



## Short communication

## Fluoroquinolone resistance of *Pseudomonas aeruginosa* isolates causing nosocomial infection is correlated with levofloxacin but not ciprofloxacin use

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## ABSTRACT

This study investigated the correlation between fluoroquinolone (ciprofloxacin or levofloxacin) use and rates of fluoroquinolone resistance in *Pseudomonas aeruginosa* isolates from patients with nosocomial infection at a medical centre in Taiwan. Antibiotic utilisation data were extracted on a monthly basis from the inpatient pharmacy computer system records from January 2003 to December 2008. Fluoroquinolone use was expressed as defined daily dose per 1000 patient-days and was correlated with rates of fluoroquinolone-resistant *P. aeruginosa* every 6 months. Regression analysis was performed to explore the relationship between ciprofloxacin and levofloxacin use (both parenteral and oral forms) and resistance of *P. aeruginosa* isolates. During the study period, the susceptibility of *P. aeruginosa* to fluoroquinolones decreased after increasing use of fluoroquinolones, and increased after decreasing use of levofloxacin. Parenteral levofloxacin use was significantly positively correlated with resistance of *P. aeruginosa* to ciprofloxacin ( $P=0.015$ ) and fluoroquinolones (either ciprofloxacin or levofloxacin,  $P=0.014$ ). Use of both parenteral and oral forms of levofloxacin was also significantly positively correlated with resistance of *P. aeruginosa* isolates to ciprofloxacin ( $P=0.029$ ), levofloxacin ( $P=0.031$ ) and fluoroquinolones ( $P=0.010$ ). The total amount of ciprofloxacin (oral and parenteral) and parenteral ciprofloxacin use were negatively correlated with resistance of *P. aeruginosa* isolates to fluoroquinolones. However, the amounts of oral ciprofloxacin, parenteral levofloxacin, oral levofloxacin and total levofloxacin use were each positively correlated with resistance of *P. aeruginosa* to fluoroquinolones. Levofloxacin use was associated with increased resistance of *P. aeruginosa* to fluoroquinolones, whereas ciprofloxacin use did not have a significant impact on fluoroquinolone resistance rates.

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### 1. Introduction

*Pseudomonas aeruginosa* is a leading cause of healthcare-associated infections worldwide [1]. This organism ranks third among all organisms causing hospital-acquired infections in Taiwan [2]. Recently, *P. aeruginosa* has become increasingly resistant to various antimicrobial agents [3]. Previous studies showed that *P. aeruginosa*-infected patients who were treated empirically with inappropriate antimicrobial agents had a significantly higher mortality rate [4].

Fluoroquinolones show potency against a broad range of pathogens responsible for community- and hospital-acquired infections [5]. Owing to its potent activity against *P. aeruginosa*, ciprofloxacin is most frequently used for treatment of infections

due to this organism [5]. Levofloxacin, a respiratory quinolone with activity against *P. aeruginosa*, has also been widely used in recent years. Increasing levofloxacin use was associated with a rising incidence of fluoroquinolone-resistant *P. aeruginosa*, whereas ciprofloxacin use did not share this association [5–8]. However, no previous studies have demonstrated a change in fluoroquinolone resistance of *P. aeruginosa* following a reduction in the use of levofloxacin.

The present study evaluated the impact of ciprofloxacin and levofloxacin use on the susceptibility of *P. aeruginosa* during a strict antimicrobial management programme from 2003–2008 at a university hospital in Taipei, Taiwan.

### 2. Materials and methods

#### 2.1. Setting

Taipei Medical University Hospital is a private, tertiary care, university-affiliated teaching hospital located in Taipei, Taiwan.

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The number of beds increased from 350 to 560 between 2003 and 2008. Specialty intensive care units in the hospital include medical, surgical/trauma and neonatal.

## 2.2. Bacterial isolates and susceptibility testing

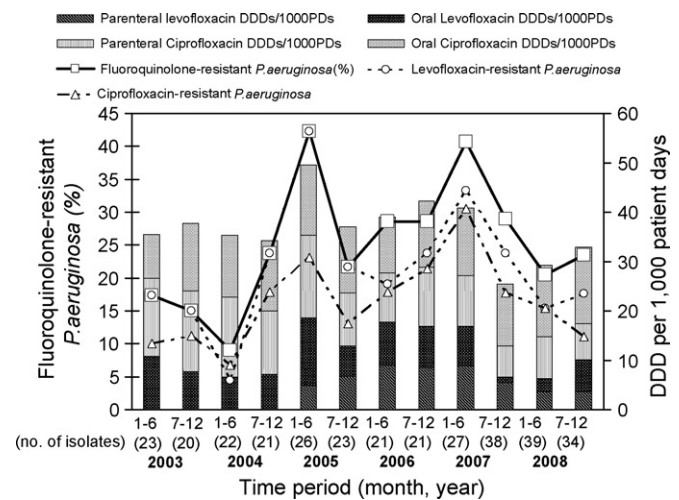
Susceptibility data for *P. aeruginosa* isolates associated with hospital-acquired infections were obtained from the infection control department. The broth microdilution method (Phoenix; Becton Dickinson, Sparks, MD) was used for susceptibility testing during the study period. Breakpoints for determining susceptibility were  $\leq 1$  mg/L for ciprofloxacin and  $\leq 2$  mg/L for levofloxacin [9] and were consistently employed throughout the study period. Susceptibility data were maintained in a laboratory information system database. Duplicate isolates, defined as isolation of the same bacterial species from the same patient with the same antibiogram, were excluded. Fluoroquinolone-resistant *P. aeruginosa* was defined as a *P. aeruginosa* isolate intermediate or resistant to either ciprofloxacin or levofloxacin.

## 2.3. Antibiotic consumption

Two fluoroquinolones, ciprofloxacin (parenteral and oral forms) and levofloxacin (oral form), were available on the hospital formulary throughout the study period. Parenteral levofloxacin was available on the hospital formulary since January 2005. Antibiotic utilisation data were collected from January 2003 to December 2008. Data were extracted on a monthly basis from the inpatient pharmacy computer system. Data on the use of fluoroquinolones (both parenteral and oral forms) were expressed as defined daily dose per 1000 patient-days (DDD/1000PD) and were correlated with rates of fluoroquinolone-resistant *P. aeruginosa* in the hospital every 6 months from 2003 to 2008. Restrictions on levofloxacin use were implemented by the Department of Infection Control and Pharmacy in July 2007. During the study period, the recommended ciprofloxacin dosage for hospitalised patients without renal impairment was 400 mg every 12 h (q12h) intravenously and 500 mg q12h orally. The recommended levofloxacin dosage for hospitalised patients without renal impairment was 500 mg daily intravenously and 500 mg daily orally between 2003 and 2006 and 750 mg daily for both oral and intravenous administration after 2007.

## 2.4. Correlation of fluoroquinolone use with fluoroquinolone resistance rates of *Pseudomonas aeruginosa*

Least-squares linear regression was used to examine the univariate relationship between fluoroquinolone (ciprofloxacin and levofloxacin) use and fluoroquinolone resistance rates of *P. aeruginosa* isolates associated with nosocomial infections. The correlation



**Fig. 1.** Trends in resistance rates of *Pseudomonas aeruginosa* isolates associated with nosocomial infections to ciprofloxacin, levofloxacin and fluoroquinolones (resistant to either ciprofloxacin or levofloxacin) and fluoroquinolone use expressed as defined daily doses per 1000 patient-days (DDD/1000PDs) in each half-year from 2003 to 2008.

coefficient values ( $r$  or  $r^2$ ) were determined. A  $P$ -value of  $<0.05$  was considered to be statistically significant.

## 3. Results

During the study period, a total of 315 *P. aeruginosa* isolates causing nosocomial infections were recovered from 299 patients. The number of *P. aeruginosa* isolates for each half-year period ranged from 20 to 39. The trends in resistance rates of *P. aeruginosa* to fluoroquinolones as well as fluoroquinolone usage (parenteral and oral) in each half-year period are shown in Fig. 1. Ciprofloxacin use decreased after July 2005, whereas levofloxacin use increased to 18.54 DDD/1000PD during the first half of 2005, more than double its average use for 2003 and 2004 (8.05 DDD/1000PD). This may have been partially attributable to the listing of parenteral levofloxacin on the hospital formulary since January 2005. Levofloxacin use decreased to 6.67 DDD/1000PD during the second half of 2007, and further to 4.99 DDD/1000PD during the first half of 2008.

The fluoroquinolone resistance rate increased to 42.3% in the first half of 2005 from the relatively low resistance rates of  $<20\%$  from 2003 to 2004. The rate of fluoroquinolone-resistant *P. aeruginosa* decreased from 40.7% in the first half of 2007 to 20.5% in the first half of 2008 and was sustained at 23.5% in the following half year.

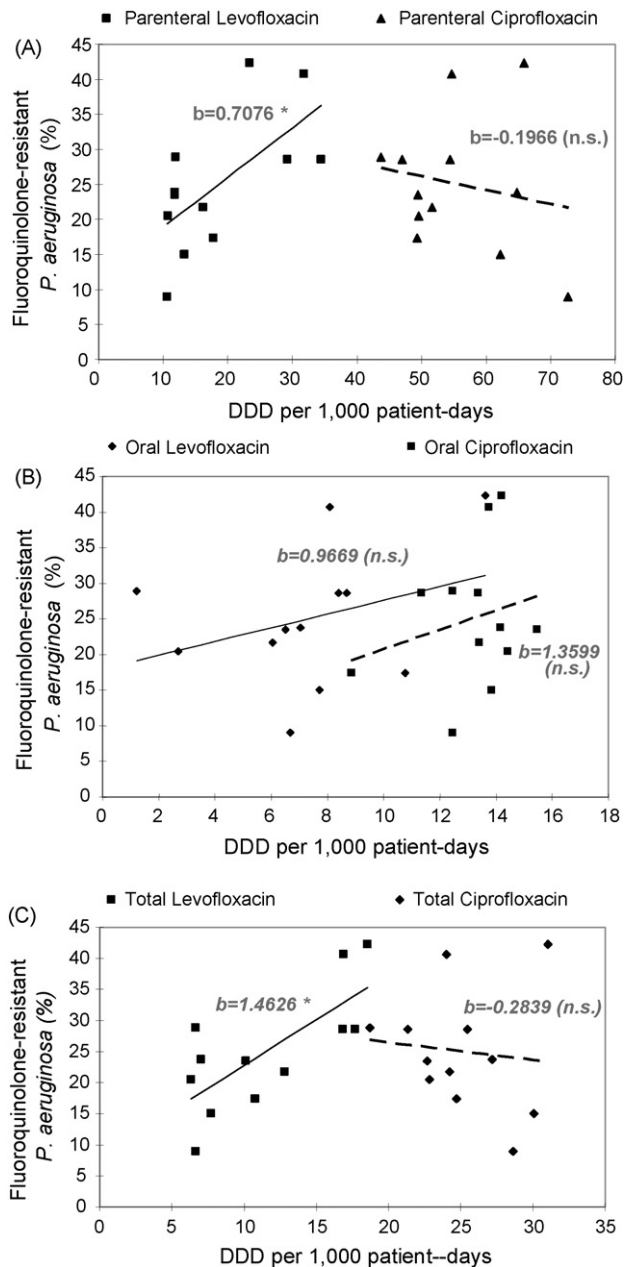
The correlation between fluoroquinolone (ciprofloxacin or levofloxacin) use and rates of fluoroquinolone-resistant *P. aeruginosa*

**Table 1**  
Correlation between fluoroquinolone (ciprofloxacin and levofloxacin) use and fluoroquinolone resistance in *Pseudomonas aeruginosa* isolates causing nosocomial infections.

	Ciprofloxacin resistance			Levofloxacin resistance			Fluoroquinolone (ciprofloxacin or levofloxacin) resistance		
	Coefficient ( $r^2$ )	Coefficient ( $r$ )	$P$ -value	Coefficient ( $r^2$ )	Coefficient ( $r$ )	$P$ -value	Coefficient ( $r^2$ )	Coefficient ( $r$ )	$P$ -value
Ciprofloxacin use									
Oral	0.076	0.277	0.384	0.056	0.237	0.458	0.072	0.269	0.398
Parenteral	0.041	0.203	0.527	$<0.001$	0.002	0.994	0.047	0.216	0.500
Parenteral and oral	0.006	0.078	0.810	0.014	0.119	0.713	0.009	0.095	0.769
Levofloxacin use									
Oral	0.049	0.222	0.489	0.179	0.423	0.171	0.114	0.337	0.284
Parenteral	0.466	0.682	0.015*	0.235	0.484	0.111	0.470	0.685	0.014*
Parenteral and oral	0.393	0.627	0.029*	0.385	0.620	0.031*	0.497	0.705	0.010*

\* Statistically significant ( $P < 0.05$ ).

isolates causing nosocomial infections is shown in Table 1 and Fig. 2. Parenteral levofloxacin use was significantly positively correlated with resistance of *P. aeruginosa* to ciprofloxacin ( $P=0.015$ ) and to fluoroquinolones (either ciprofloxacin or levofloxacin,  $P=0.014$ ). Total use of parenteral and oral forms of levofloxacin was also significantly positively correlated with resistance of *P. aeruginosa* to ciprofloxacin ( $P=0.029$ ), levofloxacin ( $P=0.031$ ) and fluoroquinolones ( $P=0.010$ ). The total amount of ciprofloxacin (oral and parenteral) use and parenteral ciprofloxacin use alone were negatively correlated with resistance of *P. aeruginosa* to fluoroquinolones. However, the amount of oral ciprofloxacin use as well as oral only, parenteral only and total levofloxacin use were all positively correlated with *P. aeruginosa* resistance to fluoroquinolones (Fig. 2).



**Fig. 2.** Linear regression analysis of fluoroquinolone use (expressed as defined daily doses per 1000 patient-days) and fluoroquinolone-resistant *Pseudomonas aeruginosa* causing nosocomial infections: (A) parenteral ciprofloxacin and levofloxacin use; (B) oral ciprofloxacin and levofloxacin use; and (C) total (parenteral and oral) ciprofloxacin and levofloxacin use.

#### 4. Discussion

Resistance of *P. aeruginosa* to antimicrobial agents involves multiple mechanisms. Mutation in the *gyrA* gene and activation of efflux pumps are responsible for resistance to fluoroquinolones [10]. In addition, resistance to fluoroquinolones in *P. aeruginosa* is linked to resistance to other antibiotics [11]. An increasing prevalence of fluoroquinolone resistance in *P. aeruginosa* has previously been reported [12,13]. In our hospital, an increasing resistance rate of *P. aeruginosa* to fluoroquinolones was noted in the first half of 2005. Despite the lack of a specific control policy, the use of both levofloxacin and ciprofloxacin decreased over the following 6 months, with a concurrent decrease in the rate of fluoroquinolone-resistant *P. aeruginosa*. However, an increasing trend of non-susceptibility was again noted during 2006–2007 and was concurrent with an increasing use of levofloxacin but stable use of ciprofloxacin.

Bhavnani et al. [14] showed that an increase in levofloxacin use was associated with a decrease in *P. aeruginosa* susceptibility to ciprofloxacin. A similar finding that use of levofloxacin, but not ciprofloxacin, contributed significantly to rates of fluoroquinolone-resistant *P. aeruginosa* has also been reported [5]. However, whether a change in susceptibility occurs with a subsequent reduction in levofloxacin use has not been documented. Taipei Medical University Hospital implemented restrictions on levofloxacin use beginning in July 2007 in an attempt to control further the resistance rate of *P. aeruginosa*. As expected, the rate of resistance of *P. aeruginosa* to fluoroquinolones subsequently decreased. This is the first study to demonstrate that susceptibility of *P. aeruginosa* to fluoroquinolones can be restored by reducing levofloxacin use.

Despite the positive correlation between oral ciprofloxacin use and the resistance rate of *P. aeruginosa* to fluoroquinolones in this study, a surprisingly negative correlation was found between parenteral ciprofloxacin use and *P. aeruginosa* resistance to fluoroquinolones. The correlations between the resistance rate of *P. aeruginosa* and fluoroquinolone use were low for both parenteral ciprofloxacin and total ciprofloxacin, suggesting that ciprofloxacin had no effect on *P. aeruginosa* susceptibility to fluoroquinolones.

Several reasons may explain these seemingly discrepant findings. First, ciprofloxacin is more active in vitro against *P. aeruginosa* than levofloxacin owing to its lower minimum inhibitory concentration [5–7]. The selective pressure of fluoroquinolones on the gastrointestinal flora also plays a role in fluoroquinolone-resistant Gram-negative bacilli [15]. Polk et al. [5] explained that the different effects of levofloxacin and ciprofloxacin on the resistance of *P. aeruginosa* were due to the higher bioavailability of levofloxacin compared with ciprofloxacin, resulting in a lower gastrointestinal concentration of levofloxacin possibly selecting for fluoroquinolone-resistant isolates [5–7,15]. However, this hypothesis could only partially explain the loss of susceptibility in our isolates, as the linear regression of levofloxacin use and fluoroquinolone-resistant *P. aeruginosa* showed a lower correlation with oral levofloxacin ( $r^2=0.114$ ) than with parenteral levofloxacin ( $r^2=0.470$ ).

Finally, the concept of mutation prevention concentration (MPC) may help explain this phenomenon. MPC is the minimum concentration that blocks growth of all single-step resistant mutants. Hansen et al. [13] found that the MPC of ciprofloxacin was four times lower than that of levofloxacin against *P. aeruginosa*.

In conclusion, increasing use of levofloxacin was positively correlated with an increase in resistance of *P. aeruginosa* to fluoroquinolones. The susceptibility of *P. aeruginosa* was recovered by reducing levofloxacin use. Ciprofloxacin does not cause increasing *P. aeruginosa* resistance to fluoroquinolones.

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**Competing interests:** None declared.

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