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ORIGINAL ARTICLE

Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant *Escherichia coli*

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Background/purpose: The relationship between fluoroquinolone resistance in *Escherichia coli* isolates causing nosocomial infection and hospital antibiotic consumption were investigated. Restriction of levofloxacin use was implemented to control the incidence of fluoroquinolone-resistant *E coli* in the hospital.
Methods: The study was conducted from January 2004 to December 2010. Antimicrobial agent consumption was obtained from the pharmacy computer system and presented as the defined daily doses per 1000 patient-days every 6 months. The incidence of fluoroquinolone-resistant *E coli* isolates causing nosocomial infections was obtained from the Department of Infection Control every 6 months. An antimicrobial stewardship program, restricting levofloxacain use, was implemented in July 2007.
Results: The incidence of fluoroquinolone-resistant *E coli* causing nosocomial infections was significantly correlated with fluoroquinolone usage ($p = 0.005$), but not with the use of third- or fourth-generation cephalosporins, piperacillin-tazobactam, or carbapenems. Parenteral ($p = 0.002$), oral ($p = 0.018$), and total levofloxacin ($p = 0.001$) use were significantly

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correlated with the extent of fluoroquinolone resistance. With a reduction of levofloxacin use, a decrease of the incidence of fluoroquinolone resistance in *E coli* isolates was observed.
Conclusion: There is a significant correlation between levofloxacin use and the incidence of nosocomial fluoroquinolone-resistant *E coli* isolates. The incidence of fluoroquinolone-resistant *E coli* could be reduced by limiting levofloxacin consumption.

Introduction

Escherichia coli is a common infection pathogen associated with both community acquired and nosocomial infections. Antibiotic resistance among *E coli* isolates continues to increase, limiting the choices of antibiotics available for treating urinary tract infections.[1] A high ratio, >20%, of fluoroquinolone resistance among *E coli* uropathogens has been reported in several countries.[2] The frequency of extended-spectrum-beta-lactamase (ESBL)-producing *E coli* bacteremia has increased worldwide; thus the use of carbapenems has increased.[3] The emergence of carbapenemases, *Klebsiella pneumoniae* carbapenemases (KPC) and New Delhi metallo-beta-lactamase-1 (NDM-1), has also been reported. The NDM-1-producing gene was identified in *Enterobacteriaceae*, mainly in *E coli* and *K pneumoniae*.[4] NDM-1-producing bacteria exhibited a high resistance rate to other classes of antimicrobial agents, such as fluoroquinolones or aminoglycosides.[5]

Fluoroquinolones were introduced as an antibiotic group in the 1980s.[6] Because of their broad antimicrobial spectrum, excellent oral and parenteral bioavailability, and low toxicity, fluoroquinolones have been widely prescribed to patients with bacterial infections.[7] Fluoroquinolone use in hospitals is reportedly associated with the emergence of resistance in a variety of bacteria, including *Staphylococcus aureus, Pseudomonas aeruginosa*, and *E coli*.[8] Antibiotic use is considered to be the main factor contributing to the emergence of resistance.[6] In this study, we investigated whether the incidence of nosocomial fluoroquinolone-resistant *E coli* can be reduced by controlling fluoroquinolone use in the hospital.

Methods

Hospital setting

Taipei Medical University Hospital (TMUH) is a private, tertiary care, university-affiliated, teaching hospital in Taipei, Taiwan. Medical, surgical, neonatal, and pediatric intensive care units and an emergency room are available at this hospital. The number of beds available was 350 in 2004, 560 in 2008, and 702 in 2010. The study period was from January 1, 2004 to December 31, 2010.

Bacterial isolates and susceptibility testing

The broth microdilution method (Phoenix; Becton Dickinson, Sparks, MD, USA) was used to determine the antimicrobial susceptibility of *E coli* isolates. Antimicrobial susceptibility tests were performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[9] Moxifloxacin susceptibility data were not available during the study period. Only the first *E coli* isolate from each patient was included. Fluoroquinolone-resistant *E coli* was defined as an *E coli* isolate exhibiting either intermediate resistance or resistance to either ciprofloxacin or levofloxacin. According to the CLSI criteria,[9] susceptibility breakpoints for ciprofloxacin and levofloxacin for *E coli* used in this study were ≤1 mg/L and ≤2 mg/L, respectively. Susceptibility data for *E coli* isolates causing nosocomial infections were collected from the Infection Control Department; these data were obtained every 6 months.

Antibiotic consumption

Fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin), third-generation cephalosporins (ceftriaxone, cefotaxime, flomoxef, ceftazidime, or cefoperazone), fourth-generation cephalosporins (cefepime or cefpirome), piperacillin-tazobactam, and carbapenems (ertapenem, imipenem, or meropenem) can be prescribed to treat nosocomial *E coli* infections at TMUH. Parenteral ciprofloxacin, oral ciprofloxacin, and oral levofloxacin were available throughout the study period. Parenteral levofloxacin was available after January 2005, and parenteral moxifloxacin between January 2004 and June 2005. Oral and parenteral moxifloxacin were listed in pharmacy formulation from January 2007. In patients with normal renal function, parenteral ciprofloxacin dose was 400 mg every 12 hours, whereas the oral dose was 500 mg every 12 hours. Before 2007, the suggested levofloxacain dose was 500 mg once daily parenterally and orally. After 2007, the suggested levofloxacin dose was 750 mg once daily parenterally and orally. The suggested moxifloxacin dose was 400 mg once daily parenterally and orally. Antibiotic utilization was expressed as the defined daily doses per 1000 patient-days (DDD/1000PD) every 6 months.

The Department of Infection Control at TMUH led the antimicrobial stewardship program, which has restricted the use of levofloxacin since July 2007. Thus, the period from January 2004 to June 2007 was the preintervention period, and July 2007 to December 2010 was the post-intervention period.

Statistical analysis

Least-squares linear regression was used to examine the univariate relationship between antibiotic use and the incidence of fluoroquinolone-resistant *E coli* isolates

causing nosocomial infections. Correlation coefficients (r or r^2) were determined. We used independent t tests to determine significant differences between the pre- and postintervention periods A p-value of <0.05 was considered statistically significant.

Results

During the study period, 647 *E coli* isolates causing nosocomial infections were collected, and 222 isolates were fluoroquinolone resistant (34.31%). The relationship between the incidence of fluoroquinolone-resistant *E coli* isolates and antibiotic prescriptions for nosocomial infections is shown in Table 1.

Least-squares linear regression analyses showed no significant correlation between the incidence of fluoroquinolone-resistant *E coli* and total consumption of third-generation cephalosporins, fourth-generation cephalosporins, piperacillin- tazobactam, or carbapenems. Only total fluoroquinolone consumption was significantly correlated with the incidence of fluoroquinolone-resistant *E coli* ($p = 0.005$). We then analyzed clinical usage of individual fluoroquinolone, and the results are shown in Fig. 1 and Table 2. Parenteral levofloxacin ($p = 0.002$), oral levofloxacin ($p = 0.018$), and total levofloxacin usage ($p = 0.001$) are significantly correlated with the incidence of fluoroquinolone-resistant *E coli* (Table 2). However, parenteral ciprofloxacin, oral ciprofloxacin, and total ciprofloxacin usage are, although not significantly, correlated with the incidence of fluoroquinolone-resistant *E coli* ($p = 0.30$, 0.63, 0.21, respectively; Fig. 1). Parenteral moxifloxacin, oral moxifloxacin, and total moxifloxacin usage are negatively correlated with the incidence of fluoroquinolone-resistant *E coli*, but this relationship was not statistically significant ($p = 0.38$, 0.42, 0.08, respectively; Fig. 1).

Under the antimicrobial stewardship program, levofloxacin prescription was restricted in the second half of 2007. Following this program, the use of all fluoroquinolones, except oral ciprofloxacin, was significantly reduced, as shown in Table 3. Total levofloxacin use decreased by 28.47% between the pre- and postintervention periods (mean ± standard deviation 14.12 ± 5.37 DDD/1000PD vs. 10.10 ± 5.72 DDD/1000PD, $p = 0.006$). This change was accompanied by a significant reduction in the incidence of fluoroquinolone-resistant *E coli*, which was reduced from 0.255 to 0.201 isolates recovered per 1000 patient-days ($p = 0.040$).

Discussion

Before the early 1990s, resistance to fluoroquinolone was rarely mentioned in clinical isolates of *E coli*,[10] and emergence of fluoroquinolone-resistant *E coli* has been reported subsequently. Livermore et al observed an increasing prevalence of fluoroquinolone-resistant *E coli* in blood cultures (0.8% in 1990 and 3.8% in 1999).[11] Shigemura et al reported that the rate of fluoroquinolone-resistant *E coli* increased from 3.5% in 2000 to 30.8% in 2007.[12] Fluoroquinolone use appears to be associated with increasing numbers of fluoroquinolone-resistant *Enterobacteriaceae* isolates.[7] Lee et al identified that fluoroquinolone resistance in *P*

Table 1 Correlation between antibiotic use and the incidence of fluoroquinolone-resistant *Escherichia coli* isolates that cause nosocomial infections

	2004		2005		2006		2007		2008		2009		2010		p
	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	
Incidence of fluoroquinolone-resistant *E coli* (isolates recovered per 1000 patient-days)	0.18	0.21	0.30	0.26	0.27	0.26	0.31	0.22	0.22	0.24	0.17	0.24	0.15	0.16	
Antibiotics use (DDD/1000PD)															
Total fluoroquinolone	36.41	36.08	50.64	38.29	41.73	44.49	41.45	27.46	32.40	37.60	35.92	35.22	33.93	28.97	0.005*
Piperacillin-tazobactam	10.73	20.66	18.92	21.12	22.12	21.37	21.41	16.67	21.58	22.26	17.41	18.98	20.06	19.04	0.125
Total carbapenem	9.36	9.85	12.99	11.80	8.96	13.01	18.95	19.79	19.16	24.40	21.78	16.95	18.58	14.69	0.691
Total fourth-generation cephalosporins	3.38	2.03	3.84	4.61	6.25	3.41	5.55	8.03	7.67	8.20	8.61	4.92	6.23	12.79	0.141
Total third-generation cephalosporins	25.30	25.60	26.90	28.50	22.30	13.53	21.82	20.93	25.82	20.55	24.94	21.28	25.15	23.94	0.449

* statistically significant.
DDD/1000PD = defined daily dose/1000 patient-days.

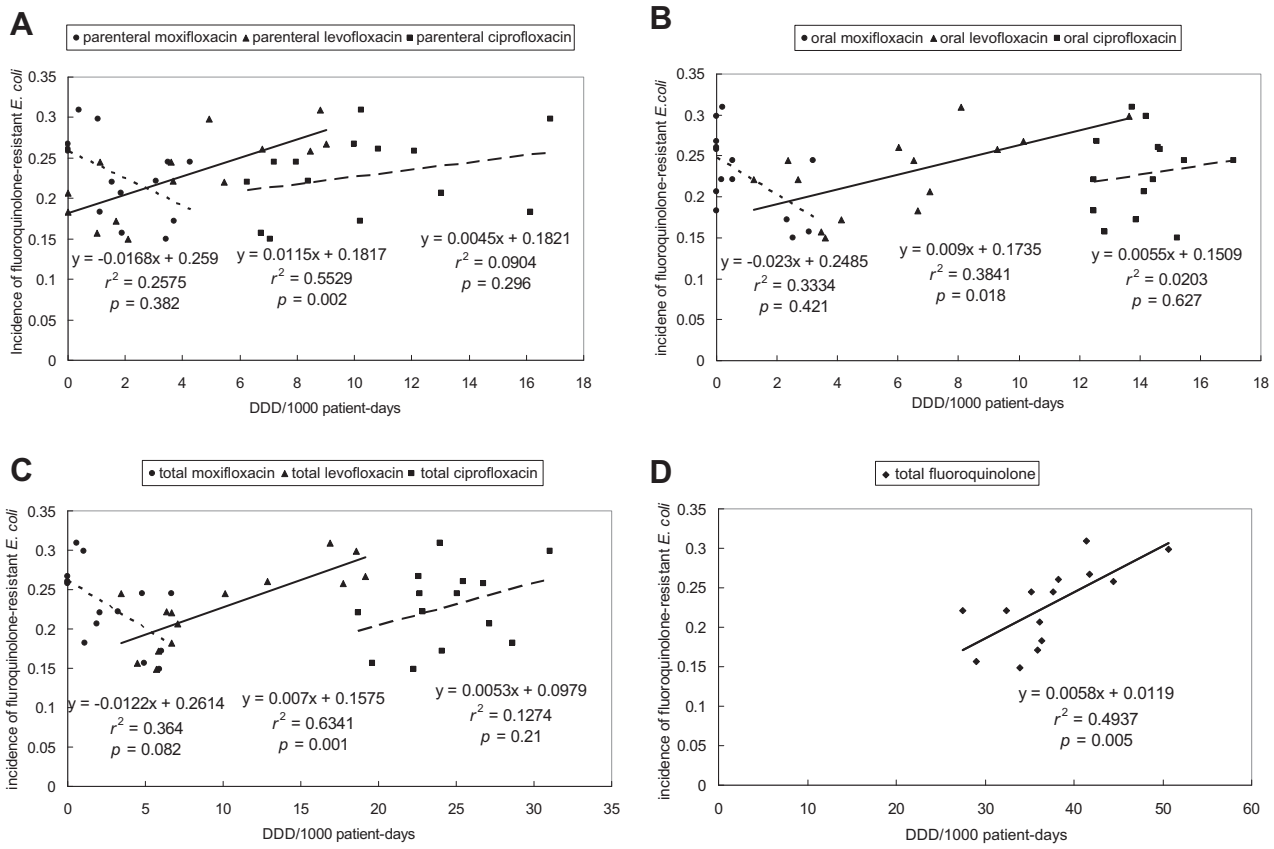

Figure 1. Linear regression analysis of fluoroquinolone use (defined daily dose [DDD]/1000 patient-days), and the incidence of fluoroquinolone-resistant *E coli* that cause nosocomial infection. (a) Parenteral moxifloxacin, parenteral levofloxacin, and parenteral ciprofloxacin; (b) oral moxifloxacin, oral levofloxacin, and oral ciprofloxacin; (c) total moxifloxacin, total levofloxacin, and total ciprofloxacin; (d) total fluoroquinolone.

aeruginosa isolates causing nosocomial infection was correlated with levofloxacin use, but not with ciprofloxacin use.[13] Previous studies have shown that potential risk factors for levofloxacin-resistant *E coli* infections included previous levofloxacin use and recent hospitalization.[1,14,15] However, it is not clear whether controlling antibiotic use could reduce the incidence of fluoroquinolone-resistant *E coli*.

An antimicrobial stewardship program was introduced in the second half of 2007 to control levofloxacin use. Through this program, fluoroquinolone resistance in *P aeruginosa* was reduced in our hospital.[13] Levofloxacin use was significantly reduced after the introduction of the antimicrobial stewardship program. The incidence of fluoroquinolone-resistant *E coli* decreased after implementing the antimicrobial stewardship program, which implies that decreased levofloxacin use reduces fluoroquinolone resistance of *E coli*. Austin et al hypothesized that a dramatic decrease in antibiotic usage is necessary to reverse the trend towards resistance.[16] This hypothesis is compatible with the present results for *E coli*.

Among the fluoroquinolones used, moxifloxacin use was negatively correlated with the incidence of fluoroquinolone-resistant *E coli*, but this relationship was not statistically significant. Ciprofloxacin and levofloxacin were both positively correlated with the incidence of fluoroquinolone-resistant *E coli*, but only levofloxacin use, either parenteral or oral, was significantly positively correlated with the presence of fluoroquinolone-resistant *E coli*. Mutation prevention concentration (MPC), defined as the lowest antibiotic concentration that prevents the growth of the least susceptible single-step mutant present in a large bacterial population,[17] may explain this phenomenon. Antibiotic concentrations should be maintained above the MPC to avoid selecting for resistance.[18,19] Linde et al reported that the MPC of ciprofloxacin was two times lower than that of levofloxacin.[20] This suggests that *E coli* resistance is induced more easily with levofloxacin use than with ciprofloxacin use.

MacDougall et al reported that fluoroquinolone use, particularly levofloxacin use, in the community showed a stronger correlation than fluoroquinolone use in the hospitals with fluoroquinolone resistance in *E coli* in the hospitals.[21] It is likely that a great proportion of nosocomial *E coli* infections may originate from the community. In this study, we found that, by controlling levofloxacin usage in the hospital, it is possible to reduce the incidence of fluoroquinolone-resistant *E coli*.

The rate of antibiotic resistance in a population can be expressed in two ways: the percentage of nonsusceptible (i.e. resistant and intermediately susceptible) isolates or the number of nonsusceptible isolates per 1000 patient-days (also referred to as the incidence). The latter appears to be a more relevant indicator of resistance rate. Patients receiving antibiotic treatment may have an ecological impact on all hospitalized patients.[22,23] Rogues et al identified that, compared to the percentage of resistant isolates, the

Table 2 Correlation between individual fluoroquinolone use and the incidence of fluoroquinolone-resistant *Escherichia coli* isolates that cause nosocomial infections

	Preintervetion period							Postintervention period							*p*
	2004		2005		2006		2007	2007	2008		2009		2010		
	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	
Incidence of fluoroquinolone-resistant *E coli*	0.18	0.21	0.30	0.26	0.27	0.26	0.31	0.22	0.22	0.24	0.17	0.24	0.15	0.16	
Antibiotic use (DDD/1000PD)															
Parenteral ciprofloxacin	16.16	13.02	16.83	10.84	10.00	12.08	10.24	6.25	8.40	7.21	10.20	7.98	7.06	6.74	0.296
Parenteral levofloxacin	0	0	4.92	6.79	9.00	8.45	8.80	5.45	3.65	3.61	1.67	1.12	2.10	1.00	0.002*
Parenteral moxifloxacin	1.11	1.86	1.06	0.00	0.00	0.00	0.37	1.54	3.07	4.28	3.71	3.48	3.41	1.89	0.382
Oral ciprofloxacin	12.47	14.15	14.20	14.62	12.58	14.67	13.75	12.47	14.43	15.47	13.88	17.10	15.24	12.84	0.627
Oral levofloxacin	6.67	7.05	13.63	6.04	10.15	9.29	8.09	1.22	2.68	6.52	4.14	2.35	3.59	3.46	0.018*
Oral moxifloxacin	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.53	0.17	0.53	2.32	3.18	2.53	3.05	0.421
Total ciprofloxacin	28.63	27.17	31.03	25.46	22.58	26.75	23.99	18.72	22.83	22.67	24.07	25.08	22.30	19.58	0.210
Total levofloxacin	6.67	7.05	18.54	12.83	19.15	17.74	16.89	6.67	6.33	10.12	5.81	3.47	5.69	4.46	0.001*
Total moxifloxacin	1.11	1.86	1.06	0.00	0.00	0.00	0.58	2.07	3.24	4.81	6.03	6.66	5.94	4.93	0.082
Total fluoroquinolone	36.41	36.08	50.64	38.29	41.73	44.49	41.45	27.46	32.40	37.60	35.92	35.22	33.93	28.97	0.005*

* statistically significant.
DDD/1000PD = defined daily dose/1000 patient-days.

Table 3 The significant changes between the pre- and postintervention periods

	Preintervention period		Postintervention period		*p*-value
	Mean	SD	Mean	SD	
Incidence of fluoroquinolone- resistant *E coli* (isolates recovered per 1000 patient-days)	0.25472	0.04576	0.20129	0.04103	0.0402*
Antibiotics use (DDD/1000PD)					
Parenteral ciprofloxacin	12.73933	2.77847	7.68995	1.32102	0.001*
Parenteral levofloxacin	5.42229	3.96458	2.65763	1.63747	0.0005*
Parenteral moxifloxacin	0.62947	0.72948	3.05274	0.99188	0.005*
Oral ciprofloxacin	13.77569	0.91030	14.48887	1.60827	0.327
Oral levofloxacin	8.70224	2.61611	3.42304	1.66782	0.0007*
Oral moxifloxacin	0.02900	0.07674	1.75832	1.29907	0.002*
Parenteral and oral Ciprofloxacin	26.51502	2.83971	22.17881	2.28762	0.008*
Parenteral and oral levofloxacin	14.12453	5.36748	6.08067	2.09814	0.006*
Parenteral and oral moxifloxacin	0.65847	0.72160	4.81106	1.64347	0.032*
Total fluoroquinolone	41.29802	5.12780	33.07054	3.71302	0.005*

* statistically significant.
DDD/1000PD = defined daily dose/1000 patient-days; SD = standard deviation.

incidence of resistant isolates has a stronger correlation with antibiotic usage.[24] Therefore, in our study, the incidence rate was used to investigate antibiotic resistance.

There are some limitations to our study. First, we only discuss the impact of antibiotic consumption on bacterial resistance. The emergence of bacterial resistance in a hospital results from multiple factors, including the occurrence of mutations, antibiotic use, and the various infection control programs such as hand hygiene. Effective infection control measurement could reduce at least 20% of nosocomial infections.[25] Therefore, we implemented an infection control program focusing on controlling antibiotic use, rather than environmental intervention. Second, only small amounts of parenteral and oral moxifloxacin were prescribed during the preintervention period, although oral moxifloxacin has been available since the 2007 and parenteral moxifloxacin was not continuously available in the preintervention period. Total moxifloxacin consumption has increased gradually over the postintervention period. It was found that use of moxifloxacin tended to be negatively correlated with the incidence of fluoroquinolone-resistance in *E coli*. An extension of the study period may be helpful to clarify the relationship between moxifloxacin use and the incidence of fluoroquinolone-resistance in *E coli*.

In conclusion, there is a significant correlation between levofloxacin use and the incidence of fluoroquinolone-resistant *E coli* isolates that cause nosocomial infections. The incidence of nosocomial infections due to fluoroquinolone-resistant *E coli* could be decreased by reducing levofloxacin use in the hospital.

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