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Management of urinary tract infection (UTI) in the emergency department setting presents special challenges in the arena of diagnosis and management. Young children, in particular, can present with little more than fever and abdominal discomfort, whereas the elderly patient may have mild bladder symptoms or, alternatively, present with urosepsis accompanied by hypotension and serious systemic complications.

Recent reports on epidemiological patterns suggest an increasing prevalence of resistance to TMP/SMX among Escherichia coli *species, requiring a shift in empiric therapy for uncomplicated UTI from this agent to fluoroquinolones for initial therapy, especially in areas where trimethoprim/sulfamethoxazole (TMP/SMX) resistance exceeds 10%. In the case of acute pyelonephritis managed in the outpatient setting, studies have found that ciprofloxacin demonstrates clinical superiority as compared to TMP/SMX, and that the mean total resource cost per patient for achieving clinical cure was 29% higher for TMP/SMX-treated patients than for ciprofloxacin-treated patients.*[1]

The purpose of this second of a two-part series on UTI management is to present a disease-based, risk stratification model for diagnosis and treatment of UTI. Evidence-based trials are used to support diagnosis, triage, and antibiotic selection strategies for a wide range of patients, and approaches to improving patient outcomes based on emerging resistance patterns are identified.

— The Editor

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

Part II: Disease-Treatment Strategies, Urosepsis, and Principles of Antibiotic Selection

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Antibiotic Treatment Guidelines. A Disease and Syndrome-Specific Stratification Model for Antimicrobial Therapy

Asymptomatic Bacteriuria. Asymptomatic bacteriuria (ASB) generally is not treated in most patients, because multiple studies have shown treatment to have little long-term significance in an otherwise healthy adult population.[2] A recent prospective study of asymptomatic bacteriuria in sexually active young women found a prevalence rate of approximately 5%, with 8% of those women developing a symptomatic UTI within one week.[3] Specific groups benefiting from

antibiotic treatment include pregnant women, neutropenic patients, patients with abnormal renal function, renal transplant recipients in the early post-transplantation period, and men and women planning to undergo urologic procedures.[2,4]

Infants with ASB represent a low-risk population for the development of UTI, and tend to undergo spontaneous abacteriuria within a few months; this group generally does not require antibiotic treatment.[5] School-age children usually are left untreated; however, patients with underlying voiding disorders should be referred appropriately for further evaluation and treatment.

Pregnant women with ASB should be treated with a three- to seven-day course of antibiotics, followed by a subsequent culture to ensure sterilization of urine. Despite increasing resistance rates to ampicillin, amoxicillin and cephalosporins remain first-line choicse in these patients. Nitrofurantoin is becoming a first-line drug, because it is efficacious, inexpensive, and well-tolerated. The only contraindication to using this drug is G6PD deficiency; hemolysis can occur in patients with this deficiency. TMP/SMX remains a first-line agent in areas of low resistance, but should be avoided in the first and third trimesters, secondary to possible teratogenic effects and the risk of kernicterus from competitive binding of TMP/SMX to bilirubin binding sites. At this time, there is no clear evidence to support a single-dose regimen over a typical three- to seven-day course.[6-8] A properly sized, randomly controlled trial is recommended for comparison of these regimens, as a single dose has lower cost, fewer adverse effects, and increased compliance compared with longer treatment regimens.[7]

In the elderly population, initial evidence has suggested an increased risk of morbidity and mortality in patients with ASB. More recent studies have challenged these reports, however, for failing to identify a connection between ASB and an increase in long-term sequelae such as hypertension and/or end-stage renal disease.[2,4] Up to 40% of the elderly will have ASB at some time. Aggressive screening and treatment have little effect on decreasing symptomatic or clinically significant infection and associated complications.[4] Catheterized patients, including those with neurologic disorders or spinal cord injuries, rarely require aggressive work-up and treatment unless symptoms intervene.[9] Interestingly, a recent study of catheterized patients found that catheter-associated UTIs rarely are symptomatic and infrequently cause bacteremia (< 1%). No significant differences were noted between symptomatic and asymptomatic bacteriuria groups with regard to signs and symptoms commonly associated with infection (e.g., fever, dysuria, urgency, or flank pain) or leukocytosis.[10] Investigations have noted that both groups are a major reservoir for antibiotic resistant organisms in the hospital setting.

Symptomatic UTI in Children. Pediatric patients with UTI require early antibiotic treatment and proper referral with follow-up to prevent renal scarring and the subsequent, severe complications of hypertension and end-stage renal disease. Simple cystitis in the pediatric population can be treated with a three- to seven-day course of antibiotics.[5] *(See Table 1.)* Some studies recommend that prepubertal children should not be treated for less than 5-10 days unless clear documentation exists that the patient has no underlying urinary tract abnormalities.[11,12] Based on a meta-analyses of 14 controlled trials, there is insufficient evidence to recommend single-dose treatment in this population, with a tendency toward a higher failure rate and reinfection in single-dose groups.[5]

Oral antibiotic choices in the pediatric group include the penicillins, cephalosporins, sulfonamides, TMP/SMX, and nitrofurantoin. Because of increasing resistance against amoxicillin and ampicillin, other antibiotics should be considered.[13] Amoxicillin/clavulanic acid is an alternative penicillinase-resistant drug with a wide spectrum of coverage, but it is not recommended as first-line therapy because of concerns about emerging resistance, higher cost, and a greater number of side effects. There is a negligible difference in clinical outcomes with amoxicillin/clavulanate as compared with other common regimens.[5,14,15] TMP/SMX is an acceptable alternative due to its minimal levels of resistance in most pediatric populations and its low cost.[13] Tetracyclines are contraindicated in children because of the drug's effects on teeth.

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Table 1. Treatment of Pediatric Patients with UTI[5,14,46,47,69]

ACUTE, UNCOMPLICATED UTI (3-5 DAYS)	
Amoxicillin	30-50 mg/kg/day PO divided tid [a]
Amoxicillin/ clavulinic acid	45 mg/kg/day PO divided bid [b]
Trimethoprim/ sulfamethoxazole	8-10 mg/kg/day of TMP PO divided bid
Nitrofurantoin	5-7 mg/kg/day PO divided qid [c,d]
Cefixime	8 mg/kg/day PO divided bid
Cephalexin	25-50 mg/kg/day PO divided qid
Cefuroxime	10-15 mg/kg/day PO bid (max, 1 g/day) [e]
Cefaclor	20-40 mg/kg/day PO divided tid [e,f]
Cefprozil	15-30 mg/kg/day PO divided bid (max, 1 g/kg/day) [e,f]
Loracarbef	15-30 mg/kg/day PO divided bid (max, 0.8 g/day) [e,f]
COMPLICATED UTI OR UTI REQUIRING ADMISSION (14 DAYS)	
Ampicillin ±	100 mg/kg/day IV divided qid
Tobramycin	6-7.5 mg/kg/day IV divided tid [g,h]
Ceftriaxone	50-100 mg/kg/day IV or IM [i]
Ceftazidime	30-50 mg/kg IV tid [i]
Cefotaxime	150 mg/kg/day IV divided tid [i]

[a] Increasing resistance rates limiting efficacy; trimethoprim/sulfamethoxazole is superior in recent studies.

[b] Reserved for patients with amoxicillin-resistant organism.

[c] Not used in patients younger than 6 weeks of age.

[d] Avoid in patients with G6PD deficiency.

[e] Not as effective in patients with enterococcus infection.

[f] Only in patients older than 28 days.

[g] Associated with ototoxicity and nephrotoxicity; adjust according to renal function and follow serum levels.

[h] Intramuscular form may be used in outpatient setting for patients with a history of allergy to cephalosporins.

[i] Significant concern about resistant enterococci; not recommended as first-line drug for recurrent infections.

Cephalosporins are used widely in the management of pediatric UTIs. Cefaclor, an oral second-generation cephalosporin, has been associated with serum sickness in as many as 0.5% of patients, thus limiting its use in children.[16] Cefprozil and loracarbef, also second-generation agents, are approved for patients ages 6 months and older. They have been found to be effective and have a lower rate of gastrointestinal side effects than amoxicillin/clavulanic acid. Cefixime, an oral third-generation cephalosporin, is an attractive alternative as it maintains a high urinary excretion level and bactericidal action, can be dosed once daily, has a relatively pleasant taste, and can be stored at room temperature for up to two weeks.[13,16] Mild gastrointestinal effects occur in as many as 25% of patients after an oral dose.

The third-generation agent, cefpodoxime, also is effective in the treatment of UTI, including pyelonephritis in infants older than 1 month of age.[16] Side effects from cefpodoxime are similar to those of other cephalosporins, with diarrhea occurring in 4-17% of patients (higher percentage in infants); vomiting is uncommon. Cephalosporins should be avoided in patients with known, severe reactions to penicillins, as a 5-10% cross reactivity has been cited.[15] If there is a history of only mild skin rash, a small test dose can be administered and the patient observed for 30-45 minutes prior to continuing use.

Adult Females. Young, sexually active females with symptomatic, uncomplicated UTI typically can be treated for three days for effective elimination of infection in the majority of patients. Three-day regimens are as effective as five-, seven-, and 10-day regimens and have the advantage of fewer side effects, lower cost, and higher levels of patient compliance.[16,17] Single-dose regimens appear to be less effective than other regimens.[18,19] Recently updated and published guidelines from the Infectious Disease Society of America recommend that TMP/SMX remain the standard first-line drug in uncomplicated cystitis in young adult women in areas where *E. coli* resistance is less than 10-20%.[20] However, the resistance landscape and preferences for initial empiric therapy are changing as a result of evidence-based trials.

For acutely symptomatic young women with cystitis, the preferred treatment is a three-day course with ciprofloxacin or TMP-SMX. TMP/SMX may be considered a first-line agent in women who can tolerate this agent and in areas where resistance is infrequent. Its status, however, is changing as resistance to TMP/SMX has emerged as a common clinical problem. Accordingly, with increasing resistance by *E. coli* to TMP/SMX, ciprofloxacin is becoming the initial antibiotic of choice, even in uncomplicated UTI. Ciprofloxacin should be considered a first-line agent in patients with allergies to other drugs or in areas where TMP/SMX resistance is high (> 10%).

Total cost outcome studies comparing antibiotics (i.e., TMP/SMX vs quinolones) used for cystitis suggest that the high cure rates, excellent compliance, and predictable and sustained antimicrobial activity against *E. coli* (resistance rates among *E. coli* < 1%), as well as the low relapse rates associated with ciprofloxacin, make this antibiotic a cost-effective first choice in patients with uncomplicated UTI. Even in cost-conscious environments (i.e., managed care settings, HMOs, military hospitals, and emergency departments [EDs]), ciprofloxacin (250 mg PO bid x 3 days) represents an outcome-effective antibiotic for initial therapy of uncomplicated UTIs. In certain regions and especially in urban areas, resistance among *E. coli* to TMP/SMX has risen to 24% over the past four years; this pattern has relegated TMP/SMX to secondary or alternative agent status for management of cystitis and uncomplicated UTI.[21,22]

When resistance is *not* an issue, TMP/SMX is effective for clearing the pathogenic organism, has minimal adverse effects on the vaginal and fecal flora, and generally is well-tolerated.[17,20,23] As already stressed, fluoroquinolones are a better choice in areas of higher TMP/SMX resistance (> 10-20%) for patients with allergies to sulfa or other drugs, and in patients returning for failed antibiotic treatment of recently diagnosed UTI.[20] Other sources, including an updated antimicrobial therapy guide, now recommend fluoroquinolones as first-line agents and TMP/SMX

as a second-line agent for all acute uncomplicated UTI infections, citing resistance to TMP/SMX in more than 18% of *E. coli* infections.[21,22] Physicians should be aware of local resistance patterns when devising antibiotic selection strategies. If local resistance patterns to *E. coli* show less than 10% resistance to *E. coli*, TMP/SMX still should be considered a first-line drug.

In a recent study, nitrofurantoin was found to have efficacy equal to other antibiotics with sustained concentration in the urine and appears to have a superior level of efficacy in vitro against multiresistant *Enterobacteriaceae*, including *E. coli*.[24] The authors suggest that nitrofurantoin be reconsidered as a first-line agent in the treatment of uncomplicated UTI. However, it should be noted that nitrofurantoin is much less effective against *Staphylococcus saprophyticus* and is not effective against *Pseudomonas* and *Proteus* species. It has minimal effects on the resident fecal and vaginal flora and leads to a low incidence of bacterial resistance.[23] Nitrofurantoin should be dosed as a seven-day regimen to ensure efficacy.[25]

An alternative for acute cystitis treatment may be fosfomycin tromethamine, which is administered as a 3 g, single oral dose.[6,26,27] This antibiotic is active against common uropathogens, including organisms resistant to other antibiotics.[26] The single dose is well-absorbed, produces therapeutic concentrations in urine for 2-4 days, and has been shown in clinical trials to be as effective as seven- to 10-day regimens of nitrofurantoin, norfloxacin, and TMP/SMX. Ampicillin should no longer be used because of high resistance rates.[28] The suprapubic discomfort or dysuria common with UTI can be treated with oral analgesics or phenazopyridine (adults, 100 mg 2 tablets tid or 200 mg 1 tablet tid not to exceed two days of therapy; children ages 6-12, 12 mg/kg/d divided into tid dosing not to exceed two days of therapy).[11] Elderly females with lower tract UTI symptoms and no systemic complications may be treated for three days with regimens similar to those prescribed for younger women.[29] *(See Table 2.)*

In patients suspected of having a complicated UTI, including patients with symptoms lasting longer than one week, diabetic patients, immunocompromised individuals, and non-toxic febrile patients without evidence of acute pyelonephritis, the treatment duration should be between five and seven days.[30] Because these patients are less able to tolerate treatment failures and are more susceptible to recurrent infection, ciprofloxacin is recommended as the initial agent of choice. Moreover, in these patients, a urine culture is recommended prior to administration of antibiotics to ensure proper management and identification of the uropathogen in the event of treatment failure or recurrence.[30]

Urethritis is common in males younger than age 50 years and should be treated based on history and physical examination. Urinalysis, urine culture, and/or urethral cultures are recommended. In men, therapy typically lasts one or two weeks for acute cystitis, four weeks for acute bacterial prostatitis, and 6-12 weeks for chronic bacterial prostatitis.[31] Ciprofloxacin is recommended because these fluoroquinolones penetrate prostatic tissue and secretions. Candidal infections usually are treated with oral fluconazole or, in catheterized patients, by continuous bladder irrigation with amphotericin B for 2-5 days.[30]

Pyelonephritis

Adults. Adult patients with pyelonephritis can be managed on an inpatient or outpatient basis, depending upon clinical severity. A retrospective comparison of inpatient and outpatient management of pyelonephritis in adults suggested that general guidelines for hospital admission should include the following: 1) Underlying anatomical urinary tract abnormality; 2) an immunocompromised host (diabetes mellitus, cancer, sickle cell disease, transplant patients); 3) urinary tract obstruction; 4) failed outpatient management of pyelonephritis; 5) progression of uncomplicated UTI; 6) persistent vomiting; 7) renal failure; 8) suspected urosepsis; 9) age older than 60 years; 10) poor social situation, and/or; 11) inadequate access to follow-up.[32] If these criteria are used for making in-hospital dispositions, it is estimated that 70% of all patients who are treated for pyelonephritis can be managed as outpatients.[32]

The general consensus for ED management of pyelonephritis is to begin parenteral therapy with ciprofloxacin intravenously in patients who meet admission criteria.[33] Non-toxic patients with uncomplicated pyelonephritis who are suitable for outpatient management may receive oral ciprofloxacin for a total of 7-14 days, depending on clinical judgment and hospital protocols.[33] Other parenteral therapies include a combination of ampicillin or a third-generation cephalosporin plus an aminoglycoside in extended interval dosing (i.e., every 24-48 hours).[1,28,34,35] The extended-spectrum cephalosporins, such as ceftriaxone, should be considered for serious urinary tract infections because of the high urinary concentrations that are achieved.[36]

If gram-positive cocci are the causative organism, ampicillin/sulbactam, with or without an aminoglycoside, is recommended.[33] Admitted patients with suspected enterococci may require extended-spectrum penicillins (ticarcillin disodium or piperacillin sodium and tazobactam sodium injection) or alternative therapies, including nitrofurantoin, to treat isolated vancomycin-resistant enterococci (VRE). Because multidrug resistance is common in VRE isolates, susceptibility testing is recommended for ampicillin, aminoglycosides, chloramphenicol, fluoroquinolones, minocycline (a tetracycline), and rifampin.[36] UTIs caused by *Pseudomonas* often will require double antimicrobial coverage.

As with children, admitted patients who remain afebrile for 24-48 hours and tolerate oral intake safely can be switched to an oral medication to complete a 14-day course. A multidisciplinary approach to patients with complicated infections is encouraged to provide adequate empiric treatment, with subsequent adjustments based on identification and sensitivities while preventing the development of further resistance.

To evaluate the efficacy and cost of antibiotics used in pyelonephritis, a recent randomized, double-blind, multicenter, national trial analyzed 255 women with acute, uncomplicated pyelonephritis. These patients received either ciprofloxacin, 500 mg twice daily (bid) for seven days; or TMP/SMX, 160/180 mg bid for 14 days.[37] More than 90% of UTI culture isolates from both groups were *E. coli.* Bacteriologic and clinical cure rates were greater at 4 to11 days in the ciprofloxacin group (99% and 96%, respectively) than the TMP/SMX group (89% and 83%,

Table 2. Antibiotic Treatment Guidelines for Outpatient and Inpatient Urinary Tract Syndromes in the Elderly

ASYMPTOMATIC BACTERIURIA
Evaluation and monitoring for symptoms, renal function, continuing bacteriuria
URINARY INCONTINENCE PLUS OTHERWISE ASYMPTOMATIC BACTERIURIA
Evaluate and treat underlying cause of incontinence
ACUTE, SYMPTOMATIC CYSTITIS
Ciprofloxacin 250 mg PO bid x 3 days (preferred)
TMP/SMX DS, one tab DS PO bid x 3 days (alternative, avoid in areas where *E. coli* resistance to TMP/SMX is > 10-20%)
CATHETERIZED PATIENT
Lower abdominal pain or new symptoms suggestive of UTI/ without fever or systemic signs
Ciprofloxacin 250 mg PO bid x 7 days (preferred)
Lower abdominal pain with fever or systemic signs:
Ciprofloxacin 500 mg PO bid x 7-10 days (preferred)
Norfloxacin/ofloxacin/levofloxacin (alternatives)
ACUTE PYELONEPHRITIS—MILD:
Ciprofloxacin 500 mg PO bid x 7-10 days (preferred)
Norfloxacin/ofloxacin/levofloxacin (alternatives)
Amoxicillin/clavulanate 500 mg PO bid x 10-14 days
ACUTE PYELONEPHRITIS—SYSTEMIC TOXICITY AND SIGNS OF BACTEREMIA:
Ciprofloxacin 400 mg IV q 12 hrs (preferred)
Ceftriaxone 1 g IV/IM q 24 hrs
Cefotaxime 1-2 g IV q 8 hrs
Levofloxacin 250 mg IV q 24 hrs
Gatifloxacin 400 mg IV q 24 hrs

respectively). At 22 to 28 days, bacteriologic and clinical cure rates were 84% vs. 74% in the ciprofloxacin group and 82% and 74% in the TMP/SMX group, respectively. Bacterial and clinical cure rates with TMP/SMX in patients found to be infected with resistant *E. coli* were only 50% and 35%, respectively. Adverse effects were similar among both groups, occurring in 24% with ciprofloxacin and in 33% with TMP/SMX. Health care resource use and estimated total treatment cost were calculated, from initial evaluation to prescription pad to "clinical cure," including needed hospitalization, lab testing, office visits, and other procedures. Mean total cost per patient was 29% higher for TMP/SMX-treated patients than for ciprofloxacin-treated patients.[37]

Because of additional interventions and antibiotic prescriptions required in the TMP/SMX group to achieve a cure, the mean cost per cure also was 25% higher in TMP/SMX group than in the ciprofloxacin-treated patients. These studies help confirm that knowledge of local resistance rates is imperative when deciding which antibiotics should be used for treatment of UTI. This study supports the use of ciprofloxacin as a first-line agent in the management of uncomplicated pyelonephritis. With the current outcome- and cost-sensitive environment of managed care, clinicians must make informed choices in the management of their patients.[37,38] A related, randomized trial found that oral and intravenous ciprofloxacin were equally effective for the empiric treatment of severe pyelonephritis or complicated UTIs, provided that severe sepsis, obstruction, and focal renal suppuration are not present.[39] Since all patients in this study were hospitalized, a direct comparison between inpatient and outpatient treatment with ciprofloxacin is still needed.

Pregnancy. In pregnant women, pyelonephritis tends to occur more commonly during the second half of pregnancy.[40] In general, outpatient treatment is not the standard of care for pregnant women. Inpatient treatment with intravenous antibiotics and close monitoring usually are required to maximize outcomes. Treatment options are similar to other adult regimens, including ampicillin with gentamicin, cephalosporins, and extended-spectrum penicillins or aztreonam.[40] Patients may be discharged home safely and parenteral therapy stopped after defervescence within 48-72 hours of admission.[23] Persistent fever or symptoms require further evaluation and consultation.

A study of more than 100 women with uncomplicated pyelonephritis at less than 24 weeks gestation found that almost 10% of those initially treated as outpatients eventually required hospitalization.[41] Two additional studies suggest that, in carefully selected patients, outpatient treatment may be a safe option.[42,43] However, without concise, evidence-based protocols or guidelines to guide this decision, the acceptable and prudent choice in pregnant women is to admit them for initial parenteral antibiotics and supportive care. In both non-pregnant adults and pregnant patients, failure to respond to appropriate antibiotics requires emergent radiologic studies, including ultrasound and possible computed tomography (CT) scan, to evaluate for obstruction, masses, and renal and perirenal abscesses. All patients should have follow-up urine cultures 1-2 weeks after completion of therapy to ensure eradication of infection.

Children. Traditionally, infants younger than 1 year of age with a fever and UTI (nearly pathognomonic for pyelonephritis) were hospitalized and treated with intravenous antibiotics and hydration.[44] *(See Table 1.)* More recently, admission recommendations have been modified to focus on certain high-risk groups, including febrile infants younger than 3 months of age, infants and children with dehydration who are unable to tolerate oral hydration or medication, immunocompromised children, and patients with a high risk of noncompliance with medication and early follow-up.[14,45] Neonates should have continued parenteral therapy for 7-14 days. Parenteral antibiotics should be continued in admitted infants and children until the patient has been afebrile for 24-48 hours and is tolerating oral intake well. The switch to oral antibiotics can be made safely based on original identification and sensitivities of the identified uropathogen.

The total treatment duration should be from 10 to 14 days.[2,14,46-48] Parenteral regimens include ampicillin plus an aminoglycoside or a third-generation cephalosporin until culture identification and sensitivities return.[14,47] The greatest concern

with using aminoglycosides is the possibility of developing nephrotoxicity or ototoxicity. Available data do not support the generally accepted belief that ototoxicity is related directly to elevated serum levels; rather, it appears that ototoxicity is related to duration of therapy, repeat courses of aminoglycosides, or high cumulative doses.[49] Daily dosing regimens currently being studied in children and neonates, including very low-birth-weight infants (< 1500 g), appear to yield enhanced antibacterial efficacy and decreased toxicity.[50,51] If *Enterococcus* is the expected organism, vancomycin is recommended because of high levels of penicillin resistance and lack of susceptibility to a cephalosporin.

Ticarcillin/clavulanate and piperacillin/tazobactam, both extended-spectrum penicillins, are not approved for use in children younger than 12 years of age.[50] In a European randomized, controlled trial of 300 children with pyelonephritis (ages 1 month to 12 years), both cefepime and ceftazidime given intravenously (50 mg/kg every 8 hours) for at least 48 hours after defervescence, followed by TMP/SMX for 12-14 days, were equally effective and well-tolerated.[52] In that trial, clinical cure rates for cefepime and ceftazidime after 4-6 weeks were 98% and 96%, respectively, with bacteriologic cure rates of 86% and 83%, respectively.

A recent, multicenter, randomized clinical trial evaluated the efficacy of initial oral cefixime vs. initial intravenous cefotaxime in children ages 1-24 months with febrile UTIs.[45] All patients had positive urine cultures and negative sonograms for urinary tract abnormalities upon enrollment, and received a total of 14 days of antibiotics (intravenous group changed over to oral cefixime after 3 days or after the child was afebrile for 24 hours).[45] In the outpatient arm, the initial oral cefixime dose was 16 mg/kg given in the ED, followed by 8 mg/kg once daily. Both groups of patients were placed on oral cefixime prophylaxis for two weeks following treatment (4 mg/kg QD) until a voiding cystourethrogram (VCUG) was performed. There were no statistically significant differences in cure rates, reinfection rates, or higher grades of renal scarring based on or 99mTc-DMSA (technetium^{99}-labeled dimercaptosuccinic acid) nuclear cortical scan.[45]

Mean costs for children treated intravenously were at least two-fold higher, including outpatient reevaluation, follow-up cultures, and radiologic imaging after appropriate referral. The authors concluded that non-toxic, young children with fever and UTI may be treated safely with oral cefixime on an outpatient basis, with the additional benefit of a significant decrease in cost compared with hospitalization. Other authors have recommended that children older than age 3 months who are non-toxic in appearance receive initial parenteral treatment with a long-acting third-generation cephalosporin such as ceftriaxone and then have close follow-up on continued oral antibiotics for 14 days, with subsequent prophylaxis.[5]

Transplant Recipients

While infection-related mortality rates in transplant recipients have dropped from 70% in the first decades of renal transplantation to less than 5% today, persistent prevention and effective treatment of infectious complications remain major concerns.[53] Immunosuppression secondary to transplant-related treatments, exposure to infectious agents in the community and hospital (especially immunomodulating viruses such as cytomegalovirus, Epstein-Barr virus, and hepatitis B and C), leukopenia, and metabolic abnormalities in patients with end-stage renal disease awaiting transplant all determine a patient's risk for infection.[53] In the first month after transplantation, urinary infections are a major complication, occurring in 35-79% of patients. Uropathogens include enteric gram-negative isolates, *Pseudomonas aeruginosa*, enterococci, and staphylococcal and fungal species. Most bacterial infections can be treated with a 10- to 14-day course of antibiotics, which may be followed by continued prophylaxis with low-dose ciprofloxacin.

Recurrent infections require further radiologic imaging, including ultrasound, CT scan, and/or nuclear imaging studies.[53]

Fungal urinary infections are common, often presenting as a relatively asymptomatic candiduria or cystitis. Severe infections caused by obstructing fungal balls result in ascending infection, overt candidal pyelonephritis, and significant fungemia.[53] Patients on large doses of corticosteroids, those with a history of multiple episodes of allograft rejection or poor allograft function, or those with baseline hyperglycemia, leukopenia, prolonged antibiotic use, or older age have an increased risk of developing fungal infections.

Aggressive treatment of suspected fungal pyelonephritis is warranted. This includes fungal stains and culture of the urine or blood, possible fine-needle aspiration of the kidney, and prompt administration of antifungal therapy. Oral fluconazole is acceptable for mild-to-moderate infections caused by *Candida albicans*, but amphotericin is the drug of choice in *C. krusei* and *C. glabrata* infections and in disseminated disease. Patients with evidence of nephrotoxicity can be treated with the liposomal formulation of intravenous fluconazole or amphotericin.[53] Patients receiving antimycobacterial therapy may develop hepatic dysfunction, hyperuricemia, and potential drug interactions with cyclosporine, which may lead to nephrotoxicity.

Bacteremia and Urosepsis

UTIs associated with obstruction caused by calculi, congenital abnormalities, an enlarged prostate gland, or any underlying neurologic condition leading to incomplete bladder emptying predispose to urosepsis.[54] Bacteremic patients usually present with classic signs and symptoms of UTI. Additional manifestations of a septic process seen in bacteremic patients include shaking chills, fever, or hypothermia (associated with worse prognosis), tachycardia, tachypnea, respiratory alkalosis and hyperventilation, changes in mental status (lethargy or possible agitation), and skin lesions (e.g., petechial rashes seen in *P. aeruginosa* bacteremia).[55]

These symptoms usually develop within the first 24 hours of infection, except in bacteremia caused by *Serratia marcescens*, from which symptoms typically develop several days later. Patients who progress to septic shock will manifest severe hypotension; metabolic acidosis; and hemocoagulative disorders, including thrombocytopenia and disseminated intravascular coagulation. Immunocompromised or neutropenic patients may have a more insidious onset secondary to an altered inflammatory

response to infection. Fever, dysuria, and pyuria may be absent, with compensatory hyperventilation and changing mental status serving as important clues.[55] Overall mortality rates for septic shock in critical care unit patients range from 20% to 80%.[55]

The diagnosis of urosepsis usually is made clinically, with blood and urine cultures obtained to guide management. Additional laboratory studies that follow cytokine plasma levels (correlation to endotoxin) and procalcitonin (closely related to plasma levels of TNF-alpha and IL-6) have been utilized in certain hospitals in selected cases for the management and follow-up of patients with sepsis.[55] Treatment requires aggressive monitoring of airway patency, breathing, and circulation. Initial interventions include obtaining intravenous access, preferably central access to allow invasive monitoring of the hemodynamic clinical status and to guide fluid and electrolyte management. Fluid resuscitation with either crystalloid or colloids is a top priority, along with the use of inotropes or pressors to treat hypotension. Dopamine is recommended as the initial drug because of its inotropic and vasopressor action, with alternative drugs including dobutamine and norepinephrine.

Broad-spectrum empiric antimicrobial therapy should be started immediately. The combination of a fluoroquinolone with anti-pseudomonal activity (ciprofloxacin) or a beta-lactam (a semi-synthetic penicillin associated with a beta-lactamase inhibitor or fourth-generation cephalosporin) plus an aminoglycoside is recommended as the first-line regimen.[55] Piperacillin/tazobactam or ticarcillin/clavulanate should be considered for two reasons: 1) the increasing prevalence of enterococci (especially in nosocomial patients); and 2) the decreased risk of expanded-spectrum, beta-lactamase-producing, gram-negative pathogens.[55]

Amakacin generally is more active than gentamicin or tobramycin against both *Enterobacteriaceae* and *P. aeruginosa*.[55] Amphotericin B or fluconazole is the preferred treatment option for UTI caused by *Candida*.[55] Once uropathogen identification and sensitivities from urine and blood cultures are available, a single agent with a narrow spectrum is recommended to decrease drug toxicity, cost, and the emergence of resistant strains.[55] Adjunctive therapies previously studied, including high-dose corticosteroids and monoclonal antibodies against endotoxins released by aerobic gram-negative bacteria, are no longer recommended.[55] Imaging to evaluate for obstruction, renal abscess, or perinephric abscess is recommended in patients with persistent fever or clinical sepsis.

Catheterized Patients. Bacteremia associated with urinary catheterization usually is asymptomatic, occurring in up to 10% of patients, with fewer than 1% of patients developing symptomatic bacteremia.[55] However, with symptomatic urinary catheter-related bacteremia, mortality is as high as 30%; therefore, the symptomatic patient requires aggressive diagnosis and therapeutic interventions. Over the past decade more susceptible pathogens *(E. coli, Proteus mirabilis, Klebsiella pneumoniae)* have shifted to more resistant pathogens (staphylococci, enterococci, *Enterobacter sp., P. aeruginosa,* and *C. albicans*).[54,55] However, *E. coli* remains the most prominent organism isolated. In most cases, bacteriuria in patients with short-term catheterization is caused by a single organism, while polymicrobial infections are more common in subjects with chronic indwelling catheters.[55] Recurrent instrumentation of the urinary tract is associated with infection caused by *P. aeruginosa* and other resistant uropathogen infections.[54] A fluoroquinolone with good anti-pseudomonal coverage, often in combination with an aminoglycoside or a beta-lactam, is appropriate as initial therapy.

Pharmacoeconomic Considerations: Cost of Resistance vs. Resistance-to-Drug Cost

Antibiotic Selection Process. Whether at the formulary level or in the practice setting, the selection process for antibiotics is never easy, even for well-educated practitioners and pharmacists at the front lines of hospital practice. Experienced, hospital-based clinicians are particularly aware of the current debate: to choose a newer, conveniently dosed, shorter-duration, and usually, more costly medication with a documented track record of antimicrobial activity, patient friendliness, and more predictable antibacterial coverage; or, to choose a less expensive, vintage, workhorse drug that is "report card" and formulary-friendly but that requires a longer duration of therapy, is compromised by evolving resistance, and has less predictable clinical cure rates. It should be stressed that, especially in elderly patients who are frail and have comorbid conditions, there are powerful incentives (e.g., cost, practice perception, and patient satisfaction) to identify agents that will cure infections the first time around (i.e., within the framework of the first prescription or antibiotic order).

Although optimizing cure rates with so-called convenient, dose- and duration-friendly branded agents that provide appropriate 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 points: Antimicrobials with these properties also can help avoid the unnecessary costs of treatment failures, patient re-evaluations, return visits, patient dissatisfaction, and the pharmacological retreatment costs associated with initiating a second course of antibiotics. In this sense, antibiotics that lower barriers to clinical cure can be seen as "productivity tools" that approve efficiency of clinical care, and potentially, reduce the overall costs associated with both outpatient and hospital-based treatment of infections.

Evidence-Based Support for Outcome-Effective Therapy. Although a number of antibiotics are approved for managing UTIs, this review has identified ciprofloxacin as a "workhorse" antibiotic with unique advantages and evidence-based support in a number of adult populations. First, the availability of effective antimicrobial therapy in oral suspension can facilitate UTI management of the elderly in the in-hospital setting. Convenience of administration may improve medication compliance which, in turn, may enhance therapeutic outcomes.[56] Please note that ciprofloxacin oral suspension should not be administered via feeding tubes due to physical characteristics of the formulation.

In this regard, bioequivalence of the oral suspension of ciprofloxacin (500 mg/10 mL) with ciprofloxacin 500 mg tablets has been documented in comparative studies evaluating the efficacy and safety of ciprofloxacin oral suspension vs. TMP/SMX oral suspension in community- and nursing home elderly women with UTI.[57] In one investigation of 261 patients, resistance rates of pretreatment bacteria was 4% to ciprofloxacin and 13% to TMP/SMX. Clinical resolution was observed in 96% of patients

on ciprofloxacin and 87% of those on TMP/SMX. In addition, adverse events occurred in fewer patients following a ciprofloxacin (17%) vs. TMP/SMX (27%) treatment regimen, including premature discontinuation (2% ciprofloxacin vs 11% TMP/SMX; $P < 0.01$). Based on these results, the authors of the study concluded that ciprofloxacin oral suspension was more effective and better tolerated than TMP/SMX and can be considered a drug of choice among elderly women with UTI.[57]

The safe and effective use of ciprofloxacin as a foundation antibiotic in the hospital and ED settings has been confirmed by a review of 127 articles in the medical literature on drug therapy in the elderly. The authors of the review conclude that: 1) ciprofloxacin is an effective agent for infections that commonly occur in the elderly population, including the full range of infections involving the urinary tract; 2) oral ciprofloxacin manifests potent antimicrobial activity that is sufficient to permit cost-effective therapy for serious infections in and out of the acute hospital setting; and 3) ciprofloxacin offers correct spectrum coverage of multiple pathogens known to cause UTI in this population.[58]

Cost of Resistance. With respect to barriers that can compromise clinical cure, in vitro activity and in vivo effectiveness against implicated pathogens are critical for cost-effective care. This is especially true for management of UTIs such as cystitis and pyelonephritis. Fortunately, recent studies now are available that have compared bacteriologic and clinical cure rates of ciprofloxacin with older agents increasingly compromised by emerging resistance.[37]

It is important to stress that the road from the clinician's prescription pad to clinical cure, in the setting of UTI, depends on many factors, including prescription resistance (the cost of the medication to the patient or health plan); patient resistance (tolerability, side effects, daily dose frequency, duration of therapy, quality of patient's life, and other patient-oriented factors that affect medication compliance); and drug resistance (the likelihood that the selected antibiotic will provide predictable coverage against organisms implicated in the infection, i.e., *E. coli* in patients with UTI).[38]

The prescription, patient, and drug resistance (PPD) approach to antibiotic selection permits pharmacists and physicians to evaluate and compare the clinical success profiles of one antibiotic vs. another. These comparisons are a synthetic approach based on multiple drug-related factors, including price, total resource cost, daily dose frequency, duration of drug therapy, side effect profile, and spectrum of coverage (bacteriologic cure rates).

With these cost, cure, and efficacy issues in clear focus, a well-designed, randomized, double-blind comparative study—the lead author of which is an ED physician—was conducted to compare the efficacy and safety of a seven-day ciprofloxacin regimen and a 14-day TMP/SMX regimen for the treatment of acute pyelonephritis in women.[37] A total of 255 patients (all ages) were included in the analysis. Patients were randomized to oral ciprofloxacin, 500 mg twice per day for seven days (with or without an initial 400 mg intravenous dose) followed by placebo for seven days ($n = 128$ included in analysis) vs. TMP/SMX, 160/800 mg twice per day for 14 days (with or without intravenous ceftriaxone, 1 g) ($n = 127$). The main outcome measure was continued bacteriologic and clinical cure, such that alternative antimicrobial drugs were not required, among evaluable patients through the four- to 11-day post-therapy visit, compared by treatment group.

This was an important study because trial results indicate superior efficacy for the ciprofloxacin group. At 4-11 days post-therapy, bacteriologic cure rates were 99% (112 of 113) for the ciprofloxacin regimen and 89% (90 of 101) for the TMP/SMX regimen (95% confidence interval [CI] for difference 0.04-0.16; $P = 0.004$). Clinical cure rates were 96% (109 of 113) for the ciprofloxacin regimen and 83% (92 of 111) for the TMP/SMX regimen (95% CI, 0.06-0.22; $P = 0.002$).

Adverse drug events occurred in 24% of 191 ciprofloxacin-treated patients and in 33% of 187 TMP/SMX-treated patients, respectively (95% CI, -0.001-0.2). Gastrointestinal events, headache, and rash tended to occur more frequently in the TMP/SMX group. Adverse events causing study drug discontinuation occurred in 11 (6%) of the ciprofloxacin-treated patients and in 21 (11%) TMP/SMX-treated patients.

E. coli, which caused more than 90% of infections, was resistant more frequently to TMP/SMX (18%) than to ciprofloxacin (0%; $P < 0.001$). Among TMP/SMX-treated patients, drug resistance was associated with greater bacteriologic and clinical failure rates ($P < 0.001$ for both). Drug-related adverse events occurred in 24% of 191 ciprofloxacin-treated patients and in 33% of 187 TMP/SMX-treated patients, respectively (95% CI, -0.001-0.2). To summarize, in this study of outpatient treatment of acute, uncomplicated pyelonephritis in women, a seven-day ciprofloxacin regimen was associated with greater bacteriologic and clinical cure rates than a 14-day TMP/SMX regimen, especially in patients infected with TMP/SMX-resistant strains.

Total Outcome Costs. The current shift to outpatient management and treatment of elderly patients in the long-term care facility (LCF) has placed an emphasis on cost-saving strategies; clinicians and pharmacists now must critically evaluate total treatment costs (i.e., beyond those associated with drug acquisition costs alone) associated with regimens used to manage acute, uncomplicated pyelonephritis. Physicians practicing in cost-conscious settings, including LCFs, need evidence-based trials to determine whether higher cure rates from drugs associated with a more predictable spectrum of coverage can reduce overall treatment costs for conditions such as pyelonephritis. The improved bacteriologic and cure rates observed with ciprofloxacin in this study suggest this may be the case. In another study, ciprofloxacin suspension showed higher clinical success and bacteriologic eradication rates compared to TMP/SMX for both community- and nursing home-residing elderly women with acute UTIs.[57] In addition, ciprofloxacin was associated with significantly lower rates of adverse events and premature discontinuations compared to TMP/SMX.[57]

To assess the possible advantages conferred by regimens that produce more predictable cure rates, the investigators of the pyelonephritis study conducted a health resource use and cost analysis for both ciprofloxacin and TMP/SMX treatment regimens. All health care resources used were collected prospectively. Additional resources required for achieving clinical cure were defined as those associated with managing clinical or bacteriologic failure, or adverse drug events. The perspective of the cost

analysis was that of the third-party payer. Direct medical costs were assigned retrospectively and were reported in 1997 dollars.

All significant, real-world costs associated with completing the journey from prescription pad to "clinical cure" were considered and included the following resource cost components: 1) the cost of the initial physician visit, including site of care (i.e., office or ED); 2) antimicrobial cultures, urinalysis, and urine culture; 3) a single follow-up visit (if there was at least one follow-up visit) with urinalysis and urine culture; and 4) additional resources used that were associated with failures and adverse drug events, including subsequent nonstudy-required medical visits, laboratory and radiology tests, hospitalizations, therapeutic adjuncts, and other antimicrobials, through the patient's last visit.

Costs of hospitalizations, office visits, laboratory tests, and other procedures were estimated by multiplying relative value units by an estimate of the average cost per relative value unit. Cost per cure was calculated based on the total costs for all patients divided by the number of cured patients in each treatment group. Safety, health resource use, and costs were evaluated for all 378 enrolled patients.

Cost Comparisons. Of special clinical importance was the finding that the total treatment costs for the seven-day course of ciprofloxacin was less than it was for those individuals treated with TMP/SMX. Additional health resource use (i.e., excluding resources required for initial management, and post-therapy follow-up visits for patients without earlier treatment failure) was higher in all categories for patients treated with TMP/SMX than ciprofloxacin, with the exception of radiological procedures. Since more TMP/SMX-treated patients had clinical failures, it is not surprising these patients accrued higher total service costs. In this regard, the mean total cost per patient was greater for TMP/SMX-treated patients ($687) than for ciprofloxacin-treated patients ($531) by 29% or $156 (95% CI, -$118-443).

Implications for Hospital Clinical Practice. The data from this landmark study suggest that excessive total treatment costs and inferior clinical cure rates associated with TMP/SMX therapy may be the consequence of an unexpectedly high prevalence of in vitro resistance to TMP/SMX among *E. coli* strains causing acute, uncomplicated pyelonephritis. In fact, the evolving resistance is a phenomenon that appears to be significant enough to alter clinical practice patterns related to antibiotic selection. As the authors point out, prior to beginning the study in 1994, resistance rates to TMP/SMX among uropathogens associated with acute, uncomplicated pyelonephritis generally were less than 10% at investigative sites.

They emphasize, however, that increasing rates of TMP/SMX resistance (reported to be as high as 25%, especially in Western states) have been observed among urinary *E. coli* isolates and that in this study, in vitro resistance to TMP/SMX was strongly associated with bacteriologic and clinical failure. They conclude that, based on their data, TMP/SMX may no longer be appropriate as empiric therapy in certain geographic areas, where a fluoroquinolone should be strongly considered as the initial agent of choice.[57,37]

Although the trial was not powered to show statistical significance in the economic differences between treatment groups for health care resource use, there was a discernible trend for more intensive resource use in all categories among TMP/SMX-treated patients, with the exception of radiological procedures. Of special importance is that despite the fact the prescription cost of the ciprofloxacin regimen was greater than that of the TMP/SMX regimen, patients treated with the TMP/SMX regimen tended to have greater overall costs, particularly those related to subsequent hospitalizations, office visits, and laboratory tests.

In addition, from a pharmatectural perspective, the findings of this study—in particular, the superior bacteriologic and clinical cure rates seen with a seven-day course of ciprofloxacin and reduced overall treatment costs support ciprofloxacin's favorable PPD profile—suggest it should considered the agent of choice in female patients with outpatient pyelonephritis. Finally, the results, conclusions, and comparative analyses from this well-designed clinical trial suggest that in the current outcome- and cost-sensitive environment of hospital practice, ciprofloxacin represents a more outcome-effective agent (i.e., cost, bacteriologic eradication, and clinical cure rate parameters) than does TMP/SMX for the management of acute, uncomplicated pyelonephritis.

Future Treatments and Directions for Research

Clinical Trials and Literature Review. An analysis has been planned to summarize the evidence regarding the effectiveness of short-course (2-4 days of oral antibiotics) compared with conventional therapy (7-14 days of oral antibiotics) for acute UTI in children.[59] Other therapies have been touted in the medical and popular literature. In this regard, a large, randomized placebo-controlled, double-blind trial is needed to determine the effectiveness of cranberry juice or tablets for prevention of UTIs in different populations. This study should be of at least six months' duration to take into account the natural course of UTIs, with its symptom-free periods and recurrences, and include specific outcomes and a detailed description of side effects and patient compliance.[60]

No clinical randomized controlled trials have conclusively shown a benefit of silver alloy catheters for the prevention of UTI. However, a recent analysis using silver-coated catheters in a hypothetical cohort of hospitalized patients requiring short-term catheterization (2-10 days) theoretically reduced the incidence of UTI and bacteremia, along with saving an estimated $4 per patient despite the $5 higher initial cost of the special catheter.[61] A large randomized, controlled trial is warranted to evaluate this type of catheter, as more than 80% of nosocomial UTIs are related to indwelling catheters. In vitro studies of catheters impregnated with quinolones or chlorhexidine gluconate have shown promising early results in the prevention of UTI. A very interesting avenue of research in in vitro and animal models involves the application of electric current to catheter surfaces, with relatively good efficacy at reducing UTIs; a practical clinical application of this technology awaits further study.[62]

In one novel study, clinicians administered an immunostimulating bacterial extract by mouth to patients with persistent recurrent UTI, with subsequent curative action and decreased frequency and severity of recurrent infections long term.[23] Similar success was found in a study using Uro-Vaxom, an oral drug prepared from immunogenic fractions extracted from *E. coli*.[23] Phase II trials have been completed for a multi-strain vaccine

administered as a vaginal suppository in women susceptible to recurrent UTI. Intervals to reinfection while off antibiotics were longer in those taking the vaccine than in the placebo group: 13 weeks vs. 8.7 weeks.[23] No serious side effects were noted. The same research group found that this vaccine had greater efficacy in patients with a specific human leukocyte antigen phenotype (HLA-DR).[63]

In patients with spinal cord injuries and a mean of 3.1 symptomatic UTIs per year, a small trial using intravesical inoculation with *E. coli* 83972, a benign pathogen, showed that successfully colonized patients had no symptomatic infection over a mean duration of 12.3 months.[64] Colonized subjects also reported subjective improvement in quality of life with respect to this improved prevention of UTIs. Authors suggest that colonization with *E. coli* 83972 may be used safely to reduce the rate of UTI in spinal cord patients with a neurogenic bladder.

Laboratory Models. In an animal model, adjunctive oral prednisolone appeared to be effective in diminishing renal scarring in severely affected kidneys.[65] Based on these results, clinical prospective trials are planned to further evaluate the possibility of oral steroids as an adjunct to the present treatment of pyelonephritis in children.[65] Additional research trials in rats found that the addition of ibuprofen to antibiotic therapy decreases renal scarring due to acute pyelonephritis, even when treatment is delayed 72 hours.[66] Further study to understand the mechanisms responsible for this finding may lead to additional treatment options for patients with pyelonephritis.

In the future, research will focus on understanding factors that lead to infection in order to develop non-antimicrobial strategies for preventing symptomatic infections. These areas of investigation include possible vaccination, colonization of patients with a virulent organism that prevents uropathogen inoculation, and selective interference with bacterial adhesion proteins or cell surface receptors.[2] One such study that is being conducted in animal models and in humans has focused on the development of a vaccine against pyelonephritis. This approach is based on current knowledge of virulence factors such as adhesive molecules on the tip of pili in some *E. coli* strains that allow binding to human uroepithelial cells.[12]

Experimental research also is being conducted to evaluate the administration of nitric oxide synthase inhibitors involved in the pathogenesis of sepsis.[55] Other investigational studies of inflammatory cytokines (IL-10), soluble TNF-alpha or IFN-gamma receptors, anti-IFN gamma monoclonal antibody, platelet-activating factor receptor antagonists, and antibodies directed against endotoxin-binding proteins also may provide insight and lead to new treatments for severe UTIs.[55]

Antimicrobials. The management of severe, multidrug resistant infections continues to become more challenging. Newer alternatives to standard therapies that may be used for UTIs include 1) Quinupristin/dalfopristin, the first injectable streptogramin antibiotic with substantial efficacy against VRE, and 2) colistin, polymyxin, that, in a small trial, showed improved outcomes in patients with severe infections with multidrug-resistant *P. aeruginosa* and *Acinetobacter baumani*.[67,68]

Summary

Outcome-effective management of UTIs requires a detailed clinical history, careful physical examination, and limited initial laboratory testing. This approach is essential for appropriate triaging of patients and initial management. Populations at risk for increased morbidity and mortality include neonates, patients of any age with signs of systemic toxicity, pregnant women, immunocompromised patients (those with the human immunodeficiency virus and transplant recipients), and any adult or elderly patient with significant co-morbid illnesses.

Rapid assessment and resuscitation are mandatory for hemodynamic instability or shock, and should be accompanied by prompt antimicrobial treatment. Initial empirical choice of antibiotics and duration of treatment has been influenced by the rapid emergence of significant resistance to nearly all classes of antibiotics used in the management of UTIs. In this regard, previous first-line agents, including amoxicillin and TMP/SMX, can no longer be recommended in the setting of *E. coli* resistance higher than 10%. In this increasingly common situation, ciprofloxacin has emerged as the preferred agent. A thorough understanding of the common side effects, drug interactions, and contraindications is essential for preventing any untoward consequences in patients with UTI.

Recent trials have shown that appropriately selected patients that once required admission for parenteral treatment may be discharged safely and treated with oral regimens. The greatest experience and trial data have been reported with ciprofloxacin, although other fluoroquinolones also may provide advantages of outpatient management. Close follow-up and appropriate referral are key to successful management of these patient populations.

Infants and children are at the highest risk of long-term complications from renal scarring, including hypertension and end-stage renal disease. These complications require clinicians to raise their awareness and suspicion for UTI in younger patients. Although mostly evaluated in the outpatient setting for asymptomatic bacteriuria, pregnant women with UTI require special care and follow-up to prevent premature labor, low-birth-weight infants, and intrauterine growth retardation.

Advances in biotechnology and molecular science are enhancing our understanding of the establishment of UTI, as well as the cascade of events leading to renal damage. This expanded knowledge base eventually may lead to newer, more effective prevention strategies and treatment regimens and, in the process, decrease morbidity and mortality associated with UTI.

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Physician CME Questions

49. A recent, prospective study found the prevalence rates of asymptomatic bacteruria to in sexually active young women to be:
    A. less than 1%.
    B. about 1%.
    C. about 2%.
    D. about 5%.
    E. about 10%.

50. Oral antimicrobial agents that can be used in children include all of the following *except*:
    A. cephalosporins.
    B. trimethoprim/sulfamethoxazole.
    C. fluoroquionolones.
    D. amoxicillin-clavulanate.
    E. None of the above

51. Fluoroquinolones are a better choice for treating uncomplicated UTI under which of the following condition or conditions?
    A. In areas where *E. coli* resistance to TMP/SMX is greater than 10%-20%
    B. For patients with allergies to sulfa or other drugs
    C. In patients returning for failed antibiotic treatment after having used non-fluoroquinolone antibiotics for UTI
    D. All of the above
    E. None of the above

52. Admission recommendations for pediatric patients with UTI include which of the following feature(s)?
    A. Febrile infants younger than 3 years of age
    B. Infants and children with dehydration who are unable to tolerate oral hydration or medication
    C. Immunocompromised children
    D. Patients with a high risk of noncompliance with medication and early follow-up
    E. All of the above

53. In certain regions of the United States, resistance among *E. coli* to TMP/SMX has risen to as high as:
    A. 4%.
    B. 14%.
    C. 24%.
    D. 64%.
    E. None of the above

54. Superior bacteriologic and clinical cure rates seen with a seven-day course of ciprofloxacin, compared to a 10-day course of TMP/SMX, and reduced overall treatment costs, suggest ciprofloxacin should be considered an agent of choice in female patients with outpatient pyelonephritis.
    A. True
    B. False

55. In young women with uncomplicated UTI, the preferred duration of treatment with ciprofloxacin or TMP-SMX is:
    A. three days.
    B. five days.
    C. seven days.
    D. 10 days.
    E. 14 days.

56. Which of the following agents is acceptable for mild to moderate pyelonephritis caused by *Candida albicans?*
    A. Ciprofloxacin
    B. Oral amphotericin B
    C. Oral nystatin
    D. Oral fluconazole
    E. None of the above

In Future Issues: Congenital Bleeding Disorders