



Proceedings

# Recent trend in oral quinolone use and emergence of antibiotic resistant pathogens after intervention of antimicrobial stewardship program <sup>†</sup>

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**Abstract:** The over- and misuse of broad-spectrum antibiotics increase the risk of disruption of normal bacterial flora and the development of antimicrobial resistance. Recently, oral broad-spectrum antimicrobials, such as quinolones, cephalosporins, and macrolides, have been more frequently prescribed in Japan than in Europe or the United States. In particular, the use of oral quinolones increased from 2009 to 2013 in Japan. Therefore, the National Action Plan on Antimicrobial Resistance was formulated in April 2016 with the aim of reducing oral broad-spectrum antimicrobial use by 50% by 2020. We opted to promote appropriate quinolone use through lectures for all medical staff, including physicians. This study aimed to evaluate the trend of oral quinolone use and the antibiotic susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* from 2013 to 2020 in our hospital. To investigate oral antibiotic use, the yearly days of therapy per 100 patient days were investigated among inpatients and outpatients, excluding those with chronic diseases that required long-term quinolone prescriptions. Additionally, data on the susceptibility of *E. coli* and *K. pneumoniae* to levofloxacin were analyzed. The use of oral quinolones for outpatients significantly decreased by approximately 50% from 2013 to 2020, but no significant differences were observed in the use of oral quinolones for inpatients and the susceptibility of the bacteria to levofloxacin. More rigorous antimicrobial stewardship interventions are necessary to optimize oral quinolone use and minimize the prevalence of resistant pathogens.

**Keywords:** antimicrobial stewardship; oral quinolone; bacterial resistance

## 1. Introduction

Recently, medical issues have become more complicated and further subdivided. The spread of antibiotic-resistant pathogens will lead to serious health threats that affect clinical outcomes, including higher rates of mortality and increased healthcare costs. A related review by Jim O'Neil in 2014 estimated that antimicrobial resistance could cause 10 million deaths each year by 2050 [1]. The overuse and misuse of broad-spectrum antibiotics are associated with antimicrobial resistance to bacteria, longer duration of hospital stay, increased medical costs, and increased risk of adverse drug reactions [2]. Oral broad-spectrum antibiotics, such as quinolones, cephalosporins, and macrolides, are effective against a wide range of bacteria. Repeated exposure to broad-spectrum

antibiotics may lead to the acquisition and development of resistant mutations. The prescription of broad-spectrum antibiotics is more common in Japan than in Europe and the United States [3]. In particular, the use of oral quinolones in Japan increased from 2009 to 2013 [4].

Antimicrobial stewardship programs (ASPs) have been associated with appropriate antibiotic use, reduced prevalence of antibiotic-resistant pathogens, and improved clinical outcomes [5–7]. The National Action Plan on Antimicrobial Resistance was formulated in April 2016, and the goals of the plan were set to reduce oral broad-spectrum antimicrobial use by the year 2020 by 50% of its use in 2013 [3]. Therefore, we began to intervene to promote, through lectures, appropriate oral quinolone use for all medical staff in 2017. The purpose of this study was to retrospectively evaluate oral quinolone use and the antibiotic susceptibility of bacteria in our hospital between 2013 and 2020.

## 2. Methods

### 2.1. Setting and Patients

We conducted an observational retrospective study between January 1, 2013, and December 31, 2020, at Kobe University Hospital. We investigated patients who were prescribed oral quinolones and excluded those with chronic diseases that required long-term quinolone prescriptions. Patient medical data were collected from electronic medical records.

### 2.2. Educational Interventions for Promoting Antimicrobial Stewardship Programs

Educational lectures were held four times for all staff and twice for representative physicians from each department throughout the study period. The educational lecture content included problems of correlation between antibiotic consumption and antimicrobial-resistant bacteria, typical cases of inappropriate use of oral antibiotics, and rational antimicrobial strategies, including de-escalation therapy.

### 2.3. Outcomes

We retrospectively investigated the amount of oral antibiotics administered to inpatients and outpatients. The use of oral antibiotics was evaluated based on the yearly days of therapy (DOT) per 100 patient days. The outpatient numerator was calculated by dividing the total number of outpatients in each period. Classes of oral antibiotics were defined based on the WHO anatomical therapeutic chemical classification system. The susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* was evaluated using microbiological laboratory records, and the first isolate was used for analysis. We investigated the characteristics of non-extended-spectrum  $\beta$ -lactamase-producing bacteria.

### 2.4. Statistical Analysis

A single regression analysis was performed to determine the association between the year and each quinolone use (DOT); the Cochran–Armitage test for trends was used to compare the proportions of categorical variables between the groups (the susceptibility of bacteria). All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). The threshold for statistical significance was set at  $p < 0.05$ .

## 3. Results and Discussion

We investigated the amount prescribed for inpatients and outpatients among all patients at Kobe University Hospital over an eight-year period. The DOTs of inpatients are shown in Table 1. No significant differences were observed in the use of oral quinolones in inpatients during the study period ( $p = 0.8$ ). In outpatients, oral quinolone use significantly decreased from 3.4 to 1.7 DOTs per 100 patient days ( $p < 0.001$ ). The changes in the susceptibility of antibiotic-resistant bacteria are shown in Table 2. There were no significant changes in the susceptibilities of levofloxacin-resistant *E. coli* and *K. pneumoniae* over the 8-year period ( $p = 0.24$  and  $0.89$ , respectively).

Table 1. Days of therapy per 100 patient days of oral quinolone over an 8-year period

	2013	2014	2015	2016	2017	2018	2019	2020	<i>p</i>
Inpatients	2.5	2.6	2.8	2.3	2.6	2.6	2.8	2.3	<0.001
Outpatients	3.4	3.0	3.0	3.0	2.5	2.5	2.5	1.7	0.80

Table 2. Susceptibility of each bacteria to levofloxacin over an 8-year period.

	2013	2014	2015	2016	2017	2018	2019	2020	<i>p</i>
<i>Escherichia coli</i>	78.8	76.2	78.5	75.2	73.1	78.4	75.8	75	0.24
<i>Klebsiella pneumoniae</i>	100	96.8	97.1	99.5	98.8	97.9	98.1	98.9	0.89

In the era of evidence-based medicine, ASPs have been encouraged globally, and the number of related studies has increased over the last decade [8]. This study was performed at a university hospital in which many residents both worked and received their education. To promote ASPs, we intervened in the prescription of oral quinolones through educational lectures for all medical staff. In departments where no particular improvement was observed, we provided additional lectures directly to the representative doctors.

Antimicrobial stewardship programs have spread to many healthcare institutions. The main purpose of ASPs is to prevent the emergence of antibiotic-resistant bacterial infections. Many other studies have shown that ASP interventions reduce antibiotic use and improve patient outcomes, resulting in a lower incidence of antibiotic resistance [9]. In particular, education is considered an essential element of any program designed to influence prescription behavior, and can provide a foundation of knowledge that enhances and increases the acceptance of stewardship strategies [10]. Educational ASP interventions are effective in improving the prescription of antimicrobials [11,12]. We previously reported that educational lectures administered through ASP interventions are effective at reducing the use of oral 3<sup>rd</sup> cephalosporins [11]. Our previous study also revealed that the reduced use of oral quinolones in the Department of Oral and Maxillofacial Surgery had no effect on the incidence of surgical site infection and adverse effects of the prescribed antibiotics [13]. Prior use of broad-spectrum antibiotics, including quinolones, is a risk factor for acquiring quinolone-resistant *Escherichia coli* infection, which is an independent predictor of mortality [14,15]. Switching to narrower spectrum coverage via ASPs can prevent unnecessary broad-spectrum antimicrobial use, improve patient outcomes, and be cost-effective in the treatment of infectious diseases [9,16]. A previous retrospective observational study reported that ASPs decreased the consumption of antibiotics for inpatients and outpatients, and reduced surgical antibiotic prophylaxis in Beijing Chaoyang Hospital, a 1,400-bed tertiary hospital in China [17]. The investigators also demonstrated that the resistance rates of *E. coli* and *P. aeruginosa* to fluoroquinolones and the incidence rate of methicillin-resistant *Staphylococcus aureus* decreased, whereas the resistance rates of *E. coli* and *K. pneumoniae* to carbapenems increased.

We evaluated the trends in oral quinolone use and the susceptibility of *E. coli* and *K. pneumoniae* from 2013 to 2020 in our hospital. Patients who required long-term oral quinolone prescription were excluded to accurately assess the effects of the interventions. Our findings showed a significant decrease in the use of quinolones for outpatients during the study period. However, there were no significant changes in the emergence of antimicrobial-resistant strains. We conducted other ASPs, such as audit and feedback programs to promote appropriate intravenous antibiotic use, and interventions to optimize oral 3<sup>rd</sup> cephalosporin use throughout the investigation period [6,11,18]. We may not have fully evaluated the effects of our educational interventions to promote appropriate oral quinolone use.

#### 4. Conclusions

The implementation of AS educational interventions led to a decrease in the use of oral quinolones for outpatients; however, the susceptibility of bacteria did not change during the study period. Some other bacteria that become resistant to the use of antibiotics should be investigated. Furthermore, more rigorous interventions are needed to promote appropriate oral quinolone use, especially for inpatients, to prevent the spread of resistant pathogens.

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