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Prevalence of and Risk Factors for Levofloxacin-Resistant *E. coli* Isolated from Outpatients with Urinary Tract Infection

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Purpose: Levofloxacin has been widely used because of its broad spectrum and excellent penetration of the prostate. But levofloxacin-resistant *Escherichia coli (E.coli)* has been reported all over the world. We analyzed the annual levofloxacin resistance of *E. coli* and its risk factors.

Materials and Methods: From 2005 to 2009, we retrospectively analyzed patients who had undergone a urine analysis and a urine culture at the Outpatient Section of the Department of Urology of Kwangju Christian Hospital. Among them, we chose 509 patients infected by *E. coli* and evaluated the resistance rate to levofloxacin and its risk factors.

Results: The annual rates of levofloxacin resistance of *E. coli* were 29.49% in 2005, 26.51% in 2006, 40.21% in 2007, 43.20% in 2008, and 31.75% in 2009. A close correlation with the resistance rate was shown in cases that had underlying neurogenic bladder ($p=0.002$, odds ratio [OR]=4.236), a history of ciprofloxacin ($p<0.001$, OR=3.753) and levofloxacin ($p<0.001$, OR=2.996) administration for at least 48 hours in the past year, urolithiasis ($p=0.003$, OR=3.317), and older age ($p<0.001$, OR=1.027).

Conclusions: This study from 2005 to 2009 showed that the levofloxacin resistance rates of *E. coli* were high at over 25%. The risk factors that affected the levofloxacin resistance rates of *E. coli* were underlying neurogenic bladder, ciprofloxacin administration history, urolithiasis, levofloxacin administration history, and older age. Levofloxacin should be prescribed cautiously in patients with these risk factors until the pathogen is identified.

Key Words: *Drug resistance; Fluoroquinolones; Risk factors*

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INTRODUCTION

Cephalosporin and penicillin antibiotics were used to be the primary prescriptions for infections in the past. After the increase in resistant strains against these antibiotics, quinolone-class antibiotics emerged. According to IMS Health statistics, sales of quinolones reached approximately 151.3 billion won in the fourth quarter of 2010 in South Korea [1]. Sales of ciprofloxacin in the fourth quarter of 2010 increased by 75% to about 64.5 billion won over the same period in 2004, whereas sales of levofloxacin increased by 195% to about 62.1 billion won (Fig. 1) [1]. The rapid increase in sales of levofloxacin is attributed to its broader antimicrobial spectrum compared with that of ciprofloxacin. Levofloxacin has been widely used worldwide, while reports of levofloxacin-resistant *Escherichia coli* (*E. coli*) have surfaced. Domestic studies on ciprofloxacin resistance have been reported several times, but there have been few studies on resistance to levofloxacin amid the recent increase in its usage. Therefore, we performed this study to support the choice of antibiotics before the identification of the pathogen in treating urinary tract infection (UTI). We studied outpatients whose urine culture results had been identified with *E. coli*, the most common causative pathogen of UTI, within the past 5 years and analyzed the annual levofloxacin resistance of *E. coli* and

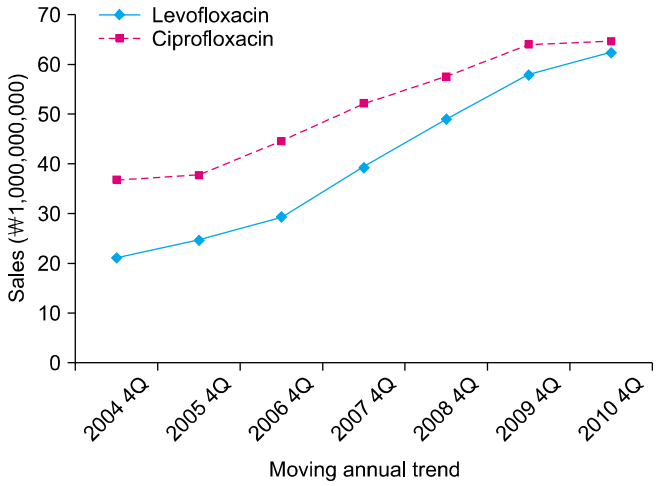

FIG. 1. Variations in sales amounts of ciprofloxacin and levofloxacin in South Korea. 4Q: the fourth quarter.

its risk factors.

MATERIALS AND METHODS

1. Inclusion and exclusion criteria

E. coli was isolated from 701 of the 8,063 patients who had visited the Outpatient Section of the Department of Urology of Kwangju Christian Hospital and had undergone a urine culture test from January 2005 to December 2009. Patients who had repeatedly undergone urine culture tests in the same year were excluded. *E. coli* was determined as the causative pathogen if the amount of the isolated *E. coli* colony was over 10^5 counts per ml of voided urine or was over 10^3 counts per ml of catheterized urine. The subjects of this study were 509 patients who met the aforementioned inclusion and exclusion criteria. The patients' mean age was 55.1±17.3 years. The ratio of males to females was 1.0 to 5.8.

2. Methods of urine collection and urine test

Urine sample collection was performed by the following methods. For patients with a urinary catheter, urine was collected by using a sterilized syringe after the tip of the catheter was washed with a boric sponge. For patients without a urinary catheter and who could self-urinate, their midstream urine was collected after the opening of their urethra and its surroundings were washed with a boric sponge. For pediatric patients who could not control their urination, urine was collected after the opening of their urethra and its surroundings were washed with a boric sponge and a feeding tube was inserted through the urethra to the bladder.

The collected urine samples were gram-stained for microscopic observation, and 0.001 ml of each sample was inoculated on a serum agar medium and a MacConkey agar medium for culture at 37°C for 24 to 48 hours. Pathogen identification was conducted by using MicroScan® of Siemens, and the antibiotic sensitivities were determined by using the minimum inhibitory concentration.

3. Various risk factors

Retrospective analyses were performed for the sex and age of the patients, their antibiotic sensitivity against *E. coli*, and various clinical factors. The patients were categorized according to age: under 10, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and over 79 years. The clinical factors included underlying diseases, medical histories, and status of the urinary catheterization of the patients at the time of their hospital visit. The underlying diseases were diabetes mellitus, hypertension, urinary incontinence, benign prostatic hyperplasia, urolithiasis, neurogenic bladder, digestive diseases, cerebrovascular diseases, and arthritis. The checked medical histories involved levofloxacin, ciprofloxacin, and antibiotics except for quinolone administration for at least 2 days in the past 12 months, regardless of the disease, hospitalization, experience of urological surgery and surgery besides urological surgery, and UTI. Also, the insertion of a Foley catheter, the insertion of a percutaneous nephrostomy (PCN) tube, and the use of clean intermittent catheterization (CIC) were checked at the time of the patient's hospital visit.

4. Statistical analysis

To examine the annual variations in resistance of *E. coli* to levofloxacin in the outpatients, the mean values in the levofloxacin-resistant cases were compared among those who had been identified as having *E. coli* in their urine culture test each year from 2005 to 2009 via ANOVA. In addition, to explore the correlation of the levofloxacin resistance of *E. coli* with various risk factors, the risk factors and the levofloxacin-resistant or levofloxacin-susceptible pathogens were cross-tabulated against *E. coli* (the chi-square method). Logistic regression analysis was used to determine whether there was a significant correlation between the factors that showed differences in the cross-tabulation with the levofloxacin resistance of *E. coli*. SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used as the statistical analysis program, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Levofloxacin-resistant *E. coli* was identified in the antibiotic susceptibility test in 178 of the 509 patients (34.97%). *E. coli* was identified in the urine culture test in 75 male patients from among the 509 patients (14.70%); of these 75 males, levofloxacin-resistant *E. coli* was identified in 32 males (42.70%). *E. coli* was identified in the urine culture test in 434 female patients from among the 509 patients (85.30%); of these 434 females, levofloxacin-resistant *E. coli* was identified in 146 females (33.60%). The annual rates of resistance of *E. coli* to levofloxacin were 23 among 78 patients (29.49%) in 2005, 22 among 83 patients (26.51%) in 2006, 39 among 97 patients (40.21%) in 2007,

TABLE 1. Annual levofloxacin resistance rate of *E. coli*

Years	2005	2006	2007	2008	2009
No. of total patients	78	83	97	125	126
No. of patients with levofloxacin-resistant *E. coli*	23	22	39	54	40
Resistance rate (%)	29.49	26.51	40.21	43.20	31.75

TABLE 2. Levofloxacin resistance rate of *E. coli* according to age

Age (yr)	No. of patients	Resistance rate (%)
0-10	10	0.00
10-19	5	20.00
20-29	27	25.93
30-39	62	14.52
40-49	63	28.57
50-59	113	34.51
60-69	115	42.61
70-79	90	43.33
80-	24	66.67
Total	509	34.97

54 among 125 patients (43.20%) in 2008, and 40 among 126 patients (31.75%) in 2009. These figures did not increase with statistical significance given the set 0.05 significance level (p=0.058), but all the resistance rates were over 25%, which was high (Table 1). In the older patients, the resistance rates were high (Table 2). The levofloxacin resistance rates of *E. coli* according to other various risk factors were calculated (Table 3). Statistically significant differences were shown in the following via cross-tabulation: older age; cases with levofloxacin and ciprofloxacin administration history for at least 48 hours in the past year, and with a history of hospitalization; maintenance of a Foley catheter, PCN tube, cystostomy tube, or CIC at the time of the hospital visit; and underlying diseases such as diabetes mellitus, hypertension, urolithiasis, neurogenic bladder, and cerebrovascular diseases. Via logistic regression analysis, a close correlation with levofloxacin-resistant *E. coli* was shown in the cases that had underlying neurogenic bladder (p=0.002, odds ratio [OR]=4.236), a history of ciprofloxacin ($p<0.001$, OR=3.753) and levofloxacin ($p<0.001$, OR=2.996) administration for at least 48 hours in the past year, urolithiasis (p=0.003, OR=3.317), and older age ($p<0.001$, OR=1.027) (Table 4). In the cases of underlying neurogenic bladder, the odds ratio was 4.236, which showed the highest statistical correlation with levofloxacin-resistant *E. coli*.

The reasons for the high rates of levofloxacin-resistant *E. coli* in 2007 and 2008 were analyzed. A close correlation with the occurrence of levofloxacin-resistant *E. coli* was anticipated in the analysis of the patients with neurogenic bladder and ciprofloxacin and levofloxacin administration history. The hospital visit rates of the patients with neurogenic bladder from 2005 to 2009 were 2.56%, 8.43%, 9.28%, 9.60%, and 7.14%, respectively, and were especially high in 2007 and 2008. In the patients who had taken levofloxacin, the hospital visit rates were 11.54%, 15.66%, 20.62%, 21.60%, and 19.84% from 2005 to 2009, respectively. In the patients who had taken ciprofloxacin, the hospital visit rates were 7.69%, 7.23%, 16.49%, 19.20%, and 13.49% from 2005 to 2009, respectively, with high rates seen in the patients with risk factors in 2007 and 2008.

TABLE 3. Levofloxacin resistance rate of *E. coli* according to various risk factors

Various risk factors	Resistance rate (%)	
	Risk group	No-risk group
Medical history		
Levofloxacin administration	65.96	27.95
Ciprofloxacin administration	68.12	29.77
Other antibiotics administration	40.65	32.49
Hospitalization	45.71	32.18
Urological surgery	42.86	34.39
Other surgery	37.89	33.62
Urinary tract infection	42.11	33.33
Underlying disease		
Diabetes mellitus	48.44	33.03
Hypertension	43.90	32.12
Urinary incontinence	46.30	33.63
Benign prostatic hyperplasia	48.78	33.76
Urolithiasis	65.79	32.48
Neurogenic bladder	79.49	31.28
Digestive disease	33.33	35.34
Cerebrovascular disease	60.87	32.40
Arthritis	45.83	34.43
Status of urinary catheterization		
Catheter	84.21	33.06
CIC	81.82	33.94

Catheter: state of Foley catheterization, percutaneous nephrostomy (PCN), or cystostomy, CIC: clean intermittent catheterization

TABLE 4. Logistic regression analysis of risk factors for levofloxacin resistance of *E. coli*

Variables	OR (95% CI)	p-value
Aging	1.027 (1.012-1.042)	<0.001
Levofloxacin administration history	2.996 (1.704-5.266)	<0.001
Ciprofloxacin administration history	3.753 (1.991-7.075)	<0.001
Admission history	0.809 (0.463-1.412)	0.456
Catheter	2.715 (0.658-11.206)	0.167
CIC	1.205 (0.208-6.977)	0.835
Diabetes mellitus	1.216 (0.637-2.319)	0.553
Hypertension	0.920 (0.538-1.572)	0.759
Urolithiasis	3.317 (1.520-7.238)	0.003
Neurogenic bladder	4.236 (1.667-10.767)	0.002
Cerebrovascular diseases	1.665 (0.780-3.555)	0.187

Catheter: state of Foley catheterization, percutaneous nephrostomy (PCN), or cystostomy, CIC: clean intermittent catheterization

TABLE 5. Variations in resistance rates of *E. coli* to antibiotics

	Resistance rate (%), Years				
	2005	2006	2007	2008	2009
Ampicillin	66.67	62.65	74.23	71.20	65.08
Ampicillin/Sulbactam	62.82	61.45	70.83	65.60	62.70
Cefazolin	23.08	22.89	37.50	33.60	19.05
Cefuroxime	14.10	16.87	27.08	25.60	14.29
Cefotetan	3.85	8.43	12.50	8.00	4.76
Ceftriaxone	7.69	4.82	18.56	16.00	9.52
Ceftazidime	3.85	3.61	15.63	16.80	9.52
Cefotaxime	7.69	3.61	17.53	16.80	9.52
Cefepime	7.69	6.02	13.54	16.00	7.94
Trimethoprime/Sulfamethoxazole	41.03	30.12	38.54	43.20	31.75
Ciprofloxacin	28.21	22.89	42.27	44.80	34.13
Levofloxacin	29.49	26.51	40.21	43.20	31.75
Moxifloxacin	29.49	37.35	39.58	40.00	32.79
Gentamicin	26.92	30.12	32.99	27.20	26.98
Amikacin	8.97	6.02	6.25	4.80	3.17
Tobramycin	29.49	30.12	37.50	25.60	26.98
Aztreonam	11.54	14.46	21.65	22.40	10.32
Imipenem	1.28	4.82	3.09	4.00	1.59
Meropenem	28.21	14.46	3.13	2.40	1.59
Piperacillin/Tazobactam	11.54	22.89	13.54	16.80	7.94
Ticarcillin/K clavulanate	21.79	12.05	28.13	21.60	16.67

The resistance rates of *E. coli* to antibiotics other than levofloxacin were also analyzed (Table 5). The annual resistance rates to ciprofloxacin from 2005 to 2009 were 28.2%, 22.9%, 42.3%, 44.8%, and 34.1%, respectively; for moxifloxacin, they were 29.5%, 37.4%, 39.6%, 40.0%, and 32.8%, respectively. They were all above 20%. Ampicillin and ampicillin/sulbactam had the highest resistance rate of over 60%. Trimethoprim/sulfamethoxazole (TMP-SMX) showed resistance rates of 41.0%, 30.1%, 38.5%, 43.2%, and 31.8%, respectively; cefazolin, a first-generation cephalosporin, had a relatively higher resistance rate than the third-generation cephalosporins. Gentamicin showed resistance rates of 26.9%, 30.1%, 33.0%, 27.2%, and 27.0%, respectively; tobramycin, 29.5%, 30.1%, 37.5%, 25.6%, and 27.0%, respectively; and amikacin, 9.0%, 6.0%, 6.3%, 4.8%, and 3.2%, respectively. Among the cabarpenem-class antibiotics, aztreonam had resistance rates of 11.5%, 14.5%, 21.7%, 22.4%, and 10.3%, respectively; imipenem, 1.3%, 4.8%, 3.1%, 4.0%, and 1.6%, respectively; and meropenem, 28.2%, 14.5%, 3.1%, 2.4%, and 1.6%, respectively. The antibiotics with *E. coli* resistance rates that were lower than 20% from 2007 to 2009 were cefotetan, ceftriaxone, ceftazidime, cefotaxime, cefepime, amikacin, piperacillin/t azobactam, imipenem, and meropenem (Table 5).

DISCUSSION

E. coli, the most prevalent pathogen of UTI, had been susceptible to ampicillin and amoxicillin, but the widespread use of these β-lactam antibiotics is associated with the emergence of resistant strains. Resistance to these agents is usually mediated by the production of β-lactamases, which inactivate these antibiotics [2]. According to a domestic report, ampicillin resistance rates of *E. coli* were 70% in 2005 and 71% in 2006 among outpatients [3].

TMP-SMX, which has been used to treat UTI, competitively inhibits folate synthetic enzymes. TMP-SMX-resistant *E. coli* bypasses the inhibition by generating insensitive targets [4]. The resistance rate of TMP-SMX had already reached a serious level in the United States, and, thus, alternatives are essential for at least certain areas. Lee et al reported in 2003 that the domestic resistance rate to TMP-SMX was 38.7%, which means that TMP-SMX can no longer be used for first-line treatment of uncomplicated UTI [5].

Since empirical first-line therapy with TMP-SMX became more difficult due to the increase in the resistant pathogens of UTI, the Infectious Disease Society of America (IDSA) suggested guidelines [6]. According to the IDSA guidelines, fluoroquinolone should be the empirical first-line choice for the treatment of uncomplicated UTI if the resistance rate of *E. coli* to TMP-SMX exceeds 20% in a territory. Thus, fluoroquinolones are suggested as alternatives for the empirical first-line treatment of uncomplicated UTI, and they are commonly prescribed worldwide. Despite the disadvantages of fluoroquinolone, such as their high price and contraindication in pediatric patients, they have been used for first-line treatment of UTI because gram-negative pathogens are very susceptible to them and fewer pathogens are resistant to them compared with other drugs. Fluoroquinolone, which inhibits DNA gyrase (topoisomerase II) to interrupt the DNA

synthesis of bacteria, has been known to be associated with very rare resistance cases that developed by natural mutation in vitro. The issue has surfaced, however, because of the recent increase in *E. coli* resistance to ciprofloxacin [7]. The decrease in fluoroquinolone susceptibility is known to have developed via the mutation of parC and gyrA, which code topoisomerase enzymes, which affects the cell efflux mechanism to primarily lower the intracellular drug accumulation [8].

According to statistical data from IMS Health, a specialized consulting firm for the health care and pharmaceutical sectors, domestic sales of quinolones reached 151.352 billion won in the fourth quarter of 2010, with ciprofloxacin and levofloxacin accounting for approximately 84% at 64.451 billion won and 62.098 billion won, respectively [1]. Among fluoroquinolones, ciprofloxacin has been prescribed most frequently so far; but the ciprofloxacin resistance rate of *E. coli* has been reported as 20% in Brazil, 20% in Spain, and 26% in Europe [9-11]. In South Korea, ciprofloxacin has been widely prescribed for the treatment of UTI, and the resistance rate due to its increased use and abuse has increased. Ko et al reported that the susceptibility of Gram-negative bacteria to ciprofloxacin was 87.8% in 1994 and 78.8% in 1998 [12]. Song and Kim reported that *E. coli* had been identified in 46.4% of 584 hospitalized patients and 305 outpatients with UTI, whereas the ciprofloxacin resistance rate was 19.8% and 18.8%, respectively, in 2003 [13]. Ryu et al also reported that the ciprofloxacin resistance rate of *E. coli* had increased from 46.8% to 52.5% among hospitalized patients and from 27.2% to 34.9% among outpatients in 2000 and 2005, respectively [14]. The ciprofloxacin resistance rate has already reached a serious level.

Levofloxacin has been reported to have excellent antimicrobial activity and to be effective for both Gram-positive bacteria and anaerobes, compared to ciprofloxacin [15,16]. Thus, it has recently been used to treat *H. pylori* infection and pneumonia and to prevent infections in hepatobiliary surgeries [17-19]. Especially in urology, with the emerging importance of Gram-positive bacteria such as *Enterococcus faecalis* and *Staphylococcus epidermidis*, as well as of Gram-negative enterobacteria including *E. coli*, which is the causative pathogen of bacterial prostatitis, levofloxacin has become the standard therapy in the treatment of chronic bacterial prostatitis [20,21]. In the United States, between 1998 and 2005, however, as prescriptions of levofloxacin increased from 3.1 to 12.7 prescriptions per 1000 outpatient visits, the rate of levofloxacin-resistant *E. coli* increased from 1% to 9%. The switch to levofloxacin for the initial management of outpatient UTI was followed by the rapid emergence of levofloxacin-resistant *E. coli* [22]. According to a Japanese report in 2008, four sepsis cases caused by levofloxacin-resistant *E. coli* had been reported among 665 patients upon ultrasound-guided transrectal prostate biopsy from July 2002 to December 2006. The authors suggested that fluoroquinolone-resistant *E.coli* infection after ultrasound-guided transrectal prostate biopsy might be increasing due to the widespread use of fluoroquinolones in both humans and food animals [23].

In South Korea, the levofloxacin resistance rate may be increasing as the use of levofloxacin has increased. Excluding 2007 and 2008, in which the percentage of patients with significant risk factors in this study was high, the levofloxacin resistance rate of *E. coli* increased through the years. The outcome of this study does not exactly represent the levofloxacin resistance rate of *E. coli* in South Korea, however, because this study was conducted at a single hospital in only one community from 2005 to 2009. To confirm the levofloxacin resistance rate of *E. coli* in South Korea, combined data from multiple community health center sites are required.

CONCLUSIONS

Although ciprofloxacin resistance of *E. coli* has been reported, reports on the levofloxacin resistance rate for over 5 years and its correlation to risk factors are rare. Thus, we studied the resistance of *E. coli* to levofloxacin, the chemical structure of which is unlike that of ciprofloxacin, even though they belong to the same class of fluoroquinolones. In addition, various factors related to the levofloxacin resistance rate of *E. coli* were investigated by using statistical analysis. The levofloxacin resistance rates of *E. coli* were high at over 25% from 2005 to 2009. The results of the regression analysis showed that the factors that affected the resistance rate were an underlying neurogenic bladder, ciprofloxacin administration history, urolithiasis, levofloxacin administration history, and older age. For patients who have risk factors for levofloxacin resistance, as analyzed in this study, levofloxacin should be cautiously prescribed until the pathogen is identified. In such cases, prescription of other antibiotics that have lower resistance rates should be considered.

Conflicts of Interest

The authors have nothing to disclose.

REFERENCES

1. Health IMS. Midas database. Korea: IMS Health; 2010 4Q.
2. Iravani A, Richard GA. Treatment of urinary tract infections with a combination of amoxicillin and clavulanic acid. Antimicrob Agents Chemother 1982;22:672-7.
3. Lee H, Kim CK, Lee J, Lee SH, Ahn JY, Hong SG, et al. Antimicrobial resistance of clinically important bacteria isolated from 12 hospitals in Korea in 2005 and 2006. Korean J Clin Microbiol 2007;10:59-69.
4. Tenover FC. Mechanisms of antimicrobial resistance in bacteria. Am J Infect Control 2006;34(5 Suppl 1):S3-10.
5. Lee SJ, Cho YH, Kim BW, Lee JG, Jung SI, Lee SD, et al. A multicenter Study of antimicrobial susceptibility of uropathogens causing acute uncomplicated cystitis in woman. Korean J Urol 2003;44:697-701.
6. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of un-

complicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis 1999;29:745-58.
7. Friedland I, Stinson L, Ikaiddi M, Harm S, Woods GL. Resistance in Enterobacteriaceae: results of a multicenter surveillance study, 1995-2000. Infect Control Hosp Epidemiol 2003;24: 607-12.
8. Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. Drugs 2003;63:2769-802.
9. Moreira ED Jr, DE Siqueira IC, Alcantara AP, Guereiro DE Moura CG, DE Carvalho WA, Riley L. Antimicrobial resistance of Escherichia coli strains causing community-acquired urinary tract infections among insured and uninsured populations in a large urban center. J Chemother 2006;18:255-60.
10. Zervos MJ, Hershberger E, Nicolau DP, Ritchie DJ, Blackner LK, Coyle EA, et al. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991-2000. Clin Infect Dis 2003;37:1643-8.
11. Mutnick AH, Rhomberg PR, Sader HS, Jones RN. Antimicrobial usage and resistance trend relationships from the MYSTIC Programme in North America (1999-2001). J Antimicrob Chemother 2004;53:290-6.
12. Ko HS, Choi DY, Han YT. A study of the changes of antibiotic sensitivity to the causative organisms of urinary tract infection for recent 5 years. Korean J Urol 1999;40:809-16.
13. Song HJ, Kim SJ. A study of antimicrobial sensitivity to the causative organism of urinary tract infection. Korean J Urol 2005; 46:68-73.
14. Ryu KH, Kim MK, Jeong YB. A recent study on the antimicrobial sensitivity of the organisms that cause urinary tract infection. Korean J Urol 2007;48:638-45.
15. Ernst ME, Ernst EJ, Klepser ME. Levofloxacin and trovafloxacin: the next generation of fluoroquinolones? Am J Health Syst Pharm 1997;54:2569-84.
16. Davis R, Bryson HM. Levofloxacin. A review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. Drugs 1994;47:677-700.
17. Li Y, Huang X, Yao L, Shi R, Zhang G. Advantages of moxifloxacin and levofloxacin-based triple therapy for second-line treatments of persistent Helicobacter pylori infection: a meta analysis. Wien Klin Wochenschr 2010;122:413-22.
18. Wispelwey B, Schafer KR. Fluoroquinolones in the management of community-acquired pneumonia in primary care. Expert Rev Anti Infect Ther 2010;8:1259-71.
19. Weinrich M, Scheingraber S, Stremovskaia T, Schilling MK, Kees F, Pistorius GA. Liver tissue concentrations of levofloxacin after single intravenous administration of 500 mg for antibiotic prophylaxis in liver surgery. Int J Antimicrob Agents 2006;28:221-5.
20. Goto T, Makinose S, Ohi Y, Yamauchi D, Kayajima T, Nagayama K, et al. Diffusion of piperacillin, cefotiam, minocycline, amikacin and ofloxacin into the prostate. Int J Urol 1998;5:243-6.
21. Nickel JC, Downey J, Clark J, Casey RW, Pommerville PJ, Barkin J, et al. Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multicenter trial. Urology 2003;62:614-7.
22. Johnson L, Sabel A, Burman WJ, Everhart RM, Rome M, MacKenzie TD, et al. Emergence of fluoroquinolone resistance in outpatient urinary Escherichia coli isolates. Am J Med 2008; 121:876-84.
23. Miura T, Tanaka K, Shigemura K, Nakano Y, Takenaka A, Fujisawa M. Levofloxacin resistant Escherichia coli sepsis following an ultrasound-guided transrectal prostate biopsy: report of four cases and review of the literature. Int J Urol 2008;15:457-9.