

Figure 2 One day after ceasing steroid administration, the corneal endothelial plaque was enlarged and a stromal fluffy abscess with hypopyon formed. **Note:** Box shows yeast surrounded by many neutrophils and few macrophages, detected by smear of retrocorneal plaque. Bar: 20 μ m.

of endophthalmitis as has been reported.¹⁻³ However, we speculate the organism invaded from ocular surface because of the below five reasons. 1) the corneal epithelium was eroded at the patient's first GP visit (Pers comm.); 2) aqueous fluid and fibrous tissue in the anterior chamber included no organism; 3) the yeast was surrounded by neutrophils as if leucocytes were preventing the organism spreading into the anterior chamber; 4) the corneal endothelium at the site of the pterygium scar is usually steady-state and may not be the special target of yeast; 5) secession of steroid encouraged mycotic keratitis to progress in the cornea rather than in the intracameral region. For these reasons, we speculate that the pathogenic organism entered through the ocular surface invade immediately through the thinning corneal region at the pterygium scar to reach the endothelium. The inflammation may have been masked by steroid administration and temporary healing of epithelial erosion. Several reports of postoperative infectious keratitis related to a corneal incision such as radial keratotomy,³⁻⁷ have shown how

the characteristics of mycotic keratitis are modified in the thinning region. *Aspergillus* keratitis and *Candida* keratitis after radial keratotomy displayed a similar clinical appearance to our case,^{5,6} that is, mycotic focus localized in the deep stromal region accompanied by endothelial plaque with no stromal infiltration, no stromal edema and no epithelial defect as if the organism was derived intracamerally. Thus steroid therapy in the postoperative condition modify the clinical appearance of infectious keratitis. We should pay special attention to prescribing steroid administration for corneal diseases especially in the postoperative condition.

Disclosure

The authors report no conflicts of interest in this work.

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**Changes in drug susceptibility and the quinolone-resistance
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Masaru Miyanaga, Ryohei Nejima, Takashi Miyai, Kazunori Miyata, Yuichi Ohashi,
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Changes in drug susceptibility and the quinolone-resistance determining region of *Staphylococcus epidermidis* after administration of fluoroquinolones

Masaru Miyanaga, MD, Ryohei Nejima, MD, Takashi Miyai, MD, Kazunori Miyata, MD, PhD, Yuichi Ohashi, MD, PhD, Yoshitsugu Inoue, MD, PhD, Masahiro Toyokawa, PhD, Seishi Asari, PhD

PURPOSE: To evaluate the correlation between changes in the susceptibility of bacteria and mutations in the quinolone-resistance determining region (QRDR) after 3 weeks of continuous fluoroquinolone instillation.

SETTING: Miyata Eye Hospital, Miyazaki, Japan.

METHODS: In this prospective randomized study, gatifloxacin 0.3% eyedrops or levofloxacin 0.5% eyedrops were administered for 1 week before cataract surgery and for 2 weeks after surgery. Samples were collected from the conjunctival sac before instillation of the antibiotic agent and 14 days after surgery. Susceptibility to the fluoroquinolones and gene mutations in the QRDR of the isolated *Staphylococcus epidermidis* were analyzed.

RESULTS: The detection rate of *S epidermidis* was 27% in the gatifloxacin group (n=79 eyes) and 21% in the levofloxacin group (n=73 eyes) before instillation of the antibiotic and 6% and 19%, respectively, 14 days postoperatively. The susceptibility rates of *S epidermidis* strains to levofloxacin were statistically significantly lower after instillation than before antibiotic instillation, and the number of gene mutations in the QRDR was statistically significantly higher after instillation. There was no difference in the gatifloxacin group between before and after antibiotic instillation. In the 9 eyes in which *S epidermidis* was detected in samples taken before and after antibiotic instillation, most strains were genetically different from each other between the 2 time points.

CONCLUSIONS: Three-week continuous instillation of levofloxacin affected the indigenous bacterial flora in the conjunctival sac, suggesting possible induction of microbial substitution to fluoroquinolone-resistant *S epidermidis*. However, there was no change with gatifloxacin.

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The causative organisms of endophthalmitis after cataract surgery are coagulase-negative staphylococci including methicillin-resistant *Staphylococcus epidermidis* (MRSE), *Staphylococcus aureus* including methicillin-resistant *S aureus* (MRSA), and *Enterococcus* species, all of which are frequently detected in the conjunctival sac after surgery.^{1,2} This suggests that infectious endophthalmitis after surgery is caused by aberrant migration of resident bacteria on the ocular surface into the anterior chamber. Resident bacteria in the conjunctival sac usually prevent invasion and settlement of pathogenic bacteria. However, these bacteria may be a cause of endophthalmitis after intraocular surgery. Once postoperative endophthalmitis develops,

the outcome can be severe and can include loss of sight.² *Staphylococcus epidermidis* is often detected in cases of endophthalmitis.^{3–6} Half the *S epidermidis* strains isolated from the conjunctival sac develop biofilm formation,⁷ which can cause postoperative endophthalmitis by adhering to the intraocular lens during surgery.

In Japan, fluoroquinolone agents are routinely used to prevent infectious endophthalmitis in the perioperative period. These agents have a potent antibacterial activity and broad antibacterial spectrum with high levels of tissue distribution and safety. Although the most recent studies report that administering eyedrops for 3 days before surgery significantly reduces

Table 1. Primers used in the study.

Target Gene	Primer Sequence (5' to 3')	Position*	Product Size (bp)
<i>gyrA</i>	ATGCGTGAATCATTCTTAGACTATGC	2 609 699-2 609 724	284
	GAGCCAAAGTTACCTTGACC	2 609 441-2 609 460	
<i>gyrB</i>	CAGCATTAGACGTTTCAAGC	2 610 508-2 610 528	251
	CCAATACCCGTACCAAATGC	2 610 278-2 610 297	
<i>parC</i>	TCGCAATGTATTCAAGTGGG	939 185-939 204	197
	ATCGTTATCGATACTACCATT	939 361-939 381	
<i>parE</i>	AAGCTCAACAAGCACGCGAGGCTG	938 196-938 219	325
	TTAAAGTCAGTACCAACACCAGCACCAA	938 493-938 520	
<i>mecA</i>	TAGAAATGACTGAAACGTCCG	2 576 834-2 576 853	154
	TGCGATCAATGTTACCGTAG	2 576 967-2 576 987	

bp = base pair

*Nucleotide positions are indicated according to GenBank sequence number NC 002976 (*S epidermidis* RP62A)

bacteria in the conjunctival sac compared with administration for 1 day or 1 hour before surgery,⁸ there is no established instillation protocol during the perioperative and postoperative period. Thus, the instillation is usually performed based on the empirical practice of each surgeon.

Emergence of resistant bacteria from long-term use of antibacterial agents is a serious problem.⁹⁻¹¹ Decreases in drug susceptibility and the emergence of or increase in resistant bacteria have been reported since the release of ofloxacin eyedrops in 1987.¹⁰ In particular, the levofloxacin-resistance rate of coagulase-negative staphylococci (including *S epidermidis*), the most common strain in the conjunctival sac, is reported to be 38.7%.¹² In addition, Yamada et al.¹³ found that 50% of *S epidermidis* strains detected in the conjunctival sacs of patients scheduled for cataract surgery had mutations in any 1 of the *gyrA*, *gyrB*, *parC*,

and *parE* genes in the quinolone-resistance determining region (QRDR) that is responsible for fluoroquinolone resistance. Iihara et al.¹⁴ found that 62.5% of MRSA strains had 4 to 5 gene mutations of QRDR, suggesting increasing resistance to fluoroquinolones. To our knowledge, however, there are no reliable data on the appropriate administration period of antibacterial eyedrops and few reports of the effects of long-term use of the eyedrops on bacterial flora in the conjunctival sac.

In this study, we evaluated bacterial flora in the conjunctival sac before instillation of an antibiotic agent and after 3 weeks of continuous instillation of gatifloxacin and levofloxacin eyedrops in patients scheduled for cataract surgery. We also analyzed the susceptibility of the isolated *S epidermidis* to the fluoroquinolones as well as gene mutations in the QRDR.

PATIENTS AND METHODS

This prospective clinical study comprised patients who had cataract surgery at Miyata Eye Hospital between November 2004 and June 2005. The study followed the tenets of the Declaration of Helsinki. All patients provided informed consent after receiving a full explanation of the nature and possible consequences of the study. Institutional review board approval was obtained.

The patients were randomized into 2 groups. One group received topical gatifloxacin 0.3% eyedrops and the other group, levofloxacin 0.5% eyedrops. In both groups, the eyedrops were administered 4 times a day for 1 week before surgery and 3 times a day for 2 weeks after surgery.

Bacterial Isolation and Susceptibility Testing

After topical anesthesia was achieved, the inferior conjunctival fornix was scraped with a sterile cotton swab. Samples were examined before instillation of the antibiotic agent (within 2 months before surgery) and after 3 weeks of continuous instillation (ie, 7 days before surgery and 14 days after surgery) by direct isolation and enrichment culture. *Staphylococcus epidermidis* was grown in trypticase

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From Miyata Eye Hospital, (Miyana, Nejima, Miyai, Miyata), Miyazaki; Department of Ophthalmology and Visual Science (Miyana), Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Tokyo; Department of Ophthalmology (Ohashi), Ehime University School of Medicine, Ehime; Division of Ophthalmology and Visual Science (Inoue), Faculty of Medicine, Tottori University, Tottori; and Laboratory for Clinical Investigation (Toyokawa) and Department of Infection Control and Prevention (Asari), Osaka University Hospital, Osaka, Japan.

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Corresponding author: Masaru Miyana, Miyata Eye Hospital, 6-3 Kurahara, Miyakonojo, Miyazaki, 885-0051, Japan. E-mail: miyanaga-tmd@umin.ac.jp.

Table 2. Bacteria detected from the conjunctival sac of the lower eyelid before and after antibiotic instillation.

Bacteria Detected	Number of Strains							
	Gatifloxacin Group (n=79)				Levofloxacin Group (n=73)			
	Before Instillation		After 3-Week Instillation		Before Instillation		After 3-Week Instillation	
	Direct Culture	Enrichment Culture	Direct Culture	Enrichment Culture	Direct Culture	Enrichment Culture	Direct Culture	Enrichment Culture
<i>Staphylococcus aureus</i>	6	4	0	0	5	2	0	0
<i>Staphylococcus epidermidis</i>	17	4	1	4	11	4	1	14
<i>Corynebacterium</i> species	21	0	3	0	20	1	3	0
<i>Propionibacterium acnes</i>	6	0	8	4	9	1	5	0
Other gram-positive bacteria	5	0	1	2	4	1	0	2
Other gram-negative bacteria	7	1	2	4	2	2	3	0

soy broth (TSB) for 24 hours from stocks stored on Microbank cryobeads (Pro-Lab Diagnostics). The bacterial suspensions in TSB were inoculated on blood agar medium and cultured for 24 hours.

The minimum inhibitory concentrations (MICs) for gatifloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin,

tobramycin, gentamicin, erythromycin, chloramphenicol, and oxacillin were assessed with the broth dilution method following Clinical and Laboratory Standards Institute guidelines.^{15,16} The MICs were determined after 16 to 20 hours of incubation at 35 °C except for oxacillin (with sodium chloride 2% for 24 hours at 35 °C). Drug concentrations ranged from

Table 3. Correlation between susceptibility of fluoroquinolones and amino acid substitution in *S epidermidis* strains isolated before and after antibiotic instillation.

Group/Mutation Type	Isolates, n*	<i>gyrA</i>		<i>parC</i>		<i>parE</i>
		84 Ser[TCT]	88 Glu[GAA]	80 Ser[TCT]	84 Asp[GAT]	397 Asp[GAT]
Wild-type	18 (15)	—	—	—	—	—
I/a	3 (1)	—	—	—	—	—
I/b	3 (3)	—	—	Phe[TTT]	—	—
II/c	1 (1)	Phe[TTT]	—	—	—	—
III/d	2 (1)	—	Lys[AAA]	Tyr[TAT]	—	—
III/e	9 (6)	Phe[TTT]	—	Tyr[TAT]	—	—
III/f	4 (2)	Tyr[TAT]	—	Tyr[TAT]	—	—
III/g	2 (0)	Phe[TTT]	—	Phe[TTT]	—	—
III/h	2 (1)	Phe[TTT]	—	Ile[ATT]	—	—
III/i	1 (0)	Phe[TTT]	—	—	—	—
IV/j	1 (1)	Tyr[TAT]	—	Phe[TTT]	—	—
IV/k	2 (2)	Tyr[TAT]	—	Phe[TTT]	—	—
IV/l	1 (0)	Phe[TTT]	—	Phe[TTT]	—	—
IV/m	3 (0)	Tyr[TAT]	—	Phe[TTT]	Ala[GCT]	Tyr[TAT]
IV/n	1 (1)	Phe[TTT]	—	Phe[TTT]	Tyr[TAT]	—
IV/o	1 (1)	Ile[ATT]	—	Phe[TTT]	Val[GTT]	—
V/p	1 (0)	Tyr[TAT]	Lys[AAA]	Phe[TTT]	Ala[GCT]	Tyr[TAT]
V/q	1 (1)	Phe[TTT]	Lys[AAA]	Phe[TTT]	Tyr[TAT]	—

Ala = alanine; Arg = Arginine; Asn = asparagine; Asp = aspartic acid; GFLX = gatifloxacin; Glu = glutamic acid; His = histidine; Ile = isoleucine; LVFX = levofloxacin; Lys = lysine; MFLX = moxifloxacin; MIC = minimum inhibitory concentration; NFLX = norfloxacin; OFLX = ofloxacin; Phe = phenylalanine; Ser = serine; Tyr = tyrosine; Val = valine

*Numbers in parentheses are represent number of strains before antibiotic instillation

0.06 µg/mL to 64 µg/mL in twofold increments except for norfloxacin (2 to 16 µg/mL). After the MICs were determined, each well was mixed sufficiently and assessed for minimum bactericidal concentration testing. Next, 1.5 µL of bacterial suspension was inoculated on Muller-Hinton agar plates. Bacterial viability was determined based on the ability to form colonies on the agar plates after incubation for 24 hours at 35°C.

DNA Amplification and Sequencing of Quinolone-Resistance Determining Region

Genomic DNA was extracted using the Wizard SV 96 genomic DNA purification system (Promega KK). In the process, 1 µL of the genomic DNA solution was applied in 20 µL of amplification mixture (5 pM each primer, 1.6 µL dNTP mixture, 2 µL Ex Taq buffer, 0.1 µL LA Taq) (Takara Bio, Inc.). Polymerase chain reaction amplification was performed with the primers shown in Table 1.¹¹ Each reaction was amplified with the following temperature profiles: 30 cycles at 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 1 minute. The amplified DNA products were separated and identified by agarose gel 2% electrophoresis.

Polymerase chain reaction-amplified DNA was purified and sequenced by the dye terminator method in the forward direction and reverse direction. The quality score of each base was calculated using Phred/Phrap/Polyphred software (CodonCode Corp.). Sample sequences were compared with a reference sequence, and mutations were detected. The strain *S epidermidis* ATCC 35984 (RP62A) was used as a reference.

Detection of *mecA* Gene

A positive result was indicated by the presence of a 154 base pair amplified DNA fragment, which was revealed by electrophoresis on agarose gel 2%.

Statistical Analysis

The McNemar test was used to compare detection rates of bacteria before instillation of the antibiotic agent and after instillation in the 2 groups of patients. The sign test was used to detect the rates of *S epidermidis*. The Wilcoxon rank-sum test was used to compare QRDR mutation sites, MIC values for each agent, the number of QRDR mutations, and susceptibility rates.

RESULTS

The study comprised 152 eyes of 92 patients. The gatifloxacin group comprised 79 eyes and the levofloxacin group, 73 eyes.

Detection Rates of Bacteria

Table 2 shows the strains of bacteria detected from the conjunctival sac of the lower eyelid before instillation and after 3 weeks of continuous instillation. Before instillation, 71 strains were detected in the gatifloxacin group and 62 strains in the levofloxacin group. After 3 weeks of instillation, 29 strains and 28 strains, respectively, were detected. Bacteria were

Table 3. (Cont.)

<i>parE</i>				Antibiotic Agent (MIC range [mg/mL])				
404 Asn[AAT]	406 Arg[CGT]	434 Asp[GAT]	473 Glu[GAA]	GFLX	LVFX	OFLX	MFLX	NFLX
—	—	—	—	≤0.06-0.125	0.125-0.25	0.25-0.50	≤0.06-0.125	≤2
Ser[AGT]	—	—	—	≤0.06-0.125	0.125	0.25	≤0.06	≤2
—	—	—	—	0.125	0.5	1	0.125	4-8
—	—	—	—	2	4	8	1	>16
—	—	—	—	1-2	2-4	4-8	0.5-1	8
—	—	—	—	1-2	2-8	4-32	0.5-4	8->16
—	—	—	—	1-2	4	8	1	8-16
—	—	—	—	1-2	4	8	1	16->16
—	—	—	—	2	8	16	2	>16
—	His[CAT]	—	—	4	8	32	4	>16
—	—	—	Lys[AAA]	2	4	16	1	>16
—	—	Asn[AAT]	—	2	8	16	2	>16
—	—	Val[GTT]	—	2	8	16	2	>16
—	—	—	—	2	8	16	2	>16
—	—	—	—	2	8	16	2	>16
Ser[AGT]	—	—	—	8	32	64	8	>16
—	—	—	—	16	64	>64	8	>16
—	—	—	—	64	>64	>64	32	>16

Table 4. Changes in fluoroquinolone susceptibility rates and the number of QRDR gene mutations in *S epidermidis* strains isolated before and after antibiotic instillation.

Group/Time	Strains Detected (n)	Rates of Fluoroquinolone Susceptibility (%) (MIC Range [μ g/mL])				
		GFLX	LVFX	OFLX	MFLX	NFLX
Levofloxacin (n=73)						
Before instillation	15	60.0 (\leq 0.06-2)	60.0 (0.125-8)	60.0 (0.25-16)	73.3 (\leq 0.06-2)	53.3 (\leq 2->16)
After instillation*	15	13.3 (\leq 0.06-16)	13.3 (0.125-64)	13.3 (0.25->64)	26.7 (\leq 0.06-8)	13.3 (\leq 2->16)
Gatifloxacin (n=79)						
Before instillation	21	47.6 (\leq 0.06-64)	47.6 (0.125->64)	47.6 (0.25->64)	57.1 (\leq 0.06-32)	47.6 (\leq 2->16)
After instillation*	5	60.0 (\leq 0.06-2)	60.0 (0.125-8)	60.0 (0.25-16)	60.0 (\leq 0.06-2)	60.0 (\leq 2->16)

GFLX = gatifloxacin; Glu = glutamic acid; LVFX = levofloxacin; MFLX = moxifloxacin; MIC = minimum inhibitory concentration; MRSE = methicillin-resistant *Staphylococcus epidermidis*; NFLX = norfloxacin; OFLX = ofloxacin; QRDR = quinolone-resistance determining region
*For 3 weeks

detected in 71 eyes (89.9%) in the gatifloxacin group and 60 eyes (82.2%) in the levofloxacin group. At 3 weeks, bacteria were detected in 26 eyes (32.9%) and 23 eyes (31.5%), respectively; the detection rate of bacteria in both groups was statistically significantly lower after antibiotic instillation ($P < .001$, McNemar test).

In the gatifloxacin group, *S epidermidis* was detected in 21 eyes (26.6%) before antibiotic instillation and in 5 eyes (6.3%) at 3 weeks. In the levofloxacin group, *S epidermidis* was detected in 15 eyes (20.5%) and 14 eyes (19.1%), respectively (Table 2). In 1 eye in the levofloxacin group, 2 *S epidermidis* strains with different mutation sites were detected at 3 weeks. After antibiotic instillation, there was a statistically significant decrease in bacteria in the gatifloxacin group ($P < .001$, sign test) but not in the levofloxacin group. However, on direct isolation culture only, *S epidermidis* was detected in 17 eyes (21.5%) in the gatifloxacin group and in 11 eyes (15.1%) in the levofloxacin group before antibiotic instillation and in 1 eye (1.3%) and 1 eye (1.4%) at 3 weeks, respectively, showing that both agents had a statistically significant bactericidal effect ($P < .001$ and $P < .01$, respectively; Fisher exact test) and that there was no significant difference between the 2 agents.

Quinolone-Resistance Determining Region Mutation Types and Susceptibility to Fluoroquinolone

Table 3 shows the QRDR mutation sites and MIC distribution of various fluoroquinolone agents in *S epidermidis* strains (total 56 strains) isolated before and after antibiotic instillation. The wild-type strains without QRDR mutation and strains with a single-point mutation in the *parE* gene (Group I/a) were susceptible to all the fluoroquinolone agents including norfloxacin. On the other hand, 3 strains

with a single-point mutation in the *parC* gene (Group I/b) had statistically significantly higher MIC values than the wild-type strains for norfloxacin, ofloxacin, and levofloxacin ($P < .01$, Wilcoxon test). The MIC values for strains with a single-point mutation in the *gyrA* gene (Groups II-IV) were higher than in Group I and statistically significantly higher than those in the wild-type strains for all the fluoroquinolones ($P < .001$, Wilcoxon test). Furthermore, 2 strains with high resistance against levofloxacin (MIC \geq 64) were isolated. Both strains had double-point mutations in 2 genes; that is, *gyrA* (codons 84 and 88) and *parC* (codons 80 and 84) (Group V). Of the 56 strains detected, 36 were from the conjunctival sac before antibiotic instillation. Of the 36 conjunctival sac strains, 21 (58.3%) had gene mutations in at least 1 point of the QRDR.

Changes in Susceptibility Rates and Number of Quinolone-Resistance Determining Region Gene Mutations

Table 4 shows the changes in fluoroquinolone susceptibility rates and the number of QRDR gene mutations in the *S epidermidis* strains isolated before and after antibiotic instillation. In the levofloxacin group, the mean susceptibility rate to fluoroquinolones of the 15 strains isolated before antibiotic instillation was $61.3\% \pm 6.5\%$ (SD) and of the 15 strains isolated after instillation, $16.0\% \pm 5.3\%$; this was a statistically significant reduction (moxifloxacin and gatifloxacin, $P < .05$; levofloxacin, ofloxacin, and norfloxacin, $P < .01$, Wilcoxon test). Comparison of the changes in the number of QRDR gene mutations in the levofloxacin group showed statistically significant decreases in detection rates of the wild-type strains after instillation and significant increases in strains with multiple-point gene mutations ($P < .05$, Wilcoxon test). In the

Table 4. (Cont.)

Wild-Type	QRDR Mutation Group, n (%)					MRSE Strains, n (%)
	I	II	III	IV	V	
5 (33.3)	4 (26.7)	0	4 (26.7)	2 (13.3)	0	5 (33)
1 (6.7)	1 (6.7)	0	9 (60.0)	3 (20.0)	1 (6.7)	11 (73)
10 (47.6)	0	1 (4.8)	6 (28.6)	3 (14.3)	1 (4.8)	9 (43)
2 (40.0)	1 (20.0)	0	1 (20.0)	1 (20.0)	0	2 (40)

gatifloxacin group, there was no significant difference in the susceptibility rates and the number of QRDR gene mutations between the strains isolated before and after antibiotic instillation. Twenty-seven strains of MRSE carried the *mecA* mutation as follows: 1 strain (5.6%) in the wild-type group; 24 strains (80%), in Groups II, III, and IV; and 2 strains (100%) in Group V.

Table 5 shows the QRDR mutations and MIC values for the 9 eyes (9 patients: 6 levofloxacin group and 3 gatifloxacin group) in which *S epidermidis* was isolated both before and after antibiotic instillation. Of the patients, 5 (3 levofloxacin group and 2 gatifloxacin group) had differences in the *mecA* gene status between before antibiotic instillation and after antibiotic

Table 5. Analysis of gene mutations in 9 cases with *S epidermidis* detected both before and after antibiotic instillation.

Group/Pt ID	Age Sampling (Y) Time*	Mutation					MIC (µg/mL)									
		<i>gyrA</i>	<i>parC</i>	<i>parE</i>	<i>mecA</i>	GFLX	LVFX	OFLX	MFLX	NFLX	TOB	GM	EM	CP		
Levofloxacin																
OML827919	67	Before	—	—	Asn404Ser	—	0.125	0.125	0.25	≤0.06	≤2	≤0.06	≤0.06	0.25	4	
	67	After	Ser84Phe	Ser80Tyr	—	+	2	4	8	1	16	32	32	64	4	
SSR362980	79	Before	—	—	—	—	0.125	0.25	0.5	0.125	≤2	0.125	0.125	>64	4	
	79	After	Ser84Phe	Ser80Phe	—	+	1	4	8	1	16	≤0.06	≤0.06	0.25	4	
YKR845236	66	Before	—	—	—	—	≤0.06	0.125	0.25	≤0.06	≤2	≤0.06	≤0.06	0.25	4	
	66	After	Ser84Phe	—	Arg406His	—	4	8	32	4	>16	≤0.06	≤0.06	0.5	4	
YKL749800	68	Before	Ser84Phe	Ser80Tyr	—	+	1	2	4	0.5	8	16	32	64	64	
	68	After	Ser84Phe	Ser80Tyr	—	+	1	2	4	0.5	16	0.125	0.125	0.25	4	
KML801943	72	Before	Glu88Lys	Ser80Tyr	—	+	2	4	8	1	8	8	16	>64	4	
	72	After	Glu88Lys	Ser80Tyr	—	—	1	2	4	0.5	8	8	32	0.25	4	
MHL477110	83	Before	Ser84Phe	Ser80Ile	—	+	2	8	16	2	>16	0.125	0.125	0.25	4	
	83	After	Ser84Tyr	Ser80Phe + Asp84Ala	Asp397Tyr	+	2	8	16	2	>16	>64	0.125	0.25	4	
Gatifloxacin																
MER848057	83	Before	—	—	—	—	0.125	0.25	0.5	0.125	≤2	16	≤0.06	64	4	
	83	After	—	—	—	—	0.125	0.25	0.5	0.125	≤2	0.125	0.125	0.25	4	
MKR847501	73	Before	Ser84Tyr	Ser80Tyr	—	—	2	4	8	1	16	8	≤0.06	64	2	
	73	After	Ser84Tyr	Ser80Tyr	—	+	1	4	8	1	8	≤0.06	≤0.06	>64	4	
KER5003812	71	Before	Ser84Ile	Ser80Phe + Asp84Val	Asn404Ser	+	8	32	64	8	>16	≤0.06	≤0.06	0.25	64	
	71	After	—	—	Asn404Ser	—	≤0.06	0.125	0.25	≤0.06	≤2	≤0.06	≤0.06	0.25	4	

Ala=alanine; Arg=Arginine; Asn=asparagine; Asp=aspartic acid; CP=chloramphenicol; EM=erythromycin; GFLX=gatifloxacin; Glu=glutamic acid; GM=gentamicin; His=histidine; Ile=isoleucine; LVFX=levofloxacin; Lys=lysine;MFLX=moxifloxacin; MIC=minimum inhibitory concentration; NFLX=norfloxacin; OFLX=ofloxacin; Phe=phenylalanine; Pt ID=patient identification; Ser=serine; TOB=tobramycin; Tyr=tyrosine; Val=valine
*Before or after 3-week antibiotic instillation

instillation; therefore, the strains were considered genetically different between the 2 time points. The other 4 patients also indicate genetic difference of the strains before and after instillation. In 3 patients (2 levofloxacin group and 1 gatifloxacin group), there was a difference in QRDR mutation sites between before antibiotic instillation and after instillation (patient MHL477110) or in the MIC values for antibacterial agents other than fluoroquinolone (patients YKL74980 and MER848057). In the other patient (patient YKR845236), the QRDR mutations (wild-type versus *gyrA/parE* mutant) in the strains isolated before and after instillation and the MIC values of fluoroquinolones varied widely; however, the MIC values of antibacterial agents other than fluoroquinolone were almost the same.

DISCUSSION

Although the incidence of endophthalmitis after surgery is low, it may result in loss of eyesight once it develops. Thus, in Japan, there is a tendency for surgeons to prescribe long-term prophylactic use of fluoroquinolone eyedrops. A questionnaire sent to members of the Japanese Society of Cataract and Refractive Surgery in 2005¹⁷ found that the most common duration of antibacterial eyedrop use after surgery was 1 month (34%), followed by 3 months (33%), 2 months (21%), and 2 weeks (11%); that is, more than 88% of patients used antibacterial eyedrops for 1 month or longer as a preventive measure. In our study, the detection rate of bacteria after 3-week continuous instillation of gatifloxacin or levofloxacin was statistically significantly less than the rate before instillation; therefore, preventive administration of the eyedrops eradicated resident bacteria in the conjunctival sac. However, long-term preventive administration of antibacterial eyedrops may result in resident bacteria developing resistance to the agent. Okumura et al.¹⁸ report that 71% (24% in control group) of bacteria in eyes in which levofloxacin was used for 3 months or longer were resistant to various fluoroquinolone antibacterial agents, including levofloxacin. Our study also showed that the rates of resistance to various fluoroquinolone agents in the *S epidermidis* strains isolated after 3-week continuous instillation of levofloxacin reached 73.3% to 86.7% (versus 26.7% to 46.7% before instillation). These results suggest that long-term prophylactic instillation of levofloxacin may increase the risk for endophthalmitis as a result of the emergence of fluoroquinolone-resistant bacteria.

On the other hand, 2 factors that might cause such increases in resistance rates are (1) the induction of resistance at bacterial level (gene mutations) or (2) a microbial substitution to fluoroquinolone-resistant

strains. Based on the analysis of drug-resistance genes and MIC values of antibacterial agents in the strains isolated before and after instillation of the agents, most strains isolated were genetically different between the 2 time points and the increases in fluoroquinolone resistance rates after levofloxacin instillation were considered to be mainly due to the microbial substitution to fluoroquinolone-resistant strains. However, in patient YKR845236 in the levofloxacin group, the MIC values of all agents other than fluoroquinolone were almost identical before and after levofloxacin instillation and there was no *mecA* mutation in the strain detected before instillation or in the strain detected after instillation. Thus, there was no conclusive evidence of genetically different strains and the possibility of induction of resistance is undeniable.

In our study, the results in the gatifloxacin group were significantly different from those in the levofloxacin group. In the gatifloxacin group, the detection rates of *S epidermidis* after antibiotic instillation were significantly lower than before instillation ($P < .001$); there were no increases in the resistance rate to fluoroquinolone after instillation, unlike in the levofloxacin group, and bactericidal effects were observed after instillation in 1 patient with high-level fluoroquinolone-resistant strains detected before antibiotic instillation. These results suggest that gatifloxacin had better bactericidal effects against *S epidermidis* than levofloxacin and a lower risk for inducing microbial substitution to fluoroquinolone-resistant strains. Gatifloxacin is a fourth-generation fluoroquinolone that strongly inhibits 2 enzymes (DNA gyrase and topoisomerase IV) and has more potent bactericidal effects than levofloxacin, which mainly inhibits topoisomerase IV.¹⁹ These differences in bactericidal properties reflect the difference in results between the 2 study groups.

On the other hand, the MIC value of levofloxacin against resistant strains of *S epidermidis* was 0.5 µg/mL in Group I/b, which carried a single-point mutation in the *parC* gene ($n=3$), indicating significantly lower susceptibility than against the wild-type strains ($P < .01$). There was no difference in the MIC value of gatifloxacin between resistant strains of *S epidermidis* and wild-type strains. In Group III ($n=20$), which carried double-point mutations in the *gyrA + parC/parE* gene, the MIC value of levofloxacin was 2 to 8 µg/mL and of gatifloxacin, 1 to 4 µg/mL. In Group IV ($n=9$), which carried triple-point or quadruple-point mutations in the *gyrA + parC + parC/parE* gene, the MIC value of levofloxacin was 4 to 32 µg/mL and of gatifloxacin, 2 to 8 µg/mL. The results in Group III and Group IV suggest that susceptibility decreased as the number of mutations increased. Two strains carrying double-point mutations each in *gyrA* and *parC*

had a higher resistance to all 5 fluoroquinolone agents tested. Fukuda et al.²⁰ report that first-stage mutation occurred in the *grlA* gene subunit topoisomerase IV (*parC* in *S epidermidis*), second-stage mutation in the *gyrA* gene subunit of DNA gyrase, third-stage mutation again in the *grlA* gene, and fourth-stage mutation again in the *gyrA* gene, resulting in a total of 4 mutations in the *grlA* gene, *gyrA* gene, *grlA* gene, and *gyrA* gene. They also found that the mutation in the *gyrA* gene significantly affected the decreases in antibacterial activity of gatifloxacin and that high resistance developed, particularly for fourth-stage mutation carrying double-point mutations in the *gyrA* gene. In our study, there was also high-level fluoroquinolone resistance caused by double-point mutations in the *gyrA* gene, suggesting that the mechanism for acquisition of resistance in *S epidermidis* will be the same as that in *S aureus*, consistent with results in studies by Yamada et al.,¹³ Li et al.,²¹ Dubin et al.,²² and Barnard and Maxwell.²³ Furthermore, 96% of the 27 MRSE strains had mutations in the *gyrA* gene and were resistant to all 5 fluoroquinolones tested.

In addition, 44% of the 36 strains detected before antibiotic instillation showed resistance to all 5 types of fluoroquinolones tested; 1 strain was highly resistant, which indicates that the strategies for the prevention of antibiotic resistance are important. In our study, there was no evidence that 3-week preventive instillation of levofloxacin directly induced mutations of the resistant genes. However, surgeons should choose an antibacterial agent that has a low risk for developing resistance as well as high levels of antibacterial activity, ocular distribution, and safety during the perioperative period. Further study with larger groups of patients is needed to determine the appropriate dosing periods and methods to prevent antibiotic resistance.

In conclusion, ocular instillation of fluoroquinolones significantly decreased the detection rates of bacteria in the conjunctival sac during the perioperative period in eyes having cataract surgery. However, results suggest that 3-week continuous instillation of levofloxacin affects indigenous bacterial flora and may induce microbial substitution to fluoroquinolone-resistant strains. No induction of microbial substitution was seen with gatifloxacin.

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First author:
Masaru Miyanaga, MD

*Miyata Eye Hospital, Miyazaki, and
Department of Ophthalmology and
Visual Science, Tokyo Medical
and Dental University Graduate School
of Medical and Dental Sciences,
Tokyo, Japan*

鳥取大学における若年者の角膜感染症の現状

池田欣史 稲田耕大 前田郁世 大谷史江 清水好恵 唐下千寿
石倉涼子 宮崎 大 井上幸次

鳥取大学医学部視覚病態学

Current Status of Infectious Keratitis in Students at Tottori University

Yoshifumi Ikeda, Kohdai Inata, Ikuyo Maeda, Fumie Otani, Yoshie Shimizu, Chizu Toge,
Ryoko Ishikura, Dai Miyazaki and Yoshitsugu Inoue

Division of Ophthalmology and Visual Science, Faculty of Medicine, Tottori University

近年、角膜感染症の若年化が問題となっており、重症例が増加している。今回、当院での若年者の角膜感染症の現状を報告する。2004年1月～2008年2月に入院加療した角膜感染症患者のうち、発症年齢が30歳未満であった13例14眼を対象に、コンタクトレンズ（CL）使用状況・治療前後の視力・起炎菌について検討した。発症年齢14～28歳。男性5例5眼、女性8例9眼。11例で頻回交換ソフトCL、1例でハードCLを使用していた。初診時視力が0.5以下は9例10眼、0.1以下は6例7眼であった。治療後の最高視力は比較的良好であったが、0.04にとどまった例が1例、治療的角膜移植施行例が1例あった。推定起炎菌はアcantアメーバ4眼、細菌10眼であり、分離培養で確認されたものは緑膿菌2眼、黄色ブドウ球菌2眼、セラチア1眼、コリネバクテリウム1眼であった。若年者角膜感染症でも特に重症例が増加しており、早期の的確な診断・治療の重要性とともにCL装用における感染予防策の必要性が示唆された。

We report the current status of infectious keratitis in students at Tottori University. We reviewed the records of 14 eyes of 13 patients below 30 years of age among those treated for infectious keratitis at Tottori University Hospital from January 2004 to February 2008. Patients were evaluated as to method of contact lens use, visual acuity before and after treatment and microbiological etiology. The age distribution ranged from 14 to 28 years. Of the 13 patients, 11 used frequent-replacement soft contact lenses and 1 used hard contact lenses. At initial visit, the visual acuity of 10 eyes (9 patients) was less than 20/40, and that of 7 eyes (6 patients) was less than 20/200. Better visual acuity was noted after treatment in all but 2 cases, 1 of which had poor visual acuity, the other having received penetrating keratoplasty. The presumed causative agents were *Acanthamoeba* species in 4 eyes and bacteria in 10 eyes. Some of these were proven by culturing to be *Pseudomonas aeruginosa* (2 eyes), *Staphylococcus aureus* (2 eyes), *Serratia marcescens* (1 eye) and *Corynebacterium* (1 eye). Reports of younger cases of contact lens-related severe infectious keratitis have been on the increase. The importance of early proper diagnosis and treatment is indicated, as is the need for strategy in preventing contact lens-related infectious keratitis.

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Key words : 角膜感染症, 若年者, アcantアメーバ, 緑膿菌, コンタクトレンズ, infectious keratitis, young generation, *Acanthamoeba*, *Pseudomonas aeruginosa*, contact lens.

はじめに

近年、角膜感染症の若年化が問題となっており、2003年に行われた感染性角膜炎の全国サーベイランス¹⁾においても、年齢分布は二峰性を示し、60歳代以外に20歳代にもピークを生じていた。さらに、若年層ではコンタクトレンズ（CL）使用中の感染が9割以上を占め、わが国の感染性角膜

炎の発症の低年齢化の大きな原因として、CLの使用がある^{1,2)}。この10数年間に、使い捨てソフトCL（DSCL）や頻回交換ソフトCL（FRSCL）の登場により、装用者は急激に増加し、CLの使用状況は大きく変わっている。約1,500万人を超えるといわれるCL装用者がいるなか、近年、CL使用の低年齢化が起り、10歳代、20歳代の若者の使用が増

〔別刷請求先〕 池田欣史：〒683-8504 米子市西町36-1 鳥取大学医学部視覚病態学

Reprint requests : Yoshifumi Ikeda, M.D., Division of Ophthalmology and Visual Science, Faculty of Medicine, Tottori University, 36-1 Nishi-cho, Yonago, Tottori 683-8504, JAPAN

加している。今後ますます若年者のCL原因の感染性角膜炎が増加すると予想される。啓発活動も含めた意味で、今回筆者らは、鳥取大学における角膜感染症のうち、特に30歳未満の若年者を対象に、CLの使用状況・起炎菌・初診時視力・治療後視力などについて検討し、予防策について考察したので報告する。

I 対象および方法

対象は、鳥取大学医学部附属病院眼科において2004年1月から2008年2月までの約4年間に、入院加療を要した角膜感染症117症例（ヘルペス感染を含む）のうち、30歳未満

の13例14眼（男性5例5眼、女性8例9眼）である。

117症例に対する若年者の割合と若年者全例の年齢・性別・発症から当院紹介までの日数・初診時視力・治療後最高視力・起炎菌・前医での治療の有無・ステロイド使用歴の有無・CLの種類や使用状況についての検討を行った。

II 結 果

角膜感染症117症例全体の若年者の年代別の割合を図1に示す。2004年は5.9%、2005年は0%、2006年は9.5%と低かったが、2007年には21.4%と上昇し、2008年には1月、2月のみで、42.9%と高かった。なお、30歳未満13例

表1 全症例(13例14眼)の内訳

症例	年齢(歳)	性別	患眼	発症から当院初診までの日数	起炎菌	初診時視力	治療後最高視力	前医での治療
1	14	女	右	42	アカントアメーバ	0.8	1.2	あり(ステロイド)
2	17	女	右	4	細菌	0.8	1.2	なし
3	22	男	右	11	細菌	0.09	1.0	なし ^{注1}
4	15	女	左	3	セラチア	0.9	1.2	あり
5	28	女	右	14	アカントアメーバ	0.2	1.0	あり(ステロイド)
6	21	男	左	22	アカントアメーバ	0.4	1.5	あり
7	19	男	左	2	緑膿菌	0.5	1.0	あり(ステロイド)
8	16	女	左	3	細菌	手動弁/30cm	0.9	あり
9	28	男	左	3	細菌	1.2	1.5	なし
10	24	女	右	4	黄色ブドウ球菌	0.03	0.9	なし
	24	女	左	4	黄色ブドウ球菌	0.01	1.2	なし
11	18	女	左	33	アカントアメーバ	指数弁/15cm	1.2 ^{注2}	あり(ステロイド)
12	16	女	左	4	緑膿菌	手動弁/10cm	0.04	あり
13	23	男	左	2	コリネバクテリウム	0.03	0.6	なし

注1: 知的障害およびアレルギーあり、注2: 治療の全層角膜移植術施行後の視力。

症例	CLの種類	CL誤使用の有無
1	FRSCL(1M)	無
2	FRSCL(2W)	有(就寝時装用)
3	なし	
4	FRSCL(2W)	無
5	FRSCL(2W)	無
6	FRSCL(2W)	無
7	FRSCL(1M)	有(使用期限超え, 消毒不適切)
8	FRSCL(1M)	有(連続装用, 消毒不適切)
9	FRSCL(2W)	有(連続装用, 消毒不適切)
10	HCL	有(消毒不適切)
	HCL	有(消毒不適切)
11	FRSCL(1M)	有(消毒不適切)
12	FRSCL(1M)	有(就寝時装用, 消毒不適切)
13	FRSCL(2W)	有(連続装用, 消毒不適切)

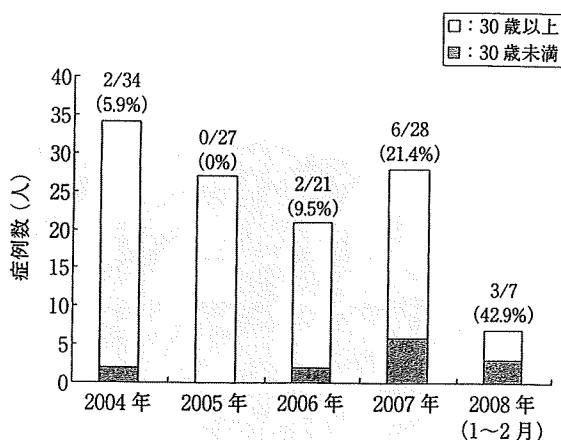


図1 鳥取大学における角膜感染症の若年者の割合の推移 (13/117症例)

上段の数値は年別の若年者数/全症例数(若年者の割合)を示す。

14眼の内訳(表1)は、男性5例5眼、女性8例9眼で、発症年齢は14~28歳(平均20±5歳)であり、10歳代が7例と半数近くを占めていた。初診時矯正視力は0.5以下が9例10眼で、0.1以下が6例7眼と重症例が目立った。治療後最高視力は0.6以上が11例12眼で、1.0以上が9例9眼と比較的良好であった。しかし、最終的に1例は治療的角膜移植術を行い、1例は最終視力0.04と視力不良であった。症例3は知的障害とアレルギー性結膜炎があり、角膜潰瘍を生じた例で、それ以外は、全例CL使用者で、11例にFRSCL、1例にハードCL(HCL)の装用を認めた。なお、CLの洗浄、擦り洗い、CLケースの定期交換などの適切な消毒を行っていない症例や、CLの使用期限を守らない、就寝時装用、連続装用など不適切なCL装用状況が8例9眼で認められた。

推定起炎菌は細菌が10眼、アcantアメーバが4眼で、細菌10眼のうち6眼が分離培養できたが、アcantアメーバは分離培養できておらず、検鏡にて確認した。HCL使用の1例2眼で黄色ブドウ球菌が検出され、FRSCLでは緑膿

菌が2眼、セラチアとコリネバクテリウムが1眼ずつ検出された。なお、セラチアは主要な細菌性角膜炎の起炎菌であり¹⁾、病巣部より分離培養できたことから起炎菌と判断した。コリネバクテリウムは結膜の常在菌であり、角膜での起炎性は低い。この例では病巣部よりグラム陽性桿菌を多量に認め、分離培養結果も一致し、好中球の貪食像も認められたため起炎菌とした。

また、発症から当院へ紹介されるまでの日数は平均11日であるが、アcantアメーバ角膜炎は平均28日と約1カ月かかっていた。さらに、前医で治療を受けた8例中半数の4例にステロイドの局所または全身投与がなされており、そのうち、3例がアcantアメーバであった。

ここで重症例の症例11と12の経過を報告する。

〔症例11〕18歳、女性。

現病歴：平成19年12月7日左眼眼痛と充血を主訴に近医を受診し、角膜上皮障害にてSCL装用を中止し、抗菌薬、



図2 症例11：初診時左眼前眼部写真(平成20年1月8日) 角膜中央に円形の角膜浸潤と毛様充血を認め、角膜擦過物よりアcantアメーバシストを認めた。VS=15cm/指数弁。

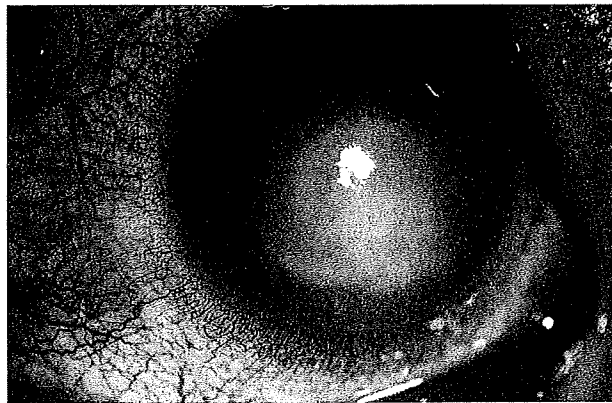


図3 症例11：左眼前眼部写真(平成20年1月22日) ステロイド中止後に角膜混濁は悪化した。



図4 症例11：左眼前眼部写真(平成20年3月12日) 2月26日に治療的全層角膜移植術を施行した。VS=(1.0)。



図5 症例11：ホスト角膜の切片(ファンギフロラY®染色) ホスト角膜にアcantアメーバシスト(矢印)が散在した。

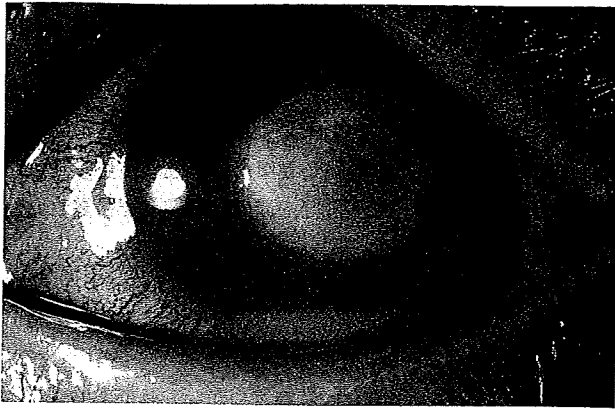


図 6 症例 12：初診時左眼前眼部写真 (平成 20 年 2 月 10 日)
角膜中央に輪状膿瘍と前房蓄膿を認めた。VS=10cm/手動弁。

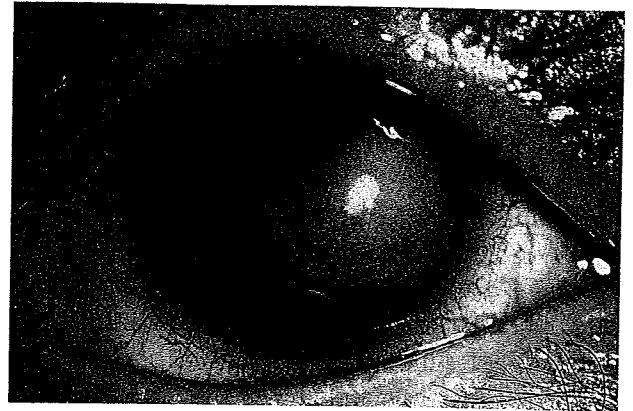


図 7 症例 12：左眼前眼部写真 (平成 20 年 3 月 11 日)
最終的に角膜中央に混濁を残して治癒した。VS=0.04 (n.c.).

角膜保護薬の点眼にて経過観察されていた。12月26日に、角膜後面沈着物が出現し、ヘルペス性角膜炎と診断され、ステロイド点眼・内服を追加されるも、改善しないため、平成20年1月7日に鳥取大学医学部附属病院眼科を紹介となった。なお、CLは1日15時間以上使用し、CLの消毒はマルチパーパスソリューション (multi-purpose solution : MPS) を使用し、週に2~3回しか消毒しておらず、CLケースもほとんど交換していなかった。

初診時所見：左眼視力は15cm指数弁で、角膜中央に円形で境界不明瞭な角膜浸潤と角膜浮腫および上皮欠損を生じており、特に下方では潰瘍となっていた (図2)。

治療：角膜擦過物のファンギフローラ Y[®] 染色にてアカントアメーバシストが確認されたため、アカントアメーバ角膜炎との診断で、ステロイド中止のうえ、角膜搔爬に加え、イトラコナゾール内服、0.02%クロルヘキシジン・フルコナゾール・1%ポリコナゾール点眼、オフロキサシン眼軟膏の三者併用療法を開始した。ステロイド中止後、角膜混濁は悪化し (図3)、ピマリシン点眼に変更するも、治療に反応せず、角膜混濁もさらに悪化したため、平成20年2月26日に治療的全層角膜移植術を施行した (図4)。術後、再発を認めず、矯正視力1.2と安定した。なお、角膜移植時に切除した宿主角膜片の病理検査でのファンギフローラ Y[®] 染色にてアカントアメーバシストが認められた (図5)。

〔症例12〕16歳、女性。

現病歴：平成20年2月7日からの左眼眼痛にて翌日近医を受診し、角膜上皮剝離の診断にて点眼加療された。2月9日角膜混濁が出現し、抗菌薬の点眼・内服を追加されるも改善せず、2月10日に、角膜潰瘍と前房蓄膿が出現したため、同日、鳥取大学医学部附属病院眼科を紹介となった。なお、CLは1日16時間以上使用し、毎日MPSにて消毒はしていたが、擦り洗いは週に1回程度であり、ときどき装着して就寝することもあった。

初診時所見：左眼視力は10cm手動弁で、角膜中央に輪状膿瘍、角膜潰瘍を認め、さらに、前房蓄膿を伴っていた (図6)。

治療：急速な進行と臨床所見から、緑膿菌感染と判断し、イミベネムの点滴、マイクロマイシン点眼、オフロキサシン眼軟膏にて治療を開始した。角膜擦過物の塗抹鏡検にてグラム陰性桿菌を認め、後日培養にて緑膿菌を検出した。治療にはよく反応し、翌日には前房蓄膿は消失し、角膜潰瘍は徐々に軽快した。しかし、最終的に角膜中央に混濁を残して治癒し (図7)、最終視力は0.04と良好な視力を得られなかった。

III 考 按

2003年の角膜サーベイランス¹⁾での年齢分布のグラフにおけるCL非使用の感染性角膜炎の年齢分布は、1972年から1992年にかけての報告を集計した金井らの論文にみられる60歳代にピークをもつ感染性角膜炎の年齢分布²⁾とあまり変わっていない。このことから、使用しやすいSCL (DSCL, FRSCl) の登場により、CL使用者 (おもに若年者) が急激に増加し、その安易な使用によって、CL使用者の感染性角膜炎が上乘せされた形となり、10歳代、20歳代にもう1つのピークが生じたとみてとれる。さらに、10歳代の感染はほぼ100%CL関連であり、20歳代もCL使用が89.8%であったと報告されている。しかも、20歳代の割合が60歳代を上回る状況となっている^{1,3)}。20歳代のCL関連の感染の増加はCL使用割合がその年代に多いためと推察されるが、10年後、20年後には、これがさらに上の年代へと拡大していく危険性ははらんでいる。

今回、筆者らは30歳未満の若年者を対象にデータ解析を行ったが、CL関連が92.3%であり、レンズの不適切な使用によると思われる感染が大半を占めていた。若年者の失明は以後のQOL (quality of life) を大きく損なうため、早期発見と適切な早期治療が必須である。

今回の4例のアカントアメーバ角膜炎では、症状発生から適切な治療までに2週間から約1カ月半が経過しており、そのうち3例はヘルペス感染との診断にて、ステロイド加療がされており、最終的に1例に治療的角膜移植術を施行した。そのため、眼科医の早期の適切な診断と治療が重要となってくる。CL装用者の場合には、ヘルペスと思われる上皮・実質病変が存在しても、ヘルペスよりもアカントアメーバの感染をまず念頭に置き、前房内炎症が生じていても、ステロイド投与の開始については慎重に考慮する必要がある。また、SCL装用による両眼性アカントアメーバ角膜炎も報告⁴⁻⁶⁾されており、診断、治療が困難な場合には、早急に角膜疾患の専門家のいる病院へ紹介することが重要である。

一方、細菌感染の場合は、アメーバと異なり進行が速いため、症状発生から紹介までは約4日と短く、抗菌薬類回点眼・点滴を含めた早期治療が大切となる。細菌性角膜炎ではアカントアメーバ角膜炎よりも診断が容易であるが、緑膿菌では進行が速く、重症化するため、症例12のように治療しても社会的失明の状態となる。

若年者の角膜感染による失明を防止するには、CL関連感染角膜炎の存在とその予防策について、若年のCL装用者に十分知識をもってもらうことが重要である。さらに、CLケースの洗浄や交換が行われていなかった例や、インターネットにて購入した例もあり、眼科専門医の適切な指導のもと、CLの処方のみならず、洗浄液も処方箋による販売が行われる体制が望ましいのではないかとと思われる。現にシリコンハイドロゲルレンズにおいて、洗浄液との相性があわず、上皮障害をひき起こす場合もあり⁷⁻⁹⁾。眼科医がしっかりとCL装用者のCL使用状況を把握するうえでも、CLと洗浄液とを同時に眼科医が処方できるようにすべきではないかと考える。今回の症例に使用されたSCLはすべてFRSCLであり、適切に使用した症例でも、感染をひき起こしていることを考慮すると、感染予防という点では、現行のMPSでは限界があり、煮沸消毒に及ばないと考えられる¹⁰⁾。また、適切に使用すれば外部からの細菌の持ち込みがないという点において、DSCLへの変更も留意する必要がある。

一番の問題点はCL使用者がCLの利便性のみにとらわれ、CLの危険性に関して無知であることである。これは、各CLメーカーの宣伝の影響が大きいと考える。SCLのパンフ

レットには注意事項は裏面に小さな字で記載されているのみで、内容も「調子よく使用し、異常がなくても、定期検査は必ず受けてください」・「少しでも異常を感じたら、装用を中止し、すぐに眼科医の診察を受けてください」といった、当たり障りのない文句が書かれている。適切な使用を怠ると、感染性角膜炎になり、失明する可能性があることを説明し、実際の感染性角膜炎の写真を掲載するなどして、視覚的に訴えていく必要がある。タバコの外箱に記載されている肺癌の危険性と同様に、常時手にとるCLのパッケージへも失明の可能性ありとの記載があると、CL装用者への啓発となると考える。

今後も、若年性CL関連角膜炎感染症は増加していくと推察されるため、CL装用指導と角膜炎感染症発症についてのCL装用者への啓発の重要性を改めて認識する必要がある。

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コリネバクテリウムが起炎菌と考えられた感染性角膜炎 の1例

稲田耕大*¹ 前田郁世*¹ 池田欣史*¹ 宮崎 大*¹ 井上幸次*¹ 江口 洋*²
塩田 洋*² 桑原知巳*³

*¹ 鳥取大学医学部視覚病態学講座 *² 徳島大学大学院ヘルスバイオサイエンス研究部視覚病態学分野
*³ 徳島大学大学院ヘルスサイエンス研究部分子細菌学分野

A Case of Infectious Keratitis Caused by *Corynebacterium*

Koudai Inata¹⁾, Ikuyo Maeda¹⁾, Yoshifumi Ikeda¹⁾, Dai Miyazaki¹⁾, Yoshitsugu Inoue¹⁾, Hiroshi Eguchi²⁾,
Hiroshi Shiota²⁾ and Tomomi Kuwahara³⁾

¹⁾ Division of Ophthalmology and Visual Science, Faculty of Medicine, Tottori University, ²⁾ Department of Ophthalmology and Visual Neuroscience, Institute of Health Biosciences, The University of Tokushima Graduate School, ³⁾ Department of Molecular Bacteriology, Institute of Health Biosciences, The University of Tokushima Graduate School

コリネバクテリウムが起炎菌と考えられた感染性角膜炎の1例を経験したので報告する。症例は23歳、男性。頻回交換ソフトコンタクトレンズを1週間連続装用していた。主訴は左眼の眼痛、羞明、視力低下。矯正視力は0.01であった。左眼角膜中央に大きさ2mm程度の不整形の上皮欠損とその辺縁の淡い浸潤を認め、小さい白色の角膜後面沈着物および角膜浮腫・Descemet膜皺襞、高度の毛様充血を伴っていた。角膜擦過物の塗抹検鏡にて多数のグラム陽性桿菌を認め、擦過培養にて *Corynebacterium mastitidis* が分離された。コリネバクテリウムは免疫抑制状態でバイオフィルムを形成したような特殊なケースでは角膜炎の起炎菌となりうると思われているが、今回のように通常の感染性角膜炎でも起炎菌となりうる可能性が示唆された。コリネバクテリウム感染と判断する際に塗抹検鏡でのグラム陽性桿菌の検出が重要と考えられた。

We report a case of infectious keratitis caused by *Corynebacterium*. The patient, a 23-year-old male, had used frequent replacement soft contact lenses with overnight wear for 1 week. He complained of pain, photophobia and reduced vision in his left eye; his left visual acuity was 0.01. Slit-lamp examination revealed a 2mm irregular epithelial defect, with mild infiltration of the defect margin, in the center of the left cornea, together with small white keratic precipitates, corneal edema, Descemet's folds and severe ciliary injection. Numerous Gram-positive rods were observed in a smear from the focus, and *Corynebacterium mastitidis* was isolated. Although it is thought that *Corynebacterium* can cause keratitis only in special cases, such as biofilm formation in immunosuppressed condition, the present case indicates that *Corynebacterium* can be a causative agent in cases of the usual infectious keratitis. This case also indicates that the detection of Gram-positive rods is a key to the diagnosis of *Corynebacterium* infections.

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Key words : コリネバクテリウム, 感染性角膜炎, グラム陽性桿菌, コンタクトレンズ, *Corynebacterium*, infectious keratitis, Gram-positive rods, contact lens.

はじめに

コリネバクテリウムは結膜嚢に常在菌叢を形成している¹⁾が、その病原性は低く、角膜炎患者で分離されることがあっても実際の起炎性については議論がある。免疫抑制状態でバ

イオフィルムを形成したような特殊なケースでは角膜炎の起炎菌となりうると思われている^{2~10)}が、通常の感染性角膜炎の起炎菌としてはあまり考慮されていない¹¹⁾。今回、免疫抑制状態にない患者においてコリネバクテリウムが起炎菌と

〔別刷請求先〕 稲田耕大：〒683-8504 米子市西町36-1 鳥取大学医学部視覚病態学講座

Reprint requests : Koudai Inata, M.D., Division of Ophthalmology and Visual Science, Faculty of Medicine, Tottori University, 36-1 Nishimachi, Yonago-shi 683-8504, JAPAN

考えられた1例を経験したので報告する。

I 症 例

患者：23歳，男性。

初診：2008年2月17日。

主訴：左眼眼痛，羞明，視力低下。

既往歴：特記すべき事項なし。

現病歴：2週間頻回交換ソフトコンタクトレンズをインターネットで購入し，1週間連続装用していた。2008年2月15日，仕事中にコンクリートの薄い溶解液が左眼に飛入したが市販の点眼薬で経過をみていた。2月16日より左眼眼痛，羞明出現。2月17日より左眼視力低下をきたしたため同日鳥取大学医学部附属病院救急外来を受診した。

初診時所見：左眼視力は0.01 (n.c.)，眼圧は20mmHgであった。高度な睫毛内反のため睫毛の角膜への接触を認め

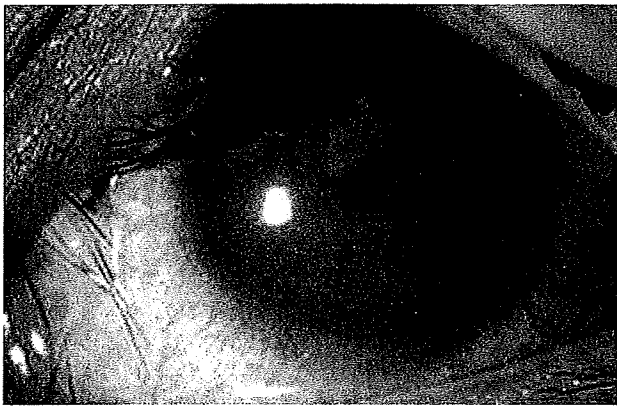


図1 初診時前眼部写真

2mm程度の不整形の上皮欠損とその辺縁の淡い角膜浸潤を認め，病巣部からコリネバクテリウムが分離された。

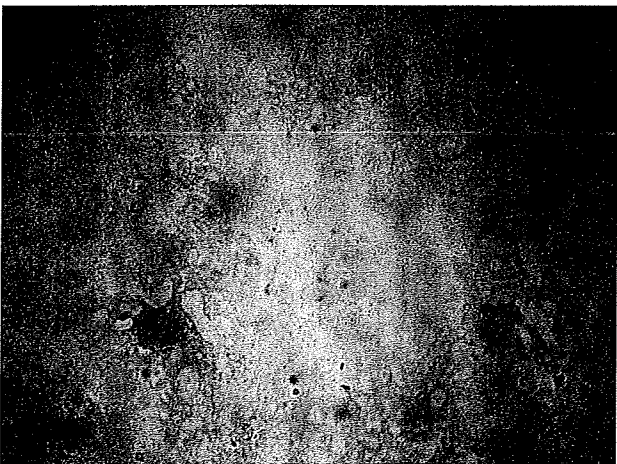


図2 角膜擦過物の塗抹検鏡

好中球に加えグラム陽性桿菌を認める。各視野で認められる菌体は多くないが，塗抹の広い範囲にわたって認められた。

表1 本症例のコリネバクテリウムの薬剤感受性 (MIC)

シプロフロキサシン	0.125	エリスロマイシン	<0.016
ノルフロキサシン	1	クロラムフェニコール	4
レボフロキサシン	0.064	ドキシサイクリン	0.5
ガチフロキサシン	0.016	イミベネム	0.008
モキシフロキサシン	0.016	セフトリアキソン	0.125
トブラマイシン	0.064	バンコマイシン	0.5
ゲンタマイシン	<0.064	テイコプラニン	0.5

単位 (μg/ml)

た。角膜中央に2mm程度の不整形の上皮欠損とその辺縁の淡い角膜浸潤を認め，角膜浮腫およびDescemet膜皺裂を呈していた。小さい白色の角膜後面沈着物と軽度の前房細胞も認めた (図1)。

経過：2月17日，感染性角膜炎の診断にて眼脂および角膜擦過物を採取し，レボフロキサシンおよびセフメノキシムの1時間ごとの点眼を開始した。2月18日，角膜浸潤の悪化を認め，セフトラジジム2g点滴を開始。角膜擦過物の塗抹検鏡にてグラム陽性桿菌を多数検出した (図2)。2月19日より入院。睫毛抜去を施行し，以後もレボフロキサシンおよびセフメノキシム点眼，セフトラジジム点滴を継続した。初診時の眼脂より *Corynebacterium* spp. および *Staphylococcus epidermidis*，角膜擦過物より *Corynebacterium* spp. が分離された。その後は順調に軽快し，3月2日退院となった。

後日，角膜擦過物から分離されたコリネバクテリウムの遺伝子解析を徳島大学にて行いrRNAの塩基配列を調べたところ，結膜常在菌として圧倒的多数を占める *C. macginleyi* ではなく，比較的少ない *C. mastitidis* 近縁種であることが判明した。また，その薬剤感受性は表1のごとくであり，フルオロキノロン系も含めて多くの抗菌薬に良好な感受性を示した。

II 考 按

コリネバクテリウムは結膜の常在菌として知られているが，その病原性は低く，角膜炎の起炎菌としてもあまり考慮されていない。しかし近年になって，コリネバクテリウムは結膜炎および眼瞼結膜炎をひき起こすことが報告され¹²⁻¹⁴⁾，免疫抑制状態でバイオフィルムを形成したような特殊なケースでは角膜炎の起炎菌にもなりうると認識されるようになった²⁻¹⁰⁾。しかし，今回筆者らが経験したような，免疫抑制状態にない患者においてコリネバクテリウムが起炎菌と考えられた症例の明確な報告はあまりなされていない。本症例において，結膜囊の培養では表皮ブドウ球菌とコリネバクテリウムが分離されているが，角膜擦過物からはコリネバクテリウムのみが分離された。また，角膜擦過物の塗抹検鏡でグラム陽性桿菌を認め，その結果が一致していることは本症例がコリネバクテリウム感染であることを裏付けている。病原性が

低いコリネバクテリウムによる感染としては強い角膜浮腫など初診時の所見が強すぎるが、これは薄いコンクリート溶解液飛入による炎症を伴っていたためと考えたと説明がつくと思われる。コリネバクテリウムが角膜炎をひき起こした機序としては、睫毛内反やコンタクトレンズの誤使用に伴い常に角膜上皮が傷害されていた可能性が高く、病原性の低い菌であっても角膜で増殖する下地を形成していたと考えられる。

今回の分離菌が *C. macginleyi* ではなく、結膜常在菌として比較的少ない *C. mastitidis* であったことは、外傷に伴って外部から *C. mastitidis* が飛入した可能性が考えられる。あるいは、従来から頻回交換レンズの連続装用、睫毛内反などがあり、結膜常在菌として少数ながら認められるとの報告がある *C. mastitidis* が眼表面に常在しており、さらに外傷が加わって角膜感染となった可能性も考えられる。残念ながら、結膜嚢から分離されたコリネバクテリウムは分離後すぐに廃棄されたため、結膜嚢にいる菌も *C. mastitidis* かどうかの確認はとれなかった。

本症例のように、コリネバクテリウムは通常の感染性角膜炎でも起炎菌となる可能性が示唆され、これまでも軽症で比較的容易に治癒したものや、起炎菌不明とされてきた角膜炎のなかにコリネバクテリウムによってひき起こされたものが含まれていた可能性も考えられる。本症例で分離されたコリネバクテリウムはフルオロキノロン系抗生物質に対し感受性を認めたが、Eguchiら¹⁵⁾は、わが国におけるフルオロキノロン系点眼薬の使用量の増加により、近年眼科領域でフルオロキノロン系抗菌薬に対して耐性を示すコリネバクテリウムの報告が増加していると指摘している。このことを考慮すると、抗菌薬に対する耐性を獲得したコリネバクテリウムによる難治性の角膜炎が増加する可能性も危惧される。コリネバクテリウムは結膜常在菌であるため、外眼部感染症患者において分離されても起炎菌であるかどうかの判断はむずかしい。コリネバクテリウム感染と判断するには塗抹検鏡でのグラム陽性桿菌の検出が重要と考えられる。

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