

High-Dose, Short-Course Levofloxacin for Complicated Urinary Tract Infections and Acute Pyelonephritis

From left to right
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Urinary tract infections (UTIs) are common. They can be classified as either an infection of the lower tract, cystitis, or the upper tract, pyelonephritis.

Pyelonephritis can be either acute or chronic. UTIs can be further classified as complicated or uncomplicated. Complicated urinary tract infections (cUTIs) are those associated with any co-morbid condition, such as obstruction, urologic dysfunction, multidrug-resistant pathogens, recent antibiotic usage, recent instrumentation, or affecting males in particular. Diagnosis is made by taking a history and physical examination, as well as a urinalysis and urine culture. Treatment is largely supportive and includes empiric antibiotics until urine culture and sensitivity data are available. Recently, antibiotic resistance in the therapy for both cUTI and acute pyelonephritis (AP) has increased, leading to new dosing regimens for existing antibiotics. This article reviews the use of high-dose, short-course levofloxacin for the treatment of cUTI and AP. A recent multicenter, randomized, double-blind controlled trial compared high-dose, short-course levofloxacin with standard dose ciprofloxacin for the treatment of cUTI and AP. In this study, subjects were randomized to either ciprofloxacin IV or PO 400/500 mg, twice daily for 10 days or levofloxacin 750 mg IV or PO once daily for 5 days. A total of 1,109 subjects were enrolled in the study and 619 of them had a confirmed diagnosis of cUTI or AP. A subgroup of the AP patients were examined in a separate study. In total, 506 subjects met the entry criteria and were included in the microbiologically evaluable (ME) population. At the end of therapy, the eradication rate for the modified intent-to-treat (mITT) population was 79.8% for the levofloxacin- and 77.5% for the ciprofloxacin-treated group (95% confidence interval [CI]: -8.8-4.1). In the ME population eradication rates were 88.3% and 86.7% for the levofloxacin and ciprofloxacin populations, respectively (95% CI: -7.4-4.2). In the subgroup with AP, microbiological eradication was 83% and 79.6% in the mITT population (95% CI: -3.4-14.4) and 92.5% vs. 93.4% in the ME population (95% CI: -7.1-8.9) for levofloxacin and ciprofloxacin, respectively. These studies demonstrated equal efficacy of the high-dose, short-course levofloxacin regimen compared with other antibiotics given in traditional regimens. Thus, high-dose, short-course levofloxacin provides a viable alternative to standard antibiotic therapy in cUTI and AP.

Introduction

Acute pyelonephritis (AP) is a urinary tract infection (UTI) that passes from the lower urinary tract to the upper tract resulting in bacterial invasion of the renal parenchyma. Hematogenous spread to the kidney can occur in cases of endocarditis and IV drug abuse. There are an estimated 250,000 cases of AP per year in the United States. Most episodes are uncomplicated but hospitalization may be re-

quired for up to 10–30% cases (1). The development of secondary conditions, such as emphysematous pyelonephritis, perinephric abscess, or sepsis, can lead to significant mortality. Thus, early recognition and treatment is extremely important. Clinical features of uncomplicated AP include flank pain, abdominal pain, nausea, vomiting, fever and/or costovertebral tenderness. Symptoms of cystitis, dysuria or frequency, may or may

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not be present. Shock, sepsis or multiple organ failure can also occur, but are rare. Most cases can be treated as outpatients; however severe illness, patients with signs of sepsis, those with high fevers, pain and debility, pregnancy, inability to tolerate oral hydration or medication should be admitted for management. If the physician questions a patient's ability to comply with antibiotics as an outpatient, that patient should also be considered for admission.

The diagnosis of AP can be made from the history and a physical examination in most cases. The physical examination should focus on vital signs, evaluation of the pelvis and abdomen, and a search for the presence costovertebral angle tenderness. In females, a pelvic examination should be performed to distinguish AP from pelvic inflammatory disease. A urinalysis should be obtained to test for pyuria, which is usually present in patients with pyelonephritis. Pyuria is defined as having more than 5–10 white blood cells (WBCs) per high power field (hpf). Patients with pyelonephritis usually have more than 20 WBCs per hpf. The use of urine dipsticks for leukocyte esterase and nitrite may also aid in the diagnosis. In the absence of pyuria, another diagnosis should be considered. Along with a urinalysis, a urine culture and sensitivity should be obtained. A positive urine culture is defined as more than 10^5 CFU/ml for clean catch specimens and more than 10^2 CFU/ml for samples obtained by catheter. A complete blood count and blood cultures should be obtained for any patient being admitted to the hospital. Imaging studies are generally not indicated unless a complication of pyelonephritis is suspected, if the patient fails to respond to therapy, or if the patient has consecutive positive blood cultures. Imaging may be used to exclude other diagnoses, such as nephrolithiasis, biliary tract disease, appendicitis and gynecological causes of the patient's symptoms. Generally, contrast-enhanced computed tomography is the method of choice, although ultrasound is an acceptable alternative, especially in patients unable to tolerate IV contrast media due to renal insufficiency or contrast allergy.

Escherichia coli is the most common microbe identified as the cause of AP, followed by *Klebsiella pneumoniae* and *Proteus mirabilis*. Other urinary pathogens, such as *Staphylococcus saprophyticus*, *Citrobacter* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, enterococci, and *S. aureus* infections are less common, but do occur. Fungal infections may also be causative agents. *E. coli* has been shown to be the major cause of uncomplicated UTI, complicated urinary tract infection (cUTI), and AP is present in 70–95% of cases (2–4). Selection of antimicrobial therapy for cUTI and AP should there-

fore include coverage for Gram-negative pathogens. High levels of *E. coli* resistance to conventional therapies with β -lactams and trimethoprim-sulfamethoxazole (TMP-SMX) are common (5, 6). Resistance to therapy with TMP-SMX and ampicillin has been found to be as high as 50.1% and 22.1% for Gram-negative pathogens, respectively (7). In another study, TMP-SMX-resistant *E. coli* clonal groups have been isolated from nearly half of women with community-acquired pyelonephritis (8). With high resistance to conventional therapies with β -lactams and TMP-SMX, fluoroquinolones have increasingly been used to treat such conditions (8, 9). Fluoroquinolones have considerably less resistance; in one study 91.9% of Gram-negative pathogens were susceptible to levofloxacin and ciprofloxacin (7). Although resistance is less common with fluoroquinolones, it is on the rise (2). There has been an increase in resistance to ciprofloxacin from 0.2 to 3.4% while, at the same time, TMP-SMX resistance has decreased to 32% (2). The increased usage of fluoroquinolones for the treatment of UTI, cUTI and AP and decreased use of TMP-SMX is thought to be the reason behind changing resistance patterns (2). To combat increasing resistance, new dosing schedules and regimen optimization have been devised, as there is a paucity of new antibiotic classes in development. An example of this approach is the use of high-dose ciprofloxacin once daily which has been shown to be as effective as standard twice daily ciprofloxacin for uncomplicated UTI (10). The strategy has also proved effective in other disease processes, such as community-acquired pneumonia and sinusitis. In addition, levofloxacin has been used in high-dose, short-course therapies to combat the problem of increasing resistance.

Levofloxacin is a fluoroquinolone antibiotic and is the optical S(-) isomer of the racemic drug ofloxacin. It has a broad spectrum of *in vitro* activity against Gram-positive and Gram-negative bacteria, as well as certain other pathogens, such as *Mycoplasma* spp., *Chlamydia* spp., *Legionella* spp. and *Mycobacteria* spp. Levofloxacin is widely distributed throughout the body, with a mean volume of distribution of 1.1 l/kg, and penetrates well into most body tissues and fluids. Levofloxacin is a concentration-dependant antibacterial which is renally excreted. Therefore, the ratio of the area under the concentration-time curve (AUC) to the minimum inhibitory concentration (MIC) is the determining factor for bacterial eradication (11, 12). Approximately 80% of levofloxacin is eliminated as unchanged drug in the urine through glomerular filtration and tubular secretion. Minimal metabolism occurs with the formation of no active metab-

olites (13). Levofloxacin has already been shown to be as effective as other fluoroquinolones, such as ciprofloxacin and lomefloxacin, in the treatment of cUTI and AP in a standard dosing regimen (14). High-dose (750 mg once daily), short-course therapy (5 days) with levofloxacin has been shown to be as effective as standard therapy in other disease processes, such as community-acquired pneumonia and sinusitis (15, 16). The success of novel dosing regimens in other conditions has led researchers to theorize that high-dose, short-course levofloxacin could be effective in the treatment of cUTI and AP. Two studies have investigated a short course (5 days) of high-dose levofloxacin (750 mg) for the treatment of cUTI and AP. Those studies are examined here.

Patients and Methods

This study was a multicenter, randomized, double-blind trial which examined levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400/500 mg twice daily for 10 days in patients with cUTI and AP. The population with AP was examined in a separate study (17). The data were derived from the larger study, and thus the methods remained the same for both studies.

Patients involved in the study were ≥ 18 years of age with a positive urine dipstick, plus two of the following symptoms: fever $\geq 38^{\circ}\text{C}$, flank pain or costovertebral angle tenderness, peripheral WBC $> 12,500$ or $\geq 10\%$ bands and/or WBC casts in the urine. In addition, the subjects needed to have one of the following symptoms: nausea, vomiting, dysuria or frequency.

Subjects were randomized to a 1:1 ratio and blinded to the study medication. The total duration of therapy was 10 days. Those randomized to levofloxacin received a placebo in the evening followed by placebo in the AM and PM for days 6–10. The use of IV versus PO preparations of the medication was left up to the discretion of the investigator.

Cure was determined by resolution of clinical signs and symptoms without additional antimicrobial therapy. Improvement was defined as incomplete resolution of symptoms without need for further therapy, and failure was defined as no response to therapy and the requirement of additional therapy. Microbiologic eradication was prospectively defined as $< 10^4$ CFU/ml of uropathogens.

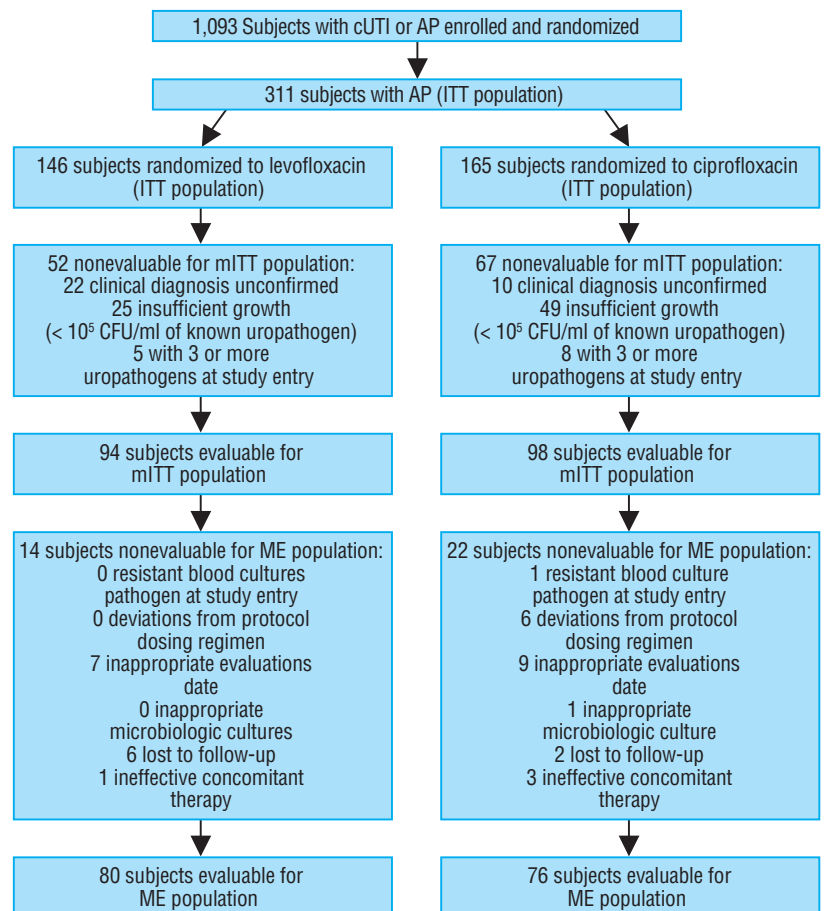
Results

The study which looked at the AP population will be examined first. Three hundred and eleven patients were enrolled in the study with a diagnosis of AP and 146 were randomized to levofloxacin

while 165 were randomized to ciprofloxacin (intent-to-treat [ITT] population). Of these 94 levofloxacin-treated and 98 ciprofloxacin-treated patients had a confirmed diagnosis of AP. A total of 80 levofloxacin- and 76 ciprofloxacin-treated subjects met the criteria for full microbiologically evaluability (ME) (see Figure 1 for full analysis population). There were no observable demographic differences between the two treatment groups. The majority of the subjects were female, with only 12 males enrolled. Sixty-one subjects (29 levofloxacin, 32 ciprofloxacin) met criteria for complicated AP and 7.7% of ITT subjects were bacteremic at study entry. Most subjects had community-acquired infections and were treated as outpatients with oral medications.

Of the recovered pathogens *E. coli* was the most common, 83.5% in the levofloxacin group and 88.1% in the ciprofloxacin group. Other Gram-negative organisms included *K. pneumoniae*, *K. oxytoca* and *P. mirabilis*. Gram-positive species were isolated in 7.3% of subjects and included *E.*

Figure 1. Analysis population



Abbreviations: cUTI = complicated urinary tract infection, AP = acute pyelonephritis, ITT = intent-to-treat, mITT = modified intent-to-treat, CFU = colony forming unit, ME = microbiologically evaluable.

Adapted from reference (17).

faecalis, *S. aureus*, *S. saprophyticus* and *Streptococcus agalactiae*. Four pathogens (2.1%) recovered from the modified intent-to-treat (mITT) group were resistant to the study drugs, although 56.4% and 31.8% of *E. coli* recovered were resistant to ampicillin and TMP-SMX, respectively.

Eradication was defined prospectively as $< 10^4$ CFU/ml of uropathogens at assessment. However, all subjects who were considered eradicated had no pathogen growth. Eradication rates at the end of the trial were similar between the two groups. For *E. coli* isolates, eradication rates were 82.7% for levofloxacin and 78.7% for ciprofloxacin in the mITT population and 91.3% vs. 94.0% in the ME population for levofloxacin and ciprofloxacin, respectively. Eradication was achieved in all of the Gram-positive pathogens (6/6) in the levofloxacin-treated group and 87.5% 7/8 in the ciprofloxacin-treated group (Table 1).

In the subjects who were bacteremic (12.5%) in the mITT group the only pathogen isolated from the blood was *E. coli*. One subject in the

ciprofloxacin group was resistant (MIC > 32) and was withdrawn from the study. Of the remaining bacteremic subjects (10 levofloxacin, 11 ciprofloxacin), 100% of pathogens were eradicated and repeat blood cultures at day 21 showed no growth regardless of the treatment group.

Clinical success rates (i.e., resolution of symptoms) at the end of the trial were 85.1% vs. 80.6% for levofloxacin- and ciprofloxacin-treated mITT subjects, respectively, and 93.8% vs. 88.2% in the ME subjects (Table 2). A total of 14 subjects failed therapy (6 levofloxacin and 8 ciprofloxacin). However, none of the pathogens isolated in the failed therapy group was resistant to levofloxacin or ciprofloxacin.

In the larger trial which encompassed patients with cUTI, as well as AP, UTI was defined as above plus one complicating factor (male sex, or females with neurogenic bladder or urinary retention, partial obstruction, renal tumor or fibrosis, distorted urethral structure and/or intermittent catheterization). The inclusion and exclusion criteria were

Table 1. Microbiologic eradication and clinical success rates at end of therapy

Population	Levofloxacin 750 mg once daily for 5 days 5–7 days postactive therapy		Ciprofloxacin 400/500 mg twice daily for 10 days 0–2 day postactive therapy		Difference (95% CI)
	n/N	(%)	n/N	(%)	
Microbiologic eradication rate ^a					
mITT	253/317	(79.8)	234/302	(77.5)	2.3 (-8.8–4.1)
ME	234/265	(88.3)	209/241	(86.7)	1.6 (-7.4–4.2)
Clinical success rate ^a					
mITT	262/317	(82.6)	237/302	(78.5)	4.1 (-10.4–2.1)
ME	242/265	(91.3)	210/241	(87.1)	4.2 (-9.6–1.2)

^a Subjects with an outcome of unknown in the mITT population are included in the denominator. Abbreviations: CI = confidence interval, mITT = modified intent-to-treat, ME = microbiologically evaluable. Adapted from reference (18).

Table 2. Microbiologic and clinical outcomes at the end-of-therapy visit (study day 11 ± 1)

Population	Levofloxacin (5–7 days after end of active therapy)			Ciprofloxacin (± 1 day after end of active therapy)			Difference (95% CI) ^a	
	n = 94, n (%)			n = 98, n (%)				
mITT	Microbiologic outcome	Eradicated	Persisted	Unknown ^a	Eradicated	Persisted	Unknown	
		78 (83.0)	2 (2.1)	14 (14.9)	77 (78.6)	0 (0.0)	21 (21.4)	-4.4 (-15.5–6.7)
	Clinical outcome	Success	Failure	Unknown	Success	Failure	Unknown	-4.5 (-15.1–6.1)
ME	Microbiologic outcome	80 (85.1)	0 (0.0)	14 (14.9)	79 (80.6)	0 (0.0)	19 (19.4)	-4.5 (-15.1–6.1)
		n = 80, n (%)			n = 76, n (%)			
	Clinical outcome	Success	Failure	Unknown	Success	Failure	Unknown	-4.5 (-14.2–5.4)
ME	Microbiologic outcome	Eradicated	Persisted	Unknown	Eradicated	Persisted	Unknown	
		73 (91.3)	2 (2.5)	5 (6.3)	66 (86.8)	0 (0.0)	10 (13.2)	-4.5 (-14.2–5.4)
	Clinical outcome	Success	Failure	Unknown	Success	Failure	Unknown	-5.6 (-14.6–3.4)
		75 (93.8)	0 (0.0)	5 (6.3)	67 (88.2)	0 (0.0)	9 (11.8)	-5.6 (-14.6–3.4)

^a Subjects with an unknown microbiological or clinical outcome at the end-of-therapy visit did not have a urine culture and/or a clinical assessment conducted at this visit or had the assessment conducted outside the visit window. Abbreviations: CI = confidence interval, mITT = modified intent-to-treat, ME = microbiologically evaluable. Adapted from reference (17).

the same as described earlier. In this larger study, which involved a total of 1,109 enrolled subjects, 1,093 (ITT population) received at least 1 dose of either medication with 619 subjects having a confirmed diagnosis of cUTI or AP (mITT population). Of these, 506 met the criteria for inclusion, and were included in the ME population (Figure 2). In addition, 311 of the mITT subjects had AP analyzed as a subgroup in the Klausner et al. study discussed above. The remaining 782 subjects in the mITT population were diagnosed with cUTI.

As far as the population with cUTI was concerned, 33 of 427 (7.7%) had a treatment-resistant Gram-negative pathogen, 29 of which were *E. coli* and 2 of which were *K. pneumoniae*, one was *P. aeruginosa* and one *P. mirabilis*. All of the Gram-negative pathogens (4) in the 192 AP subjects were *E. coli*. Resistant Gram-positive pathogens in-

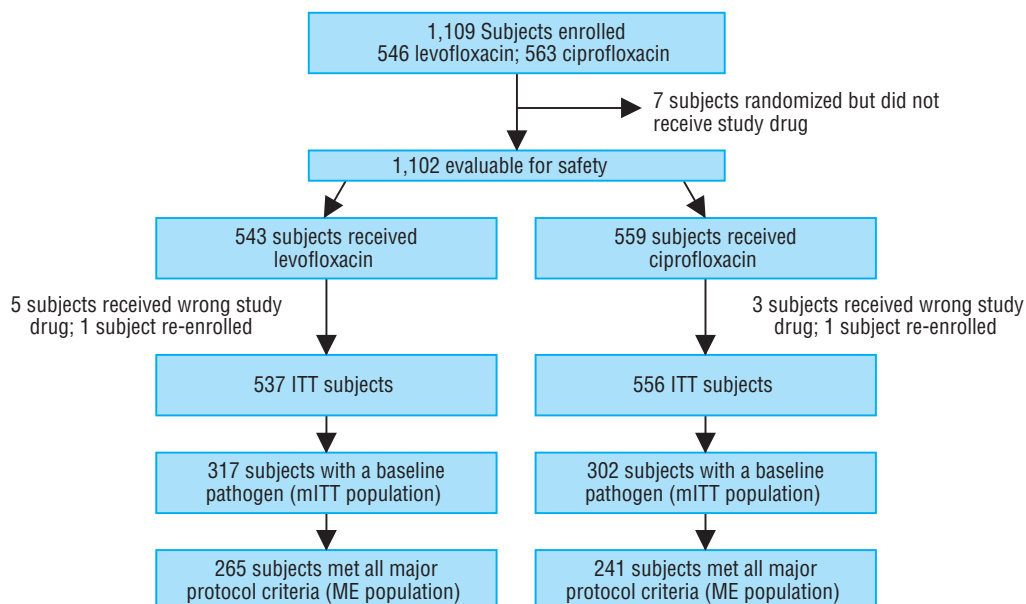
cluded *Enterococcus faecalis* (3), MRSA (3), all isolated from the cUTI subpopulation. Microbiologic eradication rates in the mITT and ME populations were comparable between treatment groups (see Table 1 and Table 3).

The clinical response in the cUTI subpopulation at the end of the trial was 78.9% vs. 79.9% for the levofloxacin-treated and ciprofloxacin-treated populations, respectively (95% confidence interval [CI]: -9.6–1.2). This is similar to the clinical success rates of the AP population, as reported above.

Discussion

Levofloxacin 750 mg once daily for 5 days is an effective treatment of cUTI and AP. It has equal efficacy to other fluoroquinolones given as a traditional course. A simplified dosing regimen may

Figure 2. Subject disposition



Abbreviations: ITT = intent-to-treat, mITT = modified intent-to-treat, ME = microbiologically evaluable. Adapted from reference (18).

Table 3. Microbiologic eradication and clinical response rates at post-therapy

Population	Levofloxacin 750 mg once daily for 5 days 10–17 days postactive therapy		Ciprofloxacin 400/500 mg twice daily for 10 days 5–12 days postactive therapy		Difference (95% CI)
	n/N	(%)	n/N	(%)	
Microbiologic eradication rate ^a					
mITT	253/317	(79.8)	241/302	(79.8)	0 (-6.3–6.3)
ME	228/265	(86.0)	215/241	(89.2)	3.2 (-2.5–8.9)
Clinical success rate ^a					
mITT	257/317	(81.1)	242/302	(80.1)	-0.9 (-7.2–5.3)
ME	229/265	(86.4)	213/241	(88.4)	2.0 (-3.9–7.8)

^a Subjects with an outcome of unknown in the mITT population are included in the denominator.

Abbreviations: CI = confidence interval, mITT = modified intent-to-treat, ME = microbiologically evaluable. Adapted from reference (18).

also lead to higher patient compliance, and may then prevent emergence of resistant strains. Furthermore, shorter courses of antibiotics could lead to shorter hospital stays and, hence, lower hospital costs. The trends of high susceptibility of uropathogens to fluoroquinolones appear to be declining as physicians increasingly prescribe these agents for the treatment of cUTI as well as AP. It is unclear

whether high-dose regimens will have the same patterns of decreasing susceptibility. However, with current high levels of resistance to β -lactams and TMP-SMX, fluoroquinolones provide high cure rates for cUTI and AP, and high-dose, short-course regimens provide an acceptable alternative to traditional therapy.

REFERENCES

- 1 Brown P, Ki M, Foxman B. Acute pyelonephritis among adults: cost of illness and considerations for the economic evaluation of therapy. *Pharmacoeconomics* 2005; 23: 1123–42.
- 2 Czaja CA, Scholes D, Hooton TM, Stamm WE. Population-based epidemiologic analysis of acute pyelonephritis. *Clin Infect Dis* 2007; 45: 273–80.
- 3 Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am* 1997; 11: 551–81.
- 4 Scholes D, Hooton TM, Roberts PL, Gupta K, Stapleton AE, Stamm WE. Risk factors associated with acute pyelonephritis in healthy women. *Ann Intern Med* 2005; 142: 20–7.
- 5 Hooton TM. The current management strategies for community-acquired urinary tract infection. *Infect Dis Clin North Am* 2003; 17: 303–32.
- 6 Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Infectious Diseases Society of America (IDSA)*. *Clin Infect Dis* 1999; 29: 745–58.
- 7 Peterson J, Kaul S, Khashab M, Fisher A, Kahn JB. Identification and pretherapy susceptibility of pathogens in patients with complicated urinary tract infection or acute pyelonephritis enrolled in a clinical study in the United States from November 2004 through April 2006. *Clin Ther* 2007; 29: 2215–21.
- 8 Manges AR, Dietrich PS, Riley LW. Multidrug-resistant *Escherichia coli* clonal groups causing community-acquired pyelonephritis. *Clin Infect Dis* 2004; 38: 329–34.
- 9 Talan DA, Stamm WE, Hooton TM, Moran GJ, Burke T, Iravani A, Reuning-Scherer J, Church DA. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. *JAMA* 2000; 283: 1583–90.
- 10 Henry DC Jr, Bettis RB, Riffer E, Haverstock DC, Kowalsky SF, Manning K, Hamed KA, Church DA. Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. *Clin Ther* 2002; 24: 2088–104.
- 11 Drusano GL, Preston SL, Fowler C, Corrado M, Weisinger B, Kahn J. Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. *J Infect Dis* 2004; 189: 1590–7.
- 12 Forrest A, Nix DE, Ballou CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993; 37: 1073–81.
- 13 Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. *Clin Pharmacokinet* 1997; 32: 101–19.
- 14 Richard GA, Klimberg IN, Fowler CL, Callery-D'Amico S, Kim SS. Levofloxacin versus ciprofloxacin versus lomefloxacin in acute pyelonephritis. *Urology* 1998; 52: 51–5.
- 15 Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, Wiesinger BA, Xiang JX, Zadeikis N, Kahn JB. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* 2003; 37: 752–60.
- 16 Poole M, Anon J, Paglia M, Xiang J, Khashab M, Kahn J. A trial of high-dose, short-course levofloxacin for the treatment of acute bacterial sinusitis. *Otolaryngol Head Neck Surg* 2006; 134: 10–7.
- 17 Klausner HA, Brown P, Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. *Curr Med Res Opin* 2007; 23: 2637–45.
- 18 Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. *Urology* 2008; 71: 17–22.