuria is approximately 5%, increasing to 20% or more in ambulatory elderly women [54]. Of these patients, symptoms developed in fewer than 10%, with most occurring within 1 week of identification of asymptomatic bacteriuria. If pyuria was present, the association between asymptomatic bacteriuria and subsequent UTI was stronger. Diaphragm use with a spermicide, sexual intercourse, the use of a spermicide alone, and the use of a cervical cap were all found to be associated with asymptomatic bacteriuria. No differences were found in virulence of the organisms as determined by genotyping between those causing symptomatic and asymptomatic bacteriuria. Women with asymptomatic bacteriuria are at increased risk for developing subsequent symptomatic UTIs, but multiple studies have shown they are not at increased risk for hypertension or renal failure [53].

Diabetic women have a prevalence of asymptomatic bacteriuria of 26% compared with 6% of women without diabetes mellitus [55]. Geerlings et al [56] found that the incidence of UTI was nearly double during an 18-month follow-up period for women with type II diabetes mellitus and asymptomatic bacteriuria at baseline, compared with those without asymptomatic bacteriuria at baseline. Asymptomatic bacteriuria at baseline was not associated with an increased incidence of UTI in women with type I diabetes mellitus. As with nondiabetic women, there was no association of asymptomatic bacteriuria with worsening renal function for either type I or type II diabetes mellitus.

Catheter-associated urinary tract infections

One quarter of hospitalized patients undergo catheterization of the urinary bladder. Urinary catheters account for up to 40% of nosocomial infections [57,58]. Bacteriuria has been demonstrated in 26% of patients with indwelling catheters from 2 to 10 days. And, among these patients, one quarter will develop symptoms of a UTI. Bacteremia from a urinary tract source develops in 3.6% of these patients [59]. Tambyah and Maki [60] found that catheter-associated UTIs were mostly asymptomatic. In their study, bacteremia was associated with asymptomatic bacteriuria in less than 1% of cases. More than half of the patients catheterized for 5 days or longer developed bacteriuria or candiduria [10]. Bacteriuria is present in virtually all patients requiring indwelling urethral catheterization for more than 30 days. Bacteriuria is frequently polymicrobial. Unfortunately, no prophylactic regimen has been shown to prevent bacteriuria, and treating asymptomatic bacteriuria does not reduce the complications of bacteriuria in catheterized patients. Fever and peripheral leukocytosis have little predictive value in making the diagnosis of a UTI, especially in cases caused by gram-positive bacteria or candida, infections which occur more frequently in catheterized patients [60]. Catheter-associated UTIs are more difficult to diagnose, need to be promptly and appropriately treated, and more importantly, should be prevented.

Most bacterial pathogens in a catheterized urinary tract attain high concentrations within a 24-hour period, unlike those in a noncatheterized urinary tract, where small numbers of organisms are eliminated efficiently [61]. Pathogenic bacteria in catheterized urinary tracts create multicellular biofilm communities creating structured groups of organisms embedded in a polysaccharide matrix that protects the bacteria from both the host immune system and from chemotherapy directed at clearing the infection [62]. Determining a mechanism to inhibit the formation of these biofilms will be a critical future step in the prevention of catheter-associated UTIs. The most common bacterial pathogens causing bacteriuria in catheterized patients are *E. coli*, *Enterococcus*, *Klebsiella*, *Pseudomonas*, *Proteus*, and *Enterobacter* [63]. *Candida* is found frequently in catheterized patients [64]. In chronically catheterized patients, complications include bladder cancer [65], urinary tract stones or obstruction [66], acute UTIs [67], and chronic pyelonephritis and renal inflammation [68]. Chronically catheterized patients are at a much-increased risk of developing bacteremia. The question of when to treat a catheter-associated UTI is a difficult one to answer, especially when one considers that most bacteriuria in such patients is asymptomatic and rarely associated with bacteremia [69].

Minimizing the duration of catheterization is an effective strategy to decrease the incidence of catheter-associated UTIs in a hospital setting [70]. Although bacteriuria does occur in male patients with chronic external urinary catheters, the incidence is much decreased compared with patients

with indwelling urinary catheters [71]. Prophylaxis with antibiotics is unnecessary and actually may promote infection with resistant organisms [72]. Factors that increase the risk of bacteriuria during indwelling urethral catheterization are female sex, elderly age, or critical illness [63,73,74]. Urosepsis is more likely to occur in catheterized patients older than 60 years of age, in those with an extended hospital stay, and in patients with an extended duration of urinary catheterization [75]. Active infection-control programs, which reduced the frequency and duration of use of indwelling urinary catheters, have been demonstrated to reduce hospital-acquired UTIs by approximately 25% [76]. A recent literature review suggests that silver alloy–coated urinary catheters are significantly more effective in preventing UTIs than silver oxide catheters (now no longer available in the United States) or uncoated urinary catheters [77]. Each episode of a symptomatic UTI in a hospitalized patient costs an additional $676, and catheter-related bacteremia will likely cost $2836 [59]. These data suggest that the additional $6 spent for silver alloy–coated catheters actually may reduce overall hospitalization costs for patients who require a urinary catheter.

Urinary tract infection in pregnancy

Two percent to 7% of pregnant women develop asymptomatic bacteriuria [78]. Without treatment, almost one third of pregnant patients with asymptomatic bacteriuria develop cystitis [79]. Pyelonephritis develops in as many as 30% to 50% of untreated cases, increasing the risk for premature labor and low-birth-weight infants [80,81]. The US Preventive Services Task Force recommends obtaining a screening urine culture between 12 and 16 weeks of gestation [78]. Gram stain of unspun urine correlates well with the presence of significant bacteriuria [82]. Short-course therapy with antibiotics that are safe for the mother and fetus, such as the aminopenicillins, cephalosporins, and nitrofurantoin, should be given [83]. Trimethoprim-sulfamethoxazole should not be used in the first trimester because of possible teratogenic potential or in the third trimester because of displacement of bilirubin from binding sites, increasing the risk for kernicterus.

Urinary tract infections are one of the most common complications of pregnancy, with an incidence as high as 8%. Pregnancy may predispose women to UTIs because of stasis from hormonal and mechanical causes, glucosuria, and proteinuria [84,85]. Predictors of UTIs diagnosed at the first prenatal visit include a pre-pregnancy history of UTIs, low socioeconomic status, and sickle cell disease [86].

The causative organisms are the same as those organisms that typically cause UTIs and include the Enterobacteriaceae, especially *E. coli*, *Klebsiella*, and *Enterobacter* species in more than 90% of cases [87]. Group B streptococcus bacteriuria is associated with neonatal sepsis, supporting the

recommendation that women with this infection should receive both intrapartum antibiotic prophylaxis and treatment at the time of diagnosis. Maternal conditions and procedures requiring urethral catheterization increase the risk for a postpartum UTI.

Urinary tract infections are associated with a number of different adverse outcomes. Maternal UTIs and asymptomatic untreated bacteriuria are associated with fetal mortality, mental retardation, or developmental delay in infants [88,89]. This excess fetal mortality is most associated with maternal UTI that occurs within 15 days of delivery [90]. There is also an association between maternal UTI and prematurity or low birth weight [91,92].

Treatment of UTIs in pregnancy must be considered with the fetus in mind. Tetracyclines can stain the deciduous teeth; trimethoprim should not be used for the previously stated reasons, and the quinolones are associated with Achilles tendon rupture in animal models, so they are not recommended for use during pregnancy. Antibiotics that are appropriate for treatment of UTIs in pregnancy include cephalexin, 250 mg by mouth four times daily; erythromycin, 250 to 500 mg by mouth four times daily; nitrofurantoin, 50 to 100 mg by mouth four times daily; amoxicillin-clavulanic acid, 250 mg by mouth four times daily; or fosfomycin, one 3-g sachet [93,94]. The course of antibiotics should be 7 to 10 days, although fosfomycin is effective as a single dose. Because UTIs recur in up to 5% of pregnancies, prophylactic treatment with nitrofurantoin or cephalexin once daily is recommended for recurrent UTIs in pregnancy [95].

Pediatric urinary tract infections

Urinary tract infections occur in 5% of febrile infants and in 1.9% of boys and 8.1% of girls older than 1 year. Urinary tract infections occur more commonly in females than in males at any age [96]. This finding is in contrast to early data that revealed that boys develop UTIs more frequently up to 1 year of age, possibly because circumcision has been shown to reduce the incidence of UTIs by 5- to 20-fold in infants less than 1 year old [97–99].

One can classify pediatric UTI as a first or recurrent infection. A first infection is simply the first UTI diagnosed. First infections are considered complicated because of the high rate of pathologic urinary abnormalities found in infants and children [100]. The clinical presentation of a UTI in children is not always a classic one. Infants and children may present with irritability, fever, poor feeding, vomiting, or diarrhea. Typical symptoms such as dysuria, frequency, and flank discomfort become more common with increasing age [101].

The diagnosis of a UTI is made with urine culture. The best rapid test to diagnose a UTI is a Gram stain of fresh, unspun urine [96]. Urine may be

obtained from the patient by suprapubic aspiration, urethral catheterization, by way of clean-catch during midstream, or by way of a plastic bag attached to the perineum. These options are listed in order from most to least sensitive and invasive [102]. Urinary tract infection is defined best by gram-negative bacteria in any number or more than a few thousand gram-positive cocci from a suprapubic aspiration; bacterial colony counts of more than 50,000 colony-forming units per milliliter of catheterized urine with more than 10 white blood cells/mL; or more than 10,000 colony-forming units/mL of a cleanly voided male specimen or more than three samples with greater than 100,000 colony-forming units/mL from a female patient [103].

According to the American Academy of Pediatrics practice parameter on UTIs, treatment must be adjusted based on age, the clinical appearance of the patient, and the ability to retain oral intake. Intravenous therapy is recommended for those unable to take oral medications. Empiric treatment with TMP-SMX demonstrates higher cure rates than amoxicillin, which is associated with higher resistance rates. Cephalosporins are effective against the typical pathogens but do not treat enterococci adequately. If an upper UTI is suspected, empiric treatment with intravenous ampicillin with an aminoglycoside or a third-generation cephalosporin alone is recommended [101]. The duration of treatment should be 7 to 14 days. Treatment may be administered orally if the drug does not have a toxic effect on the patient and he or she is greater than 3 months of age [104]. A meta-analysis revealed that a 3-day course of TMP-SMX is as effective as a conventional duration of this drug for an uncomplicated UTI.

Asymptomatic bacteriuria denotes the finding of bacteria in the urine of an asymptomatic patient. Antibiotic treatment is not indicated if the patient's voiding habits and urinary system are normal. Voiding cystourethrogram at 1 month and a dimercaptosuccinic acid scan 6 months later are recommended in these patients to assess for abnormalities of the urinary tract [105].

There is no evidence to support the myth that improper wiping techniques may increase the risk for UTIs, and bubble baths are not associated with UTIs [106]. Constipation is correlated with recurrent UTIs [107]. Functional and anatomic genitourinary tract abnormalities often predispose a child or infant to develop UTIs [96]. Treatment of these disorders will result in a decreased frequency of UTIs [108,109]. Vesicoureteral reflux is the most common abnormality of the urinary tract in children with UTIs and can lead to end-stage renal disease, hypertension, and renal scarring [110]. Renal scarring best correlates with serious adult complications, such as hypertension and end-stage renal disease, emphasizing the importance of early detection and management [111].

All patients with UTIs who are 2 months to 2 years of age should undergo evaluation with renal ultrasound, voiding cystourethrogram, or radionuclide cystography. A voiding cystourethrogram may be obtained safely within the first 7 days of the infection [112]. The incidence of

vesicoureteral reflux in siblings of children already diagnosed approaches 50%, suggesting that it is reasonable to screen all children in the family of an index case [113].

Pain may occur with upper or lower UTIs. Phenazopyridine, a local anesthetic for the urinary tract, is quite effective at a dose of 12 mg/Kg/day for children as young as 6 years. It should be used for no longer than 1 week to reduce the risks of hemolytic anemia and hepatotoxicity. Phenazopyridine is contraindicated in patients with G6PD deficiency. Relief also may be accomplished by urinating in a warm bath; drinking increased amounts of fluid to dilute the urine; or altering the pH by drinking fluids like cranberry juice.

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