ORIGINAL RESEARCH

5-Day versus 10-Day Course of Fluoroquinolones in Outpatient Males with a Urinary Tract Infection (UTI)

Geoffrey A. Mospan, PharmD, BCPS, and Kurt A. Wargo, PharmD, FCCP, BCPS (AQ-ID)

Introduction: **Current guidelines classify urinary tract infections (UTIs) in males as complicated and recommend longer treatment than for UTIs in females. The objective of this study is to demonstrate that males with UTIs may be successfully treated with an outpatient 5-day course of levofloxacin.**

Methods: **Data were obtained from a previously conducted clinical trial (www.clinicaltrials.gov identifier NCT00210886), a multicenter, double-blind, randomized, noninferiority study comparing levofloxacin 750 mg intravenously/by mouth once daily for 5 days and ciprofloxacin 400/500 mg intravenously/by mouth twice daily for 10 days in complicated UTI (cUTI). The current study was a post hoc, subgroup analysis of male and female subjects with cUTI. Subjects were stratified into groups based on sex and antibiotic received. The subjects were analyzed at the end of therapy (EOT) and post therapy (PT) for clinical success rates, defined as no further need for antimicrobial treatment.**

Results: **Totals of 427 patients (224 male, 203 female) and 350 patients (189 male, 161 female) were included in the modified intent-to-treat (mITT) population and microbiologically evaluable (ME) populations, respectively. Clinical success rates between males and females were not statistically different between antibiotic groups in either the mITT or ME populations at EOT or PT.**

Conclusion: **This study demonstrates that males with UTI may be treated with a shorter course of antimicrobial therapy for UTI than previously recommended. (J Am Board Fam Med 2016;29:654–662.)**

Keywords: **Antibacterial Agents, Anti-infective Agents, Ciprofloxacin, Double-Blind Method, Levofloxacin, Outpatients, Urinary Tract Infections**

Infections of the urinary tract caused by bacteria are a common occurrence in clinical practice. In men, however, the length of the urethra, a drier environment surrounding the meatus, and the antibacterial properties of prostatic fluid all contribute to lower rates of urinary tract infections (UTIs).[1] Therefore, when UTIs occur in men, they are deemed complicated and subject to longer treatment durations compared with infections in women.[1,2] Clinical trials demonstrating the efficacy of antimicrobials in UTIs have typically enrolled a majority of female patients. In general, clinical trials of patients with UTIs enroll small numbers of male patients, and their data are grouped with those of female patients in analyses.[3] Drekonja and colleagues[4] conducted a retrospective study of >30,000 males with a UTI in the Veterans Affairs system. The objective of their study was to evaluate the recurrence of infection in patients who received a short (<7 days) or long (>7 days) duration of treatment. The investigators found that treatment for >7 days in males with a UTI was not associated with a reduction in early or late recurrence of UTI,

This article was externally peer reviewed.
Submitted 11 February 2016; revised 16 May 2016; accepted 19 May 2016.
From the Wingate University School of Pharmacy, Hendersonville, NC.
Funding: none.
Conflict of interest: none declared.
Disclaimer: This study, conducted under Yale University Open Data Access Project no. 2015-0514, used data obtained from the Yale University Open Data Access Project, which has an agreement with Janssen Research & Development, LLC. The interpretation and reporting of research using this data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or Janssen Research & Development, LLC.
Corresponding author: Geoffrey A. Mospan, PharmD, BCPS, Wingate University School of Pharmacy, 220 Fifth Ave East, Hendersonville, NC 28792 (E-mail: g.mospan@wingate.edu).

but it did increase the risk of *Clostridium difficile* infection compared with a treatment duration <7 days. The optimal duration of therapy for the treatment of UTIs in males is still unclear, and as a result, recommendations are predominantly based on data extrapolated from clinical trials of essentially all females and from expert opinion.[1]

The most common pathogen associated with UTIs is *Escherichia coli*.[1–3] Given their broad spectrum of activity and their historic efficacy in treating UTIs caused by *E coli*, fluoroquinolones are among the first-line antimicrobials to treat these infections.[1,2] Unfortunately, widespread use of these agents has led to increased resistance of *E coli*, and their empiric use is falling out of favor among many clinicians.[5–8] A study of patients treated in an emergency department demonstrated that while resistance of *E coli* to levofloxacin was high (17%), it was significantly greater in those with hospital-acquired UTIs (38% vs 10% of patients with community-acquired UTIs), long-term medical conditions, and fluoroquinolone use within the previous 1 to 4 weeks.[7]

While resistance to levofloxacin is on the rise, so too is resistance to other antimicrobial agents. The North American Urinary Tract Infection Collaborative Alliance (NAUTICA) trial evaluated 1990 outpatient urinary tract isolates to determine changes in the epidemiology of urinary tract pathogens.[9] In that study, 20.5% of isolates came from male patients. Levofloxacin resistance was highest among males aged ≥65 years, at 19.9%. Interestingly, among males in this same age group, resistance to nitrofurantoin and trimethoprim-sulfamethoxazole were higher: 27.8% and 32.6%, respectively.

Peterson and colleagues[10] conducted a multicenter, double-blind, randomized, noninferiority study of primarily outpatient subjects comparing levofloxacin 750 mg intravenously (IV) by mouth (PO) daily for 5 days with ciprofloxacin 400 mg IV/500 mg PO twice daily for 10 days in both male and female patients with complicated UTIs (cUTIs) and acute pyelonephritis. In that study, susceptibility of *E coli* to levofloxacin was very high (94%). Furthermore, the clinical success rates for the short course of levofloxacin were shown to be noninferior to ciprofloxacin. Unfortunately, the published results of that study combined data from both male and female subjects in the analysis. Through reanalysis using the original, unpublished data, the objective of the present study is to evaluate clinical success rates in males with cUTI who received 5 days of levofloxacin or 10 days of ciprofloxacin compared with their female counterparts.

Table 1. Complicating Factors per Study Protocol

Neurogenic bladder or urinary retention
Intermittent catheterization
Partial obstruction, including:
Kidney and/or bladder stone
Renal tumor or fibrosis
Distorted urethral structure
Benign prostatic hypertrophy

Methods

Through the Yale University Open Data Access Project, deidentified, patient-level data were obtained from a previously conducted clinical trial (www.clinicaltrials.gov identifier NCT00210886), a multicenter, double-blind, randomized, noninferiority study comparing levofloxacin 750 mg once daily for 5 days and ciprofloxacin 400 mg IV/500 mg PO twice daily for 10 days in cUTI and acute pyelonephritis.[10] This study was a post hoc, subgroup analysis of male and female subjects with cUTIs only.

Male and female patients at least 18 years old, institutionalized or ambulatory, and diagnosed with a cUTI were included in this study. To be diagnosed with a cUTI, patients had to be male with or without additional complicating factors, or female with at least 1 of the complicating factors listed in Table 1, per the original study protocol.[10] Additional inclusion and exclusion criteria can be found in Table 2. Patients were randomized (1:1) to receive either levofloxacin for 5 days or ciprofloxacin for 10 days. Patients randomized to receive levofloxacin were given a placebo in the evening on days 1 to 5 and a placebo twice daily on days 6 to 10. A urine culture was obtained before administration of the first dose of study medication.

Per the original study protocol, patients were stratified into a modified intent-to-treat population (mITT) if they were randomized to and received at least 1 dose of a study medication, if they were diagnosed with cUTI, and if their culture showed 1 or 2 uropathogens.[10] Patients were further classified as microbiologically evaluable (ME) if they

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
At least 10^5 colony-forming units of 1 or 2 uropathogens	Uncomplicated UTI
	Acute pyelonephritis*
One of the following: dysuria, increased urinary frequency, urgency, WBC >12,500/mm^3 or ≥10% bands, temperature ≥100.4°F within the previous 24 hours	Chronic pyelonephritis
	Complete obstruction
	Calculated creatinine clearance <50 mL/min
	Need for additional antimicrobial therapy for a coexisting infection or for the presenting UTI
	Need for or history of surgery or lithotripsy within 7 days of study entry
	Pathogen known to be resistant to the study medication
	Received >1 dose of any antibacterial for treatment of the UTI within 5 days of study entry (unless patient received at least 72 hours of a nonfluoroquinolone antibiotic and was deemed a clinical failure)
	Renal or perirenal abscess
	Acute or chronic bacterial prostatitis
	Epididymitis
	Pregnancy

*Additional exclusion criteria added for this study.
UTI, urinary tract infection; WBC, white blood cell.

followed the study protocol and were not lost to follow-up.

Patients were evaluated at the end of therapy (EOT), post-therapy (PT), and post-study (PS) to determine clinical success rates[10] (Figure 1). Patients were deemed to achieve clinical success if they were assessed as "clinically cured" (no signs or symptoms of infection and no need for further antimicrobial therapy) or "clinically improved" (signs or symptoms of infection did not completely resolve but no need for further antimicrobial therapy) by the investigator. Patients were defined as a "clinical failure" if any of the following occurred: no response to therapy, worsening or reappearing signs or symptoms of infection, or additional antimicrobial therapy needed.[10]

Statistics

Data from the original trial were obtained from the Yale University Open Data Access Project and analyzed in this study using χ^2 and Fisher exact tests, with contingency tables for the categorical data of clinical success rates. Statistical significance was established using a 2-tailed α level of 0.05 (SYSTAT 13 version 13.1). Greater than 90% power was achieved in both the mITT and ME groups (males and females) based on the 15% noninferiority margin used by the original study investigators (PASS 14 software; NCSS, Kaysville, UT).[10]

Results

A total of 427 patients (224 male and 203 female patients) with cUTI met all inclusion criteria and

Figure 1. Study timeline.

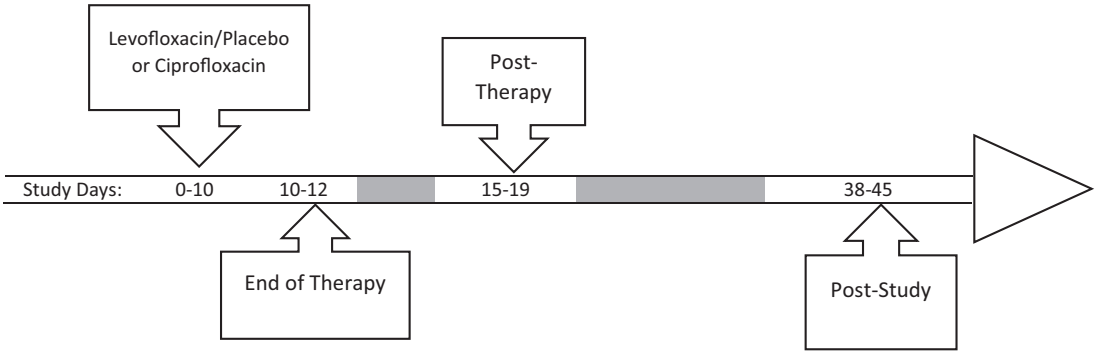
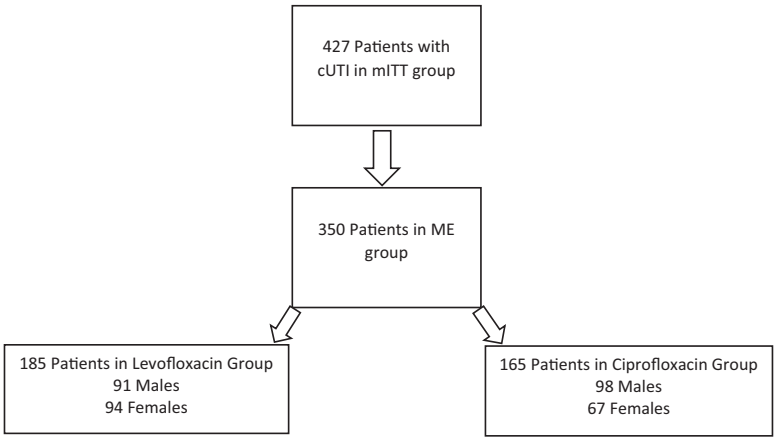


Figure 2. Patient disposition. cUTI, complicated urinary tract infection; mITT, modified intent-to-treat; ME, microbiologically evaluable.



were analyzed in the mITT group. Of those 427 patients, 350 (189 male, 161 female) adhered to the study protocol and were included in the ME group (Figure 2). Baseline demographics of the patients are listed in Table 3; approximately half of the patients in the mITT population were males and the majority of subjects were white, over the age of 60, and infected with *E coli*. Nearly all were treated in an outpatient setting, rather than in a hospital.

Overall, the clinical success rates for males and females with cUTI were similar in both the mITT and ME populations at EOT and PT (Table 4). In the mITT population, males who received levofloxacin had a success rate of 83% at EOT and 76% PT, compared with their female counterparts, who experienced success rates of 81% both EOT and PT (P = .73 and .411, respectively). In the ME population, the clinical success rate for males who received levofloxacin at EOT and PT were 87% and 81% compared with 94% and 86% in females, respectively (P = .141 and .428, respectively). Similarly, there were no statistical differences between males and females who received ciprofloxacin in the mITT and ME populations at both EOT and PT. Furthermore, when comparing the clinical success rates of either a 5-day course of levofloxacin or a 10-day course of ciprofloxacin in the male population alone, no significant differences were found in the mITT or ME population at EOT or PT (Table 5).

Further analyses were performed within the male population to determine clinical success rates for subjects with additional complicating factors (Table 6). Patients who received levofloxacin had a statistically similar rate of clinical success as those who received ciprofloxacin for all additional complicating factors, with the exception of those with a catheter. In this cohort of patients, the clinical success rate with levofloxacin (91.3%) was significantly higher than those who received ciprofloxacin (56.3%; P = .019).

Comparison of the clinical success rates among male patients within the antimicrobial group (ciprofloxacin or levofloxacin), based on additional complicating factors, yielded significantly different results (Table 7). In this analysis, males who received ciprofloxacin were less likely to have clinical success if they had a catheter, neurogenic bladder or urinary retention, and ≥2 complicating factors, compared with patients who received ciprofloxacin without the associated complicating factor (56.3% vs 91.5%, P = .002; 69.2% vs 91.7%, P = .009; and 70.4% vs 92.3%, P = .04, respectively). By contrast, there was no significant difference in clinical success rates among males with these complicating factors who received levofloxacin.

Discussion

The results of this subgroup analysis suggest that male patients with UTIs, with or without additional risk factors for cUTIs, achieved clinical success with a 5-day course of levofloxacin, rather than a traditional, prolonged course (7–14 days) of therapy. Furthermore, male patients in this

Table 3. Baseline Demographics of the Modified Intent-to-Treat Population

	Levofloxacin		Ciprofloxacin	
	Males (n = 105)	Females (n = 118)	Males (n = 119)	Females (n = 85)
Age (years)				
≥60	66 (62.9)	69 (58.5)	84 (70.6)	48 (56.5)
30–59	33 (31.4)	39 (33.1)	32 (26.9)	32 (37.6)
<30	6 (5.7)	10 (8.4)	3 (2.5)	5 (5.9)
Race				
White	78 (74.3)	92 (78)	88 (74)	76 (89.4)
Black	14 (13.3)	11 (9.3)	23 (19.3)	2 (2.4)
Asian	2 (1.9)	0 (0)	0 (0)	2 (2.4)
Hispanic	11 (10.5)	14 (11.9)	7 (5.9)	5 (5.8)
Other	0 (0)	1 (0.8)	1 (0.8)	0 (0)
Treatment setting				
Community	101 (96.2)	117 (99.2)	116 (97.5)	85 (100)
Institutional	4 (3.8)	1 (0.8)	3 (2.5)	0 (0)
Catheter use				
Intermittent/Straight	21 (20)	12 (10.2)	17 (14.3)	8 (9.4)
Chronic indwelling	4 (3.8)	0 (0)	3 (2.5)	2 (2.4)
Infection by most commonly occurring organisms				
Most common: *Escherichia coli*	50 (47.6)	75 (63.6)	68 (57.1)	59 (69.4)
Second most common	*Enterococcus faecalis*: 13 (12.4)	*Klebsiella pneumoniae*: 16 (13.6)	*E. faecalis*: 12 (10)	*K. pneumoniae*: 15 (17.6)
Third most common	*K. pneumoniae*: 10 (9.5)	*Streptococcus agalactiae*, *Proteus mirabilis*, *E. faecalis* (tie): 7 (6)	*K. pneumoniae*: 10 (8.4)	*P. mirabilis*: 3 (3.5)
Infected with >1 pathogen	7 (6.7)	4 (3.4)	7 (5.9)	3 (3.5)

Data are n (%).

Table 4. Comparison of Clinical Success Rates between Male and Female Patients with Complicated Urinary Tract Infection

	Levofloxacin			Ciprofloxacin		
	Males	Females	*P* Value	Males	Females	*P* Value
EOT						
mITT	87/105 (83%)	95/118 (81%)	.730	92/119 (77%)	66/85 (78%)	1.00
ME	79/91 (87%)	88/94 (94%)	.141	84/98 (86%)	59/67 (88%)	.817
Post-Therapy						
mITT	80/105 (76%)	96/118 (81%)	.411	93/119 (78%)	70/85 (82%)	.485
ME	74/91 (81%)	81/94 (86%)	.428	84/98 (86%)	61/67 (91%)	.342

EOT, end of therapy; ME, microbiologically evaluable; mITT, modified intent-to-treat.

Table 5. Clinical Success Rates for Male Patients with Complicated Urinary Tract Infection

	Levofloxacin	Ciprofloxacin	*P* Value
EOT			
mITT	87/105 (83%)	92/119 (77%)	.321
ME	79/91 (87%)	84/98 (86%)	.837
Post-Therapy			
mITT	80/105 (76%)	93/119 (78%)	.752
ME	74/91 (81%)	84/98 (86%)	.438

EOT, end of therapy; ME, microbiologically evaluable; mITT, modified intent-to-treat.

Table 6. Comparison of Clinical Success Rates within Complicating Factor Groups in the Microbiologically Evaluable Male Population at the End of Therapy, Based on Antibiotic Received

	Levofloxacin	Ciprofloxacin	*P* Value
Catheter use	21/23 (91.3%)	9/16 (56.3%)	.019
No catheter	58/68 (85.3%)	75/82 (91.5%)	.138
Neurogenic bladder or urinary retention	23/26 (88.5%)	18/26 (69.2%)	.173
No neurogenic bladder or urinary retention	56/65 (86.2%)	66/72 (91.7%)	.413
Partial obstruction (including BPH)	38/45 (84.4%)	43/48 (89.6%)	.544
No obstruction	41/46 (89.1%)	41/50 (82%)	.393
No additional complicating factors	30/34 (88.2%)	36/39 (92.3%)	.698
≥1 additional complicating factor	49/57 (85.9%)	48/59 (81.4%)	.618
≥2 additional complicating factors	26/30 (86.7%)	19/27 (70.4%)	.195

BPH, benign prostatic hypertrophy.

analysis had clinical success similar to that of their female counterparts in both the 5-day course of levofloxacin and the 10-day course of ciprofloxacin. In addition, the results suggest that male patients with complicating risk factors have a higher rate of clinical success with a 5-day course of levofloxacin than a 10-day course of ciprofloxacin. While it would be unwise to conclude that high-dose, short-course levofloxacin should be used in all male patients with cUTIs, the data presented here support its utility for outpatient therapy.

Even though the results of this analysis are positive and suggest shorter courses of antibiotics can be considered in males with UTIs, there are limitations to this study. One caution when applying these results to the male population is to not deviate from the original inclusion and exclusion criteria, as well as the added exclusion criteria for our analysis—acute pyelonephritis. While the original study did not exclude patients with acute pyelonephritis, there were only 18 males with the diagnosis. As such, to represent a fair comparison of patients, the data from all

Table 7. Comparison of Clinical Success Rates within Antibiotic Groups in the Microbiologically Evaluable Male Population at the End of Therapy, Based on Additional Complicating Factors

Antibiotic	Complicating Factors		*P* Value
	Catheter	No catheter	
Levofloxacin	21/23 (91.3%)	58/68 (85.3%)	.723
Ciprofloxacin	9/16 (56.3%)	75/82 (91.5%)	.002
	Neurogenic bladder or urinary retention	No neurogenic bladder or urinary retention	
Levofloxacin	23/26 (88.5%)	56/65 (86.2%)	1.000
Ciprofloxacin	18/26 (69.2%)	66/72 (91.7%)	.009
	Partial obstruction (including BPH)	No obstruction	
Levofloxacin	38/45 (84.4%)	41/46 (89.1%)	.551
Ciprofloxacin	43/48 (89.6%)	41/50 (82%)	.389
	No additional complicating factors	≥2 Additional complicating factors	
Levofloxacin	30/34 (88.2%)	26/30 (86.7%)	1.000
Ciprofloxacin	36/39 (92.3%)	19/27 (70.4%)	.040

BPH, benign prostatic hypertrophy.

patients with acute pyelonephritis were excluded from this analysis. Because of this, it would be inappropriate to apply these results to males with acute pyelonephritis. In addition, male patients with prostatitis, epididymitis, or perirenal abscesses were excluded from the study and should be treated according to currently recommended treatment algorithms rather than 5 days of levofloxacin. Furthermore, nearly all patients included in the study were outpatients, rather than hospitalized. Therefore it would be difficult to apply these results to hospitalized patients.

The results of this study should be applied only to susceptible microorganisms, in regions where resistance of uropathogens to levofloxacin is relatively low, and in patients with few to no risk factors for *E coli* resistance.[7] As stated previously, the subjects in this study were nearly entirely treated in an outpatient setting where the resistance of *E coli* to the fluoroquinolones was low. Therefore, attempting to infer clinical success of levofloxacin in a environment where *E coli* resistance to fluoroquinolones is known to be high might be futile. Several studies have demonstrated increasing resistance of uropathogens to not only levofloxacin but also other agents typically used to treat these infections.[7–9] Globally, *E coli* resistance to fluoroquinolones is becoming significant, ranging from 2% to 69% for those with uncomplicated, community-acquired UTIs and up to 98% for those cUTIs.[11] Because of this, it becomes important to treat such infections with the agent that has the greatest likelihood of clinical success. While a fluoroquinolone may not be the first option to treat some UTIs, it would be reasonable to treat outpatient males without previous exposure to fluoroquinolones (within the previous 4 weeks) with a 5-day course of levofloxacin 750 mg PO daily. Close follow-up to ensure resolution of symptoms is also advised, especially when the causative organism is unknown.

While the results were not reported in the previous trial, because of the small samples, in our study there were some interesting findings among those patients who clinically failed therapy. In males who received ciprofloxacin, 12 of the 14 clinical failures (85.7%) occurred with *E coli* as the pathogen in the ME group PT. By contrast, only 6 of the 17 clinical failures (35%) in the levofloxacin group were infected with *E coli*. As a result, clinical success rates for male patients initially infected with *E coli* were 86% and 77% for levofloxacin and ciprofloxacin, respectively.

One analysis not performed in our post hoc study was the evaluation of microbiologic eradication rates (elimination or reduction to $<10^4$ colony-forming units/mL of uropathogens at study entry), despite being performed in the original trial. In the male population, urine cultures were not available at EOT for approximately 12% of subjects in the ME group, and therefore evaluation of microbiologic eradication rates was not included as an objective of this study. For male patients in the ME group PT, however, microbiologic eradication rates were found to be 72 of 91 (79.1%) and 84 of 98 (85.7%)

in the levofloxacin and ciprofloxacin groups, respectively.

Finally, the US Food and Drug Administration (FDA) recently advised health care professionals and consumers not to use fluoroquinolone antibiotics for uncomplicated infections because of increased risks of serious adverse events that outweigh the benefits of therapy.[12] Furthermore, the FDA stated that fluoroquinolones should only be used when alternative agents are not available to treat these types of infections. In the original study, the authors reported 192 patients in the levofloxacin group and 185 patients in the ciprofloxacin group had at least one adverse event; the most common were nausea, headache, and diarrhea.[10] The authors went on to state that 17 patients in the levofloxacin group and 15 in the ciprofloxacin group had significant adverse drug events. Unfortunately, they failed to report any episodes of *C difficile* infection, QTc prolongation, or tendon rupture—all of which can occur with these agents. Furthermore, while adverse events associated with fluoroquinolone use can occur after a single dose, the risks increase with prolonged courses.[13] Given this information and the recent advice from the FDA, it is particularly important to give the shortest, most effective duration of fluoroquinolone therapy for the treatment of complicated infections. The results of our analysis suggest that if a fluoroquinolone is used in males with a UTI, short courses may be as effective as longer courses, thereby decreasing their risk of serious adverse events.

While the results of this analysis demonstrated the utility of levofloxacin in males with cUTIs in an environment where resistance was low, an even greater finding was that the clinical success rate of a short course of antibiotics to treat cUTI was similar in male and female patients. Without question, 1 contributing factor leading to increased bacterial resistance is prolonged use of antimicrobial agents; therefore, shorter courses in males with cUTIs could help alleviate some of the resistance problems.[14,15] A larger-scale study comparing short courses of antimicrobials in males and females should be conducted to validate the results of this study. Until then, in outpatient males with cUTIs without acute pyelonephritis or other exclusions defined in this study, we recommend a duration of therapy similar to that used for female patients. Furthermore, if this strategy is used, we recommend follow-up with an appropriate health care practitioner to ensure clinical success.

Conclusion

Males who develop a UTI have historically been given the classification of cUTI, and therefore it has been suggested that they be treated for an extended duration. The results of our analysis suggest shorter courses of levofloxacin are as effective as longer courses of ciprofloxacin in males in the outpatient setting. Furthermore, levofloxacin may be more effective than ciprofloxacin when males have additional complicating factors.

References

1. Gaspari R, Bosker G. Urinary tract infection: risk stratification, clinical evaluation, and evidence-based antibiotic therapy. Primary Care Consensus Reports, January 15, 2003. Atlanta, GA: American Health Consultants; 2003.
2. Hooton TM. Uncomplicated urinary tract infection. N Engl J Med 2012;366:1028–37.
3. Lipskv BA. Urinary tract infections in men. Epidemiology, pathophysiology, diagnosis and treatment. Ann Intern Med 1989;110:138–50.
4. Drekonja DM, Rector TS, Cutting A, Johnson JR. Urinary tract infection in male veterans. JAMA Intern Med 2013;173:62–8.
5. Sanchez GV, Master RN, Karlowsky JA, Bordon JM. In vitro antimicrobial resistance of urinary Escherichia coli isolates among U.S. outpatients from 2000 to 2010. Antimicrob Agents Chemother 2012;56: 2181–3.
6. Meyer E, Gastmeiera P, Dejab M, Schwaba F. Antibiotic consumption and resistance: data from Europe and Germany. Int J Med Microbiol 2013;303: 388–95.
7. Khawcharoenporn T, Vasoo S, Ward E, Singh K. High rates of quinolone resistance among urinary tract infections in the ED. Am J Emerg Med 2012; 30:68–74.
8. Gottesman BS, Carmeli Y, Shitrit P, Chowers M. Impact of quinolone restriction on resistance patterns of Escherichia coli isolated from urine by culture in a community setting. Clin Infect Dis 2009; 49:869–75.
9. Zhanel GG, Hisanaga TL, Laing NM, et al. Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents 2005;26:380–8.

10. 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.
11. Dalhoff A. Global fluoroquinolone resistance epidemiology and implications for clinical use. Interdiscip Perspect Infect Dis 2012;2012:976273.
12. U.S. Food and Drug Administration. FDA drug safety communication. FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. May 12, 2016. Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM500591.pdf. Accessed May 16, 2016.
13. Liu HH. Safety profile of the fluoroquinolones: focus on levofloxacin. Drug Saf 2010;33:353–69.
14. Levy SB. Factors impacting on the problem of antibiotic resistance. J Antimicrob Chemother 2002;49: 25–30.
15. Dellit TH, Owens RC, McGowan JE, et al. Guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159–77.