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Urinary Tract Infection (UTI): New Diagnostic Modalities, Alterations in Drug Resistance Patterns, and Current Antimicrobial Guidelines

Part I: Diagnosis, Evaluation, and Principles of Antibiotic Selection

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In the constantly shifting landscape of drug resistance, antibiotic options, and pharmacoeconomic considerations, urinary tract infection (UTI) continues to be one of the most frequently diagnosed conditions in patients presenting to emergency departments (EDs) and hospital-based clinics.

It is estimated that practitioners manage 7 million new cases of cystitis in the United States each year, and UTIs now account for approximately 1 million hospitalizations annually.[1,2] Moreover, UTIs are the leading cause of gram-negative bacteremia in patients of all ages, and are associated with a high risk of morbidity and mortality, especially in the elderly.[3] The total annual cost of treatment is more than a billion dollars.[4]

Among common infections managed in the ED and acute hospital setting, few conditions have treatment guidelines, antibiotic selection strategies, or diagnostic protocols that have changed or evolved as rapidly as those used for UTI. Despite a general consensus that empiric treatment of UTI in adult women requires, at the very least, mandatory coverage of Escherichia coli *and other gram-negative organisms, antibiotic selection strategies, including initial choice of therapy and duration of treatment, vary widely among practitioners and institutions.*

There are many reasons for inconsistencies in the current approach to UTI management among hospital-based physicians. Unfortunately, deciphering the strengths and weaknesses of recommendations issued by different authoritative sources can be problematic and confusing, especially since resistance patterns of infecting uropathogens may vary among geographic regions, and because outcome-effectiveness, failure rates, total-resource costs to achieve clinical cure, the risk of recurrent infection, and evolving bacterial resistance issues are not always entered into the drug selection equation.

Because no single set of guidelines is applicable to every patient or hospital practice environment, management guidelines for UTI must be "customized" for the local practice set-

ting, and as always, clinical judgment must prevail. This means taking into account local antibiotic resistance patterns, epidemiological and infection incidence data, and patient demographic features.

Even when these factors are considered, a number of important questions about drug selection issues for UTI still remain: 1) What is the appropriate initial, empiric choice for uncomplicated UTI, ciprofloxacin or trimethoprim/sulfamethoxazole (TMP/SMX); 2) What are the specific intensification and treatment trigger criteria that support amplifying initial spectrum of coverage from TMP/SMX to a fluoroquinolone; 3) How should evolving resistance of E. coli *to TMP/SMX affect initial antimicrobial therapy in hospitalized patients with UTI; 4) What is the role of risk-stratification guidelines for initial antibiotic selection in elderly patients with UTI; 5) What is the optimal duration of therapy for uncomplicated and complicated UTIs; 6) What type of therapy and its duration can be characterized as "optimal;" and 7) Which antibiotic currently provides correct spectrum coverage, safety, and reliability for outpatient and inpatient treatment of UTI?*

Although optimizing cure rates with so called convenient, dose- and duration-friendly branded agents that provide appropriate and predictable coverage with a low risk of antimicrobial resistance may be perceived as costly on a drug-acquisition basis, it is important to stress the following point: Antimicrobial agents with more predictable coverage against pathogens implicated in UTI can help avoid the unnecessary costs of treatment failures, disease progression, patient re-evaluations, return visits, patient dissatisfaction, and the pharmacological re-servicing costs associated with initiating a second course of antibiotics.[5]

In this sense, antibiotics that lower barriers to clinical cure and provide a predictable spectrum of coverage can be seen as "productivity tools" that improve efficiency of clinical care, and potentially, reduce the overall costs associated with inpatient and acute outpatient management of UTI. These benefits are especially important in the older patient, in whom repeated hospitalizations increase the risk of nosocomial infections and drug-related complications.

In light of the important advances, changes, and refinements that have occurred in the area of UTI treatment over the past year, this comprehensive, state-of-the-art review presents a revised and updated set of guidelines outlining UTI epidemiology and management in the ED and hospital-based setting. Special emphasis has been given to both epidemiological data, demonstrating the importance of correct spectrum coverage with specific fluoroquinolones, and to the selection of initial antibiotics for patients deemed suitable for discharge.

In addition, a detailed, evidence-based analysis comparing ciprofloxacin and TMP/SMX is presented to guide antibiotic selection in patients with uncomplicated UTI and pyelonephritis.[5] *Cautionary notes about the overuse of extended-spectrum fluoroquinolones are outlined, and evidence-based studies confirming ciprofloxacin's workhorse role in hospital-based treatment of UTI is discussed. Drawing upon consensus panels, expert opinion, and clinical trials, this clinical consensus report presents antimicrobial protocols and treatment guidelines linked to, and driven by, risk-stratification criteria, evidence-based trials, and specific clinical profiles of patients presenting to the hospital with symptoms and signs suggestive of UTI.*

— The Editor

Introduction

The prevalence of UTIs varies greatly with age, race, and gender. Between 4.1% and 7.5% of serious bacterial infections in febrile pediatric patients are attributed to UTIs, with the highest prevalence (17%) in white females.[6,7] The majority of patients with UTIs are female, with close to a 50% lifetime occurrence rate.[3,4] As both sexes age, the incidence of bacteriuria increases from fewer than 5% in young adult women and fewer than 0.1% in young adult males to at least 20% of women and 10% of men older than age 65.[8]

Because younger patients are at low risk for occult genitourinary tract abnormalities and are less likely to have comorbid

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conditions, they respond predictably to empiric antibiotic therapy. Certain patient subgroups, however, have complicating conditions that increase the risk of acquiring invasive, systemic infection or for having therapy fail. Complicated UTI may occur in men, children, and pregnant women, but it is especially common in the elderly, in immunocompromised patients, and in individuals with neurologic disorders.

Severity of infection in these patient subgroups ranges from mild cystitis to life-threatening urosepsis, which may be more difficult to treat because of: 1) associated structural or functional genitourinary tract abnormalities; 2) resistant organisms; and/or 3) inadequate host defenses. Accordingly, special consideration to antibiotic selection must be given to elderly patients, who require prompt, appropriate therapy and thorough evaluation of their UTIs to avoid prolonged infection or serious renal sequelae.

Diagnosis: Screening, Culture, and Radiographic Studies

Confirming the clinical diagnosis of UTI may be challenging in both the younger and older patient populations. Detection of UTI is especially important in these patient subgroups because inadequate or delayed therapy may lead to renal deterioration and life-threatening systemic toxicity.

The Elderly. UTI in the elderly may present in a manner that is different from its typical presentation in younger adults. For example, the classic lower tract symptoms of frequency, urgency, and dysuria, accompanied by upper tract findings of chills, flank pain, and tenderness, may be altered or absent in the geriatric patient. Moreover, the fever may be absent and some patients may be hypothermic.[9] Although acute pyelonephritis in the elderly typically exhibits a septic syndrome manifested as fever, tachycardia, and altered mental status, UTIs in the elderly may present with a wide range of chief complaints, which may include mental status deterioration, nausea, vomiting, abdominal pain, or respiratory distress.[10,11]

In one study of community-dwelling adults older than age 50, bacteremic UTIs most commonly presented as confusion, cough, and dyspnea. New urinary symptoms were the chief complaint in only 20% of cases.[11] In another study, only one-half of older bacteremic UTI patients were febrile. However, older patients were no more likely to be afebrile than were younger bacteremic patients (40% of whom had normal temperatures).[12] Because of the wide range of presenting symptoms, the misdiagnosis of UTI in the geriatric patient ranges from approximately 20% to 40%.[5,10,13]

The high misdiagnosis rate can be attributed to patients presenting with non-urinary complaints. In light of the possible difficulties with identifying elderly patients with UTI and the significant mortality rate associated with inadequate or delayed therapy, clinicians must maintain a high index of suspicion for this condition. In addition, certain laboratory and microbiological procedures, in combination with uncharacteristic clinical findings, will optimize detection of UTI in the geriatric patient.

It may be clinically impossible to ascertain whether fever in the bacteriuric elderly patient lacking urinary symptoms is an invasive urinary infection. The majority of febrile episodes in the bacteriuric, non-catheterized elderly are unlikely to be due to invasive infection.[14,15] Foul-smelling urine is sometimes considered a symptom in the elderly adult, especially in the institutionalized patient. Urinary bacteria produce polyamines, which account for the odor, and although antibiotic therapy may ameliorate the odor, use of antibiotics for this exclusive purpose is not advocated.[14] Management of incontinence and improved urinary hygiene, especially in the institutionalized patient, usually will solve this problem.

Pediatric Age Group. Extensive research conducted over the past few years evaluated the diagnostic approach to the diagnosis of UTI in children younger than 5 years of age, and especially in those younger than 2 years of age. The difficulty with making this diagnosis is evident from studies showing that fever and irritability are the most common complaints in children.[16,17] In fact, up to 80% of infants with culture-proven UTIs present with only fever or failure to thrive as their chief symptom.[16-18] Furthermore, the presence of nonspecific symptoms in children with UTIs also are common to other childhood infections, including viral syndromes, gastroenteritis, otitis media, and upper respiratory infections.[16,17]

In one study of 200 febrile infants with UTI diagnosed by urine culture, 64% were initially diagnosed by the examining physician with another cause as a source of their fever.[19] Pediatric investigators identified risk factors associated with an increased risk of UTI in children younger than 2 years of age. They include: temperature greater than 39°C (> 103.5°F), fever for longer than two days, white race, age younger than 1 year, and no other obvious source of fever.[19] The presence of two or more of the above risk factors yielded a sensitivity of greater than 99% and specificity of 71% for detection of UTI in children in this age group.[19]

Screening and Culture. The most common screening tests for UTI include urine dipstick and microscopic urinalysis, with a combination of leukocyte esterase (LE) and nitrate testing achieving sensitivities of 78-92% and specificities of 65-98%.[20,21] Enhanced microscopic analysis of centrifuged urine from pediatric patients has been found to have a sensitivity of 94% and a specificity of 84-92%.[12] The authors of a recent study using enhanced urinalysis (coupling a white blood cell [WBC] count by hemocytometer and a gram stain on uncentrifuged urine) recommend a urine dipstick as a reliable and economic screening test. In their view, enhanced urinalysis should be reserved for use in neonates (infants < 8 weeks of age) and in patients with comorbid conditions, including underlying anatomic renal abnormalities.[20]

Urine culture remains the definitive test for confirming the diagnosis of UTI.[16,18] Culture recommendations differ depending upon the risk group. Adult patients who require hospitalization for presumptive UTI should be cultured to confirm an etiologic diagnosis. In children, the approach is more complicated. The updated American Academy of Pediatric recommendations for diagnosis of UTI in children ages 2 months to 2 years with an unexplained fever offer the following guidelines regarding urine culture: 1) Culture a specimen obtained by suprapubic aspiration (SPA) or bladder catheterization or; 2) Obtain a urine specimen

by the most convenient method and analyze it by urine dipstick or urinalysis.[18] If the urine specimen is positive for LE or nitrite, obtain a culture by SPA or bladder catheterization. The importance of accurate diagnosis in infants and young children, in part, is related to the concern over renal scarring, subsequent hypertension, and end-stage renal disease, which may manifest years later in approximately 10-15% of patients who have had pyelonephritis.[17,22]

Urine cultures rarely are indicated to diagnose simple cystitis in otherwise healthy adults. However, they should be obtained from pregnant women for detection of both asymptomatic and symptomatic bacteriuria. They also are required or recommended if the patient has: 1) continued symptoms of UTI while on treatment; 2) suspected pyelonephritis; 3) a history of recurrent UTI; 4) used antibiotics recently; or 5) any comorbid neurologic or anatomic abnormalities.[23] Blood cultures can be obtained in children younger than 6 months of age with presumed pyelonephritis, although bacteremia is rare in this age group.[24]

A recent study of 391 pregnant women with pyelonephritis found that initially prescribed antibiotics were changed in only 1% of cases after confirmation of bacteremia (positive blood cultures).[25] In addition, these patients had a similar clinical course to those without bacteremia. Based on this work and previous studies, the authors suggest eliminating blood cultures in the routine management of pyelonephritis in pregnant women, citing possible significant cost savings (approximately $15 million annually) and no significant compromise in patient care.

Radiographic Advances with Imaging and Ultrasound. The goal of radiologic evaluation is: 1) to identify renal scarring or parenchymal damage at the time of diagnosis; 2) to identify the presence of underlying functional or anatomic abnormalities that predispose the patient to UTIs or renal damage; and 3) to provide a baseline for further comparisons.[26,27] As a rule, a renal ultrasound is the first step for identifying parenchymal disease or signs of obstructive uropathy such as a hydroureter or hydronephrosis in infants, children with suspected pyelonephritis, and children with a known immunodeficiency or suspected anatomic abnormality.[16,18,27] Renal ultrasound can be performed at any time during the course of treatment. A voiding cystourethrogram (VCUG) is excellent for identifying vesico-ureteral reflux—the most common abnormality associated with UTI in infants. This condition is present in more than 50% of infants with UTI who are younger than 1 year of age.[3]

Although new ultrasonographic techniques are not always available or appropriate in the ED setting, emergency physicians should be aware of their indications and limitations. It also should be stressed that these techniques are very operator dependent. The development of a fluoroscopic VCUG is a recent advance in imaging. It allows continued monitoring of the urinary system for intermittent reflux, which may be missed with conventional modalities.[3] A VCUG generally is performed when there is evidence of urine sterilization. Some experts wait for four weeks after treatment initiation due to concerns that bladder spasms will interfere with the quality of the study.[27] A 99mTc-DMSA (technetium^{99}-labeled dimercaptosuccinic acid) nuclear cortical scan generally is considered the gold standard for identifying previous renal parenchymal damage. It is recommended in patients with abnormalities noted on renal ultrasound or VCUG and for toxic patients who are unresponsive to parenteral antibiotic treatment.[28] These tests generally have replaced intravenous pyelography (IVP) as the studies of choice, although in certain cases IVP still is performed.

Recently introduced, power Doppler ultrasonography was developed as an alternative to standard B-mode ultrasound. This technique has demonstrated great promise, as it displays an image analogous to a perfusion map that is sensitive to the low-flow states seen in acute pyelonephritis.[29] Preliminary reports reveal an 89% sensitivity relative to CT and a 75% sensitivity relative to nuclear renal scans. This test is noninvasive and avoids radiation, intravenous injection, and sedation for the majority of patients. Some centers prefer CT to ultrasound for stones, hydronephrosis, or pyelonephritis. In the future, however, power Doppler ultrasonography may replace CT or nuclear scans for suspected pyelonephritis.[29] Limitations of this modality include its being operator and reader dependent, motion sensitive, and difficult to perform on an uncooperative child.

Imaging studies rarely are indicated in adult patients with UTI. Patients with fever, despite antibiotic treatment, for longer than 48-72 hours who have signs of systemic toxicity or bacteremia should be suspected of having a complicated infection with renal or perirenal abscess, anatomic obstruction, or nephrolithiasis.[30] Ultrasound has become more available in the ED and has been recommended by the American College of Emergency Physicians as a valuable tool for the ED evaluation of selected medical and traumatic conditions.[31]

The diagnosis of renal abscess is most reliably made with CT scans; however, one group of investigators retrospectively studied the use of ultrasound by emergency physicians for the diagnosis of renal abscess in the ED setting.[32] The physicians were trained for at least three months in the use of abdominal ultrasonography by the radiology department, and senior radiologists verified that the emergency physicians were able to recognize the imaging of renal abscess. Although a high rate of success was achieved for diagnosis of renal abscesses, the study was limited by the small numbers of enrolled patients and lack of control patients.

Clearly, a prospective study of ultrasonographic evaluation by emergency physicians for screening high-risk patients suspected of having renal abscesses is needed to obtain sensitivity and specificity rates.[32] Currently, this study group recommended that emergency physicians focus on patients with diabetes, renal stones, history of renal transplant, immunosuppression, longer duration of symptoms of UTI, and renal failure. Ultrasound or CT scan should be used promptly in the ED to aid in the early diagnosis of renal abscess. Ultrasound also is useful for establishing adequate vascular perfusion in renal transplant recipients.

Bacteriologic Resistance Patterns

The emergence of resistance to antibiotics, especially to TMP/SMX, is changing initial selection patterns in patients with both uncomplicated and complicated UTI. Antibiotic

Table 1. Pathogens Responsible for Uncomplicated and Complicated Urinary Tract Infections[§]

1. *Escherichia coli*
2. *Staphylococcus aureus**
3. *Klebsiella pneumoniae*
4. *Proteus mirabilis*
5. *Enterococcus** *faecalis*
6. *Pseudomonas aeruginosa*
7. *Enterobacter cloacae*
8. *Citrobacter*

[§] = Listed in order of decreasing frequency
* = Gram-positive organisms

selection should be determined by local antibiotic resistance patterns. To appreciate the scope of the problem, a brief review of the common uropathogens is warranted. The most common uropathogens identified in adult patients with UTI include enteric gram-negative bacteria, with *E. coli* being the most common (60-80% of UTIs). *(See Table 1.)* The remainder of infections are caused by coagulase-negative *Staphylococcus saprophyticus* (10-20%), while *Proteus mirabilis, Klebsiella,* and *Enterococcus* account for fewer than 5%.[3,8,33] Other aerobic, gram-negative bacteria of the *Enterobacteriacea* family include *Citrobacter, Enterobacter, Serratia,* and *Salmonella*.[16,18,22] Non-enteric aerobic gram-negative rods such as *Pseudomonas* and aerobic gram-positive cocci such as *Enterococcus* are less prevalent in immunocompetent hosts. *(See Table 1.)* Group B streptococci infection is observed in neonates secondary to inoculation from a colonized mother during delivery through the vaginal canal.

Anaerobic bacteria rarely are pathogenic despite their prevalence in fecal flora. The *Lactobacillus* species, coagulase-negative staphylococci, and *Corynebacterium* are not considered clinically significant isolates in the urine of healthy children between 2 months and 2 years of age.[17,18] *Corynebacterium, Lactobacillus,* and *Streptococcus* species are identified only rarely; when they are present, they nearly always represent contamination of the specimen rather than a true pathogen. In complicated UTI, in addition to *E. coli,* there is a higher prevalence of *Pseudomonas, Enterobacter* species, *Serratia, Acinetobacter, Klebsiella,* and enterococci.[30] There are anecdotal reports of treatment for *Gardnerella vaginalis,* Lactobacilli, *Chlamydia trachomatis,* and *Ureaplasma urealyticum* in pregnant women, but it is unclear whether these organisms represent true pathogens in this population.[34,35] Candidal species are now emerging in greater numbers, especially in catheterized patients and those who have received previous treatment for enterococcal UTIs.[30]

The high incidence of UTIs, the potential for complications, and the associated costs of treatment emphasize the importance of appropriate antibiotic therapy. Microbial resistance to nearly all classes of antimicrobials continues to rise despite increasing awareness and concerns worldwide. European studies have shown *E. coli* resistance rates to multiple antibiotics, specifically TMP/SMX, in as many as one-third of patients.[36,37] Similar trends in the United States have prompted a shift to fluoroquinolones as preferred initial agents for empiric intravenous and/or oral therapy of UTI in the hospital and ED setting.[38]

In a cross-sectional survey of ED urine cultures from an urban tertiary care center in the United States, microbial resistance was as high as 48% to ampicillin, 25% to tetracycline, 14-28% to TMP/SMX, and 13% to nitrofurantoin.[39] Similar studies have shown that the resistance to ciprofloxacin among common uropathogens, including *E. coli,* frequently encountered in hospital-managed UTI is as low as 1-2%.[40-47] These epidemiological data have important treatment implications, since recent studies also are already demonstrating differences in clinical efficacy and patient cure rates between UTI patients managed on TMP/SMX and those managed on ciprofloxacin.[48] As would be expected, maintenance of predictable antimicrobial activity by ciprofloxacin against the anticipated spectrum of uropathogens has solidified the role of this antibiotic in treatment pathways for UTI among all institutional settings.

Hospitals affiliated with managed care organizations also have been prompted to re-evaluate their initial approach to antibiotic selection for UTI. A cross-sectional survey of 4000 urine cultures obtained from women ages 18-50 years in an HMO setting between 1992 and 1996 showed *E. coli* prevalence to be 86%, with the resistance rate to TMP/SMX increasing over this period from 9% to 18%. Recent data suggest that in some regions of the country, especially the West and Southwest, and in most major urban centers, the resistance rate to TMP/SMX has risen to as high as 35%.[5,36,37,49-52] The overall resistance to multiple groups of antimicrobials, including the penicillins, cephalosporins, and sulfa drugs, doubled from 8% to 16%.[53] In pregnant patients, *E. coli* resistance to ampicillin, which at one time was a drug of choice for UTI in this population, is now about 20-30%.[35]

Fortunately, one class of antimicrobials to which sensitivity rates have remained consistently high is the fluoroquinolone group, of which ciprofloxacin is the most frequently used as the agent of choice in the adult population. A two-tiered study from 1989 to 1991 and 1996 to 1997 at an urban sexually transmitted disease clinic evaluated young, sexually active females diagnosed with a UTI and found *E. coli* resistance to ampicillin, cephalosporins, or tetracycline in as many as 25% of patients. There was very little change in the low prevalence of organisms resistant to fluoroquinolones.[54]

Additional studies at student health clinics in California over a five-year period demonstrated significant increases in the resistance of *E. coli* to ampicillin (30% to 45%), tetracycline (29% to 40%), and TMP/SMX (15% to 32%), with resistance to fluoroquinolones in fewer than 5% of organisms.[33] In a recent analysis of young women with uncomplicated pyelonephritis, *E. coli* was isolated in more than 90% of cultures and was resistant to TMP/SMX in 18%, compared with a 0.4% resistance to ciprofloxacin. A significant variance in resistance patterns existed in different geographic regions, with resistance to TMP/SMX as high as 35% on the West Coast of the United States as opposed to 14% in the Midwest and 7% on the East Coast.[48]

Table 2. Recommended Oral Antibiotics for Uncomplicated UTI and Intravenous Agents for Hospital-Based Management of Pyelonephritis[18,24,33,38,60,61,64,66,70-76]

ACUTE UNCOMPLICATED UTI IN ADULTS, CYSTITIS (3-DAY REGIMEN)

First-line agents

Fluoroquinolone (initial agent of choice)

Ciprofloxacin (preferred)	250 mg PO bid x 3 days

Fluoroquinolone (alternative)

Enoxacin	200 mg PO bid x 3 days
Gatifloxacin	200-400 mg PO qd x 3 days
Levofloxacin	250 mg PO qd x 3 days
Ofloxacin	200 mg PO bid x 3 days
Lomefloxacin	400 mg PO qd x 3 days
Norfloxacin	400 mg PO bid x 3 days

Secondary alternatives

Trimethoprim/ sulfamethoxazole*	160/800 mg PO bid x 3 days

* Only if *E. coli* resistance is < 5-8% in patient population.

** Alternatives: Oral cephalosporin, nitrofurantoin, doxycycline, trimethoprim, or amoxicillin/clavulinic acid.

ACUTE UNCOMPLICATED PYELONEPHRITIS, OUTPATIENT TREATMENT

A fluoroquinolone for 7 days*:

Preferred:

Ciprofloxacin	500 mg PO bid x 7 days

Alternative:

Enoxacin	400 mg PO bid x 7 days
Gatifloxacin	400 mg PO qd x 7 days
Levofloxacin	500 mg PO qd x 7 days
Ofloxacin	400 mg PO bid x 7 days
Lomefloxacin	500 mg PO bid x 7 days

* Recommendations for other (alternative) fluoroquinolones based on limited studies and generalization of efficacy of ciprofloxacin, which has greatest body of evidence-based trials in UTI.

** Secondary Alternatives: Amoxicillin/clavulinic acid, cephalosporin, TMP/SMX-DS for 14 days.

ACUTE UNCOMPLICATED PYELONEPHRITIS, INPATIENT TREATMENT

Fluoroquinolone IV (initial empiric agent of choice)

Preferred:

Ciprofloxacin	400 mg IV bid

Alternative:

Gatifloxacin	400 mg IV qd
Levofloxacin	250 mg IV qd
Ofloxacin	400 mg IV bid
Ampicillin (+ gentamicin)	150-200 mg/kg/day divided q 3-4 h (+ 5-7 mg/kg qd)
Cefotaxime	1-2 g q 4-12 h
Ceftriaxone	1-2 g IV qd
Pipercillin	3 g IV q 6 h

COMPLICATED PYELONEPHRITIS, UROSEPSIS, OR INDWELLING CATHETER

Ciprofloxacin (+ tobramycin)	400 mg IV q 8 hr (+ 5-7 mg/kg/day)
Ampicillin (+ tobramycin)	150-200 mg/kg/day IV divided q 4 h (+ 5-7 mg/kg/day)
Pipercillin/tazobactam	3.4 g IV q 6 or 4.5 g q 8
Ticarcillin/clavulinic acid	3.1 g IV q 6
Imipenim	0.5 g IV q 6

Note: Any patients receiving advanced generation penicillins and aminoglycosides or fluoroquinolones may need adjustments of their dosing and or intervals if they have renal impairment.

One caveat regarding bacterial resistance is that in vitro sensitivity results may not correlate with clinical cure rates and in vivo sensitivity. Eradication of a uropathogen depends on the concentration of antibiotics in the urine as opposed to serum, which may be higher than the levels used in in vitro studies.[30]

Antibiotic Selection for UTI: General Principles and Overview of Therapeutic Options

The optimal antibiotic for in-hospital management of UTI requires evidence-base trials demonstrating high clinical and bacteriocidal cure rates and a low potential for resistance. It also should be associated with a reasonable acquisition cost, a convenient dosing schedule that is conducive to patient compliance, and minimal side effects; it also should be easily available to prescribing practitioners and their patients. *(See Table 2.)*

Fluoroquinolones, Agents of Choice. With rapidly changing resistance patterns among the common uropathogens, standard first-line treatments in many instances are being replaced by one of the newest classes of antimicrobials, the fluoroquinolones. The mechanism of action, side effects, drug interactions, and contraindications of the fluoroquinolones are reviewed in Table 3.

Derivatives of nalidixic acid, fluoroquinolones were discovered accidentally in the early 1960s during the synthesis of the anti-malarial agent, chloroquine.[38] To date, more than 10,000 analogues of nalidixic acid have undergone initial screening, and the first fluoroquinolone antibiotic was approved for clinical use in the late 1980s.[38] These highly effective antimicrobials act on bacterial topoisomerases, a class of enzymes that is essential for maintaining the physicochemical stability and biological activity of bacterial DNA.[38] In general, the newer quinolones have longer serum half-lives and proven post-antibiotic effects from one to six hours, allowing patient-friendly once- or twice-daily dosing and higher peak levels for maximal bactericidal activity.[38]

In addition, fluoroquinolones are well absorbed from the gastrointestinal tract, and in the case of ciprofloxacin, equivalent clinical outcomes in selected patient populations with moderate-to-severe UTI have been established between patient groups who received this drug intravenously and those who received oral

Table 3. Adverse Effects of Fluoroquinolones[24,38,57,58,60,61,66,68,71-73,77-81]

	Ciprofloxacin	*Levofloxacin*	*Lomefloxacin*	*Ofloxacin*	*Gatifloxacin*
SKIN/MUCOCUTANEOUS					
Photosensitivity[a,b]	✓	✓	✓	✓	
Rash	✓	✓	✓		
Pruritus	✓	✓			
GASTROINTESTINAL					
Dyspepsia	✓	✓			
Gastrointestinal upset	✓	✓			
Diarrhea	✓	✓	✓	✓	
Vomiting					
LFT abnormalities[c,d]	✓				✓
Taste perversion					✓
Abdominal pain		✓			✓
Nausea		✓		✓	✓
NEUROLOGIC					
Headache	✓	✓			✓
Insomnia					✓
Somnolence	✓				
Dizziness	✓	✓			✓
Seizure[e]	✓	✓	✓	✓	✓
CARDIOVASCULAR					
Prolongation of QT interval[f,g]					✓
Theophylline toxicity	✓			✓	
Digoxin toxicity[g]	✓	✓	✓	✓	✓
Warfarin potentiation[h]	✓	✓	✓	✓	✓
MUSCULOSKELETAL					
Arthritis	✓	✓		✓	
Tendonitis	✓	✓		✓	
Tendon rupture[i]	✓	✓		✓	
GENITOURINARY					
Vaginitis	✓	✓			✓

* Other, very infrequent side effects include drug fever, serum-sickness-like reaction, angioedema, anaphylaxis, vasculitis.

[a] Photosensitivity is rare in association with ciprofloxacin and levofloxacin (< 1.0%) and high with sparfloxacin (8%).

[b] Caveat to Note a: Up to 50% photosensitivity in patients with cystic fibrosis.

[c] LFT abnormalities are mild and of unclear significance. No clear evidence of hepatitis or hepatotoxicity except in association with trovafloxacin.

[d] LFT, liver function test

[e] Seizures are rare. Concomitant use of NSAIDS may lower seizure threshold.

[f] Sparfloxacin, moxifloxacin, and gatifloxacin are contraindicated in patients taking medications that prolong the QT interval.

[g] Fluoroquinolones may elevate digoxin levels. Watch for signs of toxicity (nausea, vomiting, CNS disturbances, arrythmias).

[h] Closely monitor PTT and INR to prevent bleeding complications.

[i] Rare.

therapy.[40,45,55] The fluoroquinolones have excellent penetration into various tissues; are well distributed intracellularly; and have the added benefit of eliminating perineal, vaginal, and perirectal reservoirs of uropathogens without altering normal bowel or vaginal flora.[38,56]

As mentioned, the high oral bioavailability of fluoroquinolones allows switching from intravenous to oral therapy without dosage adjustments.[57] Excretion primarily is renal, although some of the compounds have exclusive hepatic metabolism or a combination of the two.[38] They have an extended spectrum of bactericidal activity against gram-negative rods, including *Pseudomonas*, gram-positive cocci, and intracellular pathogens.[56,57] Fluoroquinolones remain classified as category C drugs, requiring practitioners to rule out pregnancy before prescribing them to potentially pregnant females.[38]

The armamentarium of commonly used fluoroquinolones is expanding at a rapid rate. Ciprofloxacin (Cipro), which has been a clinically proven gold standard of choice for oral and intravenous-based UTI therapy, has been joined by other agents, many of which also are indicated for community-acquired pneumonia (CAP). Newer members of this class include enoxacin (Penetrex), gatifloxacin (Tequin), levofloxacin (Levaquin), lomefloxacin (Maxaquin), and ofloxacin (Floxin). Low levels of resistance to fluoroquinolones are beginning to appear through two mechanisms: chromosomal mutations, or alterations affecting the ability of fluoroquinolones to permeate the bacterial cell wall.[38] Fortunately, separate isomerases are required to produce this form of resistance; therefore, the emergence of a predictably resistant organism would require a rare double mutation.[38]

An extensive body of clinical research confirms that fluoroquinolones are extremely effective for the treatment of UTIs ranging in severity from uncomplicated cystitis to urosepsis.[58] As would be expected, many studies evaluating newly introduced quinolones compare clinical trial outcomes to the established track record of ciprofloxacin, which has become a standard choice for initial, empiric therapy for most UTIs. In a clinically controlled trial comparing three days of oral ciprofloxacin with seven days of TMP/SMX or nitrofurantoin, bacteriologic cure rates for uncomplicated UTI after 4-6 weeks were 91%, 79%, and 82% for ciprofloxacin, TMP/SMX, and nitrofurantoin, respectively.[59] Clinical cure rates after 4-10 days were similar among the three groups, as was the overall incidence of adverse events. The superior efficacy of ciprofloxacin as compared to TMP/SMX and nitrofurantoin also has been confirmed in patients with acute pyelonephritis.[48]

In certain studies of acute uncomplicated cystitis, levofloxacin preliminarily has been shown to have equal efficacy in single doses as the standard, longer dosing regimens.[58,59] Ciprofloxacin and norfloxacin are effective as twice daily dosing regimens in uncomplicated UTI.[60,61] For complicated UTIs, including pyelonephritis, levofloxacin, lomefloxacin, and ciprofloxacin have equivalent bacteriologic and clinical cure rates. Of the newer fluoroquinolones, only levofloxacin is approved for both upper and lower UTIs.

Overuse of the extended spectrum fluoroquinolones (e.g., levofloxacin, gatifloxacin) for hospital-based management of UTI must be considered in light of recommendations made by the Centers for Disease Control and Prevention (CDC) and concerns about emerging resistance to pathogens implicated in CAP.[62]

The fluoroquinolone ciprofloxacin is a preferred oral agent for the treatment of *Pseudomonas aeruginosa* urinary infections.[48] It should be emphasized that although other quinolones may demonstrate activity against and may be indicated for treatment of gram-negative organisms implicated in UTI, some of these antibiotics, especially the extended spectrum fluoroquinolones used for initial, empiric treatment of CAP, also are approved for or are active against drug-resistant *Streptococcus pneumoniae* (DRSP). Consequently, the use of such quinolones as an initial, first-line agent for UTI in the elderly should be considered with reservation, because of concerns about emerging resistance among DRSP which have been implicated in CAP. This cautionary approach is supported by a recent guidelines document issued by the CDC's Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group.[62]

In this regard, because of significant concerns about emerging resistance, the CDC panel has recommended that extended-spectrum fluoroquinolones (i.e., levofloxacin, gatifloxacin) with activity against DRSP be "reserved" for selected patients with CAP.[62] In light of this position, it appears prudent to limit the potential for inducing resistance in these pathogens, and reserve such antibiotics as alternative agents in patients with UTI, especially because effective and safe fluoroquinolones such as ciprofloxacin are available that do not have significant activity against DRSP. Accordingly, ciprofloxacin is recommended as the initial fluoroquinolone of choice for managing patients with UTI.

Fluoroquinolones are not approved by the Food and Drug Administration (FDA) for use by patients younger than 18 years of age in the United States. This status is based on studies in young animals showing damage to articular cartilage in weight-bearing joints.[16,38,63,64] The association and true incidence of quinolone-induced arthropathy in children still is uncertain. It should be emphasized that fluoroquinolones have been used in more than 8 million children and infants worldwide, most commonly for the treatment of *Pseudomonas* infections in patients with cystic fibrosis, with a 1.3% incidence of reversible arthralgias.[63,65] There have been no reported cases of unequivocal quinolone-induced arthropathy. However, there have been three cases of suspected quinolone-induced arthropathy in children without underlying medical disorders such as cystic fibrosis or salmonellosis (baseline rates of arthropathy in these specific populations are approximately 10% and 7%, respectively).[63] All three cases involved the use of the fluoroquinolone perfloxacin. One patient required surgical intervention and arthroplasty, and the remaining two showed complete resolution of pain 1-8 weeks after perfloxacin was discontinued.[63] The safety and side effect profiles of fluoroquinolones in children are otherwise similar to those in adults.[63] Until clinically controlled trials determine the true efficacy, safety, and optimal dosing regimens of fluoroquinolones in the pediatric population, these drugs should be used only as a last alternative in a multidisciplinary approach to treatment.

Side effects that may be observed in the quinolone antiinfective class are outlined in Table 3. The most common side effects are neurologic (headache, dizziness), gastrointestinal (nausea, diarrhea), and dermatologic (photosensitivity).[66] Patients taking fluoroquinolones that have a greater propensity to cause photosensitivity reactions should be advised to avoid exposure to the sun, bright natural light, and ultraviolet rays throughout the duration of treatment and for five days after completion of treatment.

More than 300 cases of fluoroquinolone-induced tendonitis, arthralgias, and tendon rupture in adult patients have been documented in the literature.[63] Those identified to be at risk included patients older than age 60 and patients on long-term steroid therapy.[63,65] The pathophysiology of fluoroquinolone-induced tendon disorders is unclear, and the onset of symptoms can occur within one or two days after starting therapy. Patients affected typically develop joint pain and swelling (arthralgia), followed by difficulty with movement; some progress to tendon rupture, with accompanying nodules and ecchymoses.[63,65] Diagnosis usually is made clinically, although ultrasound is helpful as an adjunct evaluation. Tendon rupture may require surgical intervention and has caused prolonged disability.[63] In response to these reports, the FDA has asked clinicians to alert their patients to this potential side effect and has requested that manufacturers revise the package inserts to include similar warnings.[63]

The potential for drug interactions between fluoroquinolones and other medications has been well-documented. Serious though rare adverse events include cardiotoxicity (QT prolongation,

torsade de pointes, cardiac arrest).[66] In this regard, sparfloxacin, grepafloxicin, gatifloxacin, and moxifloxacin generally are contraindicated in patients taking other medications (e.g., cisapride, Class Ia and III antiarrhythmics, and phenothiazines) that prolong the QT interval.[38,66,67] Quinolones have been reported to enhance the effects of warfarin anticoagulation when administered concomitantly. No specific dosage adjustments are needed with either medication, but prothrombin time (PTT) and the internationalized ratio (INR) should be monitored closely to prevent bleeding complications.[67] The mechanism of this interaction is unclear.

Patients receiving digoxin and quinolones may have an increased risk of digoxin toxicity and should be monitored for clinical signs of this interaction, including nausea, vomiting, and cardiac arrhythmias.[67] Selected fluoroquinolones inhibit the cytochrome p450 1 A2 isoenzyme, an enzyme responsible for metabolization of methylxanthine derivatives, including theophylline.[38] Increases in serum theophylline levels secondary to decreases in total body clearance can be as high as 30% to 84%, respectively (ciprofloxacin vs enoxacin).[68] These levels have been associated with theophylline toxicity manifesting as nausea, vomiting, and in rare cases, seizures. Gatifloxacin, levofloxacin, and moxifloxacin do not alter theophylline metabolism. Grepafloxacin, levofloxacin, and ofloxacin, in rare cases, have been shown to have a synergistic interaction with nonsteroidal anti-inflammatory agents, resulting in an altered seizure threshold. The mechanism involves inhibition of gamma-aminobutyric acid (GABA), resulting in central nervous system (CNS) excitation; therefore, caution should be used in patients with baseline seizure disorder or those with increased risk of seizure activity.[38,67] Theoretically, this risk extends to the entire class of fluoroquinolones.

Ciprofloxacin has been noted in rare cases to cause fluctuations in phenytoin levels, but this appears to have little clinical significance.[67] Case reports have documented that interactions between ciprofloxacin and glyburide resulted in resistant hypoglycemia in patients receiving glyburide therapy.[67,69] It is unclear if this hypoglycemia was secondary to ciprofloxacin inhibition of the cytochrome P-450 hepatic enzyme that metabolizes glyburide. Ciprofloxacin, enoxacin, and ofloxacin also have been shown to increase caffeine levels, resulting in increased CNS stimulation. Patients should be cautioned to decrease or avoid caffeine while on these quinolones. Sucralfate and antacid products containing aluminum, magnesium, iron, calcium, and zinc can significantly decrease the bioavailability of the fluoroquinolones.[38] Administration of these medications should be staggered, giving the fluoroquinolones two hours before or four hours after the other agent.

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Physician CME Questions

41. In children younger than 2 years of age with a urinary tract infection (UTI), the most common presenting complaint at evaluation is:
    A. vomiting.
    B. dysuria.
    C. abdominal pain.
    D. fever.

42. Which of the following populations has a 10-15% risk of developing renal scarring, subsequent hypertension, and end-stage renal disease from pyelonephritis?
    A. Pediatric
    B. Adult
    C. Pregnant
    D. Elderly

43. The most common (> 50%) anatomic abnormality associated with UTIs in infants is:
    A. renal calculus.
    B. urethral stricture.
    C. vesico-ureteral reflux.
    D. bladder spasm.

44. The most common uropathogen in UTIs in all age groups is:
    A. *Proteus mirabilis.*
    B. *Escherichia coli.*
    C. *Klebsiella.*
    D. *Enterococci.*

45. In the inpatient management of pyelonephritis or complicated UTI in adults, all of the following drug regimens are recommended as first-line therapies *except*:
    A. ampicillin + gentamicin.
    B. a fluoroquinolone.
    C. erythromycin.
    D. an extended-spectrum penicillin.

46. Significant adverse effects and drug interactions associated with fluoroquinolones include all of the following *except*:
    A. cardiotoxity in patients taking medications that prolong the QT interval.
    B. tendonitis, arthritis, and tendon rupture.
    C. acute renal failure.
    D. increased risk of theophylline and digoxin toxicity.

47. In acute cystitis, which of the following antibiotics is now recommended as a first-line agent in most adult populations?
    A. TMP/SMX
    B. Amoxicillin/clavulinic acid
    C. Nitrofurantoin
    D. Fluoroquinolone

48. Patients receiving digoxin and quinolones have increased risk of digoxin toxicity and should be monitored for which of the following?
    A. Nausea
    B. Vomiting
    C. Cardiac arrhythmias
    D. All of the above

In Future Issues:

Urinary Tract Infection: Part II

Correction

In the September 25, 2000 (vol. 21, no. 20), issue of *Emergency Medicine Reports*, a portion of the text was not referenced. Scott T. Wilber, MD, contributed to the issue. Dr. Wilber is Assistant Professor of Emergency Medicine, Northeastern Ohio Universities of Medicine, and Associate Director, Emergency Medicine Research Center, Summa Health System, both in Akron. We apologize for the oversight and any inconvenience this may have caused. ■