

## Increasing Ofloxacin Resistance of Bacterial Flora from Conjunctival Sac of Preoperative Ophthalmic Patients in Japan

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**Purpose:** To examine the in vitro resistance to ofloxacin of preoperative bacterial isolates from the conjunctival sac of Japanese patients.

**Methods:** The database of bacterial flora cultured preoperatively from the conjunctival sac of 1455 Japanese patients (1455 eyes) between 1995 and 1999 was reviewed retrospectively.

**Results:** The incidence of resistance of isolates to ofloxacin in vitro increased from 13.5% in 1995 to 32.8% in 1999. The percentage of *Staphylococcus epidermidis* and *Staphylococcus aureus* isolates resistant to ofloxacin was 19.6% and 15.0%, respectively, in 1995 and 33.7% and 28.1%, respectively, in 1999. Logistic regression analysis showed that diabetes mellitus and aging were significantly associated with ofloxacin-resistant strains of bacteria.

**Conclusion:** Clinicians should be aware of the increased likelihood that conjunctival sac flora is resistant to ofloxacin, especially in elderly and diabetic patients. **Jpn J Ophthalmol 2002;46:586–589** © 2002 Japanese Ophthalmological Society

**Key Words:** Bacterial flora, conjunctival sac, ofloxacin resistance, *Staphylococcus aureus*, *Staphylococcus epidermidis*.

### Introduction

Ofloxacin, a fluoroquinolone, which has a broad spectrum of antibacterial activity and low toxicity, has been available commercially in Japan as a 0.3% ophthalmic solution since 1987. This antibiotic has been used as a first-line treatment for bacterial eye diseases in Japan because monotherapy with fluoroquinolone is as effective as combination therapy. Recently, ofloxacin was approved for use in the United States. A significant increase in the percentage of bacteria resistant to fluoroquinolones has been reported worldwide.<sup>1–4</sup>

The purpose of this report is to present our analysis of the in vitro ofloxacin resistance among the bacteria isolated from the conjunctival sac of patients in Japan in the late 1990s.

### Materials and Methods

A database of the bacterial flora isolated from the conjunctival sac of preoperative ophthalmic patients was retrospectively reviewed. Included were data from 1455 Japanese patients (1455 eyes) who underwent ophthalmic surgery at the National Tokyo Medical Center in Japan between 1995 and 1999. There were 248 patients in 1995, 226 in 1996, 191 in 1997, 367 in 1998, and 423 in 1999. The preoperative clinical diagnosis in the 1455 patients was as follows: 1169 patients with cataract, 192 with vitreo-retinal diseases, 35 with glaucoma, 22 with strabismus, and

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37 with other eye diseases. The patients did not have any bacterial eye disease at the time of the sampling. They included 943 women and 512 men whose ages ranged from less than 1 to 97 years. Scrapings of the inferior conjunctival fornix were obtained preoperatively using a sterile dry swab without topical anesthetic. The samples were immediately inoculated into Heart Infusion bouillon and incubated for 24 hours at 37°C then inoculated onto blood agar plates and incubated for 24 hours at 37°C.

A total of 1107 bacterial isolates were identified and tested for in vitro susceptibility to ofloxacin by the Kirby-Bauer disc diffusion method using KB Disc (Eiken Chemical, Tokyo). In addition, sensitivity to erythromycin and gentamycin was determined by the microdilution broth procedure using Micro-Scan (Dade Behring, West Sacramento, CA, USA). When the susceptibility of an organism was graded as resistant or of intermediate sensitivity, we classified it as "not sensitive."

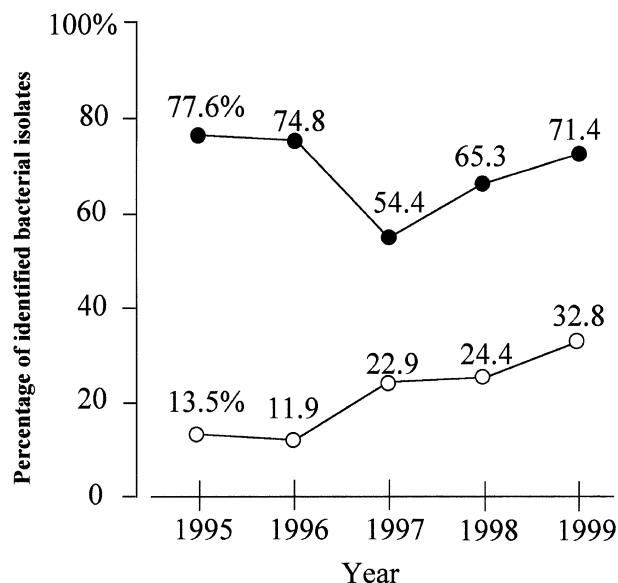
Statistical analysis of the changing percentages over time was performed using regression analysis.

## Results

The prevalence of patients with positive cultures from the conjunctival sac did not change significantly ( $P = .53$ ) between 1995 with 77.6% (191/248) and 1999 with 71.4% (302/423) (Figure 1). However, the percentage of isolates resistant to ofloxacin in vitro increased annually from 13.5% (30/222) in 1995 to 32.8% (115/352) in 1999. This increase was statistically significant ( $P = .015$ ).

Of the 1107 bacterial isolates from the conjunctival sac (Table 1), the most frequently identified organisms were *Staphylococcus epidermidis* (46.4%, 514 isolates), followed by *Corynebacterium* species (11.5%, 127 isolates), *Staphylococcus aureus* (8.8%, 97 isolates), and *Enterococcus faecalis* (6.1%, 68 isolates). For these bacteria, resistance to ofloxacin was compared to their resistance to erythromycin and gentamycin (Table 2). The *Corynebacterium* species showed a significant increase in the frequency of resistance to all three drugs from 1995 through 1999. In contrast, the resistance of *S. epidermidis* and *S. aureus* to ofloxacin increased during the study period but resistance of these organisms to erythromycin and gentamycin did not change.

The characteristics of patients that were associated with bacterial isolates sensitive to ofloxacin were evaluated. Logistic regression analysis including the factors of age, sex, and existence of atopic dermatitis or diabetes mellitus revealed that diabetes



**Figure 1.** Annual prevalence of all identifiable bacteria cultured from the conjunctival sac of 1455 preoperative patients at the National Tokyo Medical Center in Japan between 1995 and 1999. Closed circles indicate the percentage of patients with identifiable bacterial isolates. Open circles indicate the percentage of isolates resistant to ofloxacin in vitro.

and aging were significantly associated with ofloxacin resistance ( $P = .013$  and  $P = .007$ , respectively), while sex- and atopic dermatitis-related factors were not found ( $P = .312$  and  $P = .242$ , respectively).

## Discussion

Ofloxacin has been used in Japan as the first and most common treatment for bacterial infections as well as for topical prophylaxis. However, an increase in resistance has been reported in this country,<sup>5</sup> as confirmed by the present study, for the late 1990s. In India, 30.7% of corneal isolates were not sensitive to ciprofloxacin, and there was a significant increasing trend of ciprofloxacin-insensitivity in bacteria between 1992 and 1997.<sup>1</sup> Resistance of *S. aureus* to ofloxacin increased significantly from 4.7% in 1993 to 35.0% in 1997 in the United States.<sup>2</sup> In south Florida (USA), there was an increase in the laboratory resistance of *S. aureus* isolates to fluoroquinolones in patients with keratitis (11% in 1990 to 28% in 1998), but the resistance patterns to aminoglycosides remained unchanged.<sup>3</sup> In the present study, the laboratory resistance pattern of *S. epidermidis* and *S. aureus* to erythromycin or gentamycin has remained approximately the same. In London, on the other

**Table 1.** Distribution of Bacterial Isolates Identified by Year

Organisms	1995	1996	1997	998	1999	Total Number
Total gram-positive cocci	188	134	79	212	256	869
<i>Staphylococcus epidermidis</i>	112	77	53	130	142	514
<i>Staphylococcus aureus</i>	20	18	7	20	32	97
<i>Enterococcus faecalis</i>	9	15	8	19	17	68
<i>Staphylococcus haemolyticus</i>	5	4	1	2	9	21
other gram-positive organisms	42	20	10	41	56	169
Total gram-positive bacilli	21	27	21	38	44	151
<i>Corynebacterium</i> species	17	17	19	36	38	127
<i>Bacillus</i> species	4	10	2	1	2	19
<i>Bacillus cereus</i>	0	0	0	1	4	5
Total gram-negative cocci/bacilli	13	15	16	25	18	87
<i>Acinetobacter lowffii</i>	2	1	2	5	6	16
<i>Neisseria</i> species	0	0	0	6	4	10
<i>Pseudomonas fluorescens</i>	2	2	3	3	0	10
<i>Escherichia coli</i>	0	2	1	0	2	5
<i>Acinetobacter anitratus</i>	2	2	0	0	0	4
Other gram-negative organisms	7	8	10	11	62	
Total isolates	222	176	116	275	318	1107

hand, ofloxacin has recently been reported to be still effective in vitro against 97% of isolates from patients with keratitis, indicating that there has not been an increase in resistance since 1995.<sup>5</sup>

The efficacy of antibiotics for topical prophylactic treatment of, for example, corneal disease associated with contact lens wear, is controversial. Recently, fluoroquinolones have been commonly used for prophylaxis in Japan, which coincides with the increase in resistance to ofloxacin in the late 1990s. Clinicians should be aware of the increasing resistance of bacteria to ofloxacin, especially in elderly and diabetic patients, because ofloxacin is used frequently in Ja-

pan as a first line antibiotic for bacterial infection and for prophylaxis.

We examined the bacterial flora from the conjunctival sac of all preoperative patients at the National Tokyo Medical Center between 1995 and 1999. In the selection of postoperative antibiotic ophthalmic solutions, we used ofloxacin for 1 month after the operation only if the bacteria from the conjunctival sac preoperatively were sensitive to ofloxacin. If not, we used other antibiotics to which the organisms were sensitive in addition to ofloxacin. We have not had any patients develop endophthalmitis during the 5 years now being surveyed.

**Table 2.** Percentage of In Vitro Resistance of Bacterial Isolates to Ofloxacin (OFLX), Erythromycin (EM), and Gentamycin (GM)

	<i>Staphylococcus epidermidis</i>			<i>Corynebacterium</i> Species			<i>Staphylococcus aureus</i>			<i>Enterococcus faecalis</i>		
	OFLX	EM	GM	OFLX	EM	GM	OFLX	EM	GM	OFLX	EM	GM
1995	19.6%	19.6	20.5	5.9	35.3	5.9	15.0	30.0	20.0	22.2	55.6	77.8
1996	19.5	15.6	13.0	23.5	47.1	17.6	5.6	27.8	0	0	73.3	73.3
1997	20.0	20.0	10.0	31.6	63.2	21.1	14.3	28.6	0	75.0	50.0	100
1998	25.4	13.8	13.8	44.4	72.2	38.9	25.0	35.0	15.0	21.1	78.9	89.5
1999	33.7	14.3	19.4	57.9	68.4	47.4	28.1	12.5	15.6	29.4	76.5	100
P*	.051	.22	.94	.004	.02	.002	.11	.37	.87	.74	.32	.12

\*Regression analysis.

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