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Haemophilus influenzae Adherent to Contact Lenses Associated with Production of Acute Ocular Inflammation

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Ten episodes of adverse responses to contact lens wear, including contact lens-induced acute red eye (CLARE), in which *Haemophilus influenzae* was isolated from contact lenses and/or from one of the external ocular sites at the time of the event, are described. All episodes occurred in patients wearing disposable hydrogel lenses on a 6-night extended-wear schedule. Two of the patients had recurrent episodes. *H. influenzae* was usually isolated in large numbers, and other bacteria or fungi colonizing the contact lens or the external ocular surface were usually present in low numbers. Those patients who were colonized with *H. influenzae* were more than 100 times as likely to have had a CLARE or infiltrative response than those subjects who were not colonized with this bacterium. *H. influenzae* colonization of the contact lens and eye may be subsequent to colonization of the nasopharynx because four of the seven patients presented with fever at the time of the event, with concurrent upper respiratory tract infection. Contact lens wearers should be made aware of the potential risk of CLARE associated with the wearing of contact lenses for extended periods during and subsequent to upper respiratory tract infection.

Haemophilus influenzae is a major human pathogen, with various types being associated with meningitis, otitis media, and ocular inflammatory diseases and sequelae including conjunctivitis, keratoconjunctivitis, endophthalmitis, and Brazilian purpuric fever. Of the ocular inflammatory responses, by far the most serious is Brazilian purpuric fever, which is manifested several weeks after an acute attack of conjunctivitis and which leads to massive vascular collapse and death of the patient. Brazilian purpuric fever is produced by a clone of a subspecies of *H. influenzae* named *H. influenzae* subsp. *aegyptius* and occurs in children (4). So far outbreaks of this disease have been found only in Brazil and Australia (4, 14, 15). Less serious, but far more common, is acute conjunctivitis produced by other types of *H. influenzae*. Bacterial infection, particularly with *H. influenzae*, causes 80% of all cases of conjunctivitis in children (12, 24). There is evidence that *H. influenzae* can cause relapsing conjunctivitis (11), and people may harbor *H. influenzae* in their conjunctival sacs (21) but be asymptomatic.

The resident microbiota of the human eye is chiefly gram-positive staphylococci and corynebacteria (16, 22), with the source of these bacteria being the normal skin microbiota. These bacteria do not normally cause overt signs of disease, and their levels are controlled in the eye by powerful ocular defense mechanisms such as eye blinking, epithelial cell desquamation, and the antibacterial tear proteins lysozyme, secretory immunoglobulin A, and lactoferrin. Contact lens wear has been found to increase the risk of corneal infection, particularly during the extended wear of hydrogel lenses (1, 17, 19). The principal organisms associated with corneal disease are *Pseudomonas* spp. and other gram-negative bacteria (6, 8). The ocular inflammatory disease contact lens-induced acute red eye (CLARE) has been shown to be associated with the contamination of contact lenses with large numbers of *Pseudomonas aeruginosa* and *Serratia marcescens* isolates (10).

CLARE is characterized by pain, irritation, increased lacrimation, lid swelling, and conjunctival redness, which occur during sleep, with the subject being awakened in the early morning by the irritation and pain or noticing pain and irritation immediately upon awakening. On examination of the affected eyes, there is usually severe conjunctival hyperemia and limbal injection. Diffuse and focal subepithelial and anterior stromal infiltrates in the cornea are seen with a slit-lamp biomicroscope. Another adverse reaction to contact lens wear is corneal infiltration by inflammatory cells. This can also be produced by *P. aeruginosa* or *S. marcescens* (10). This reaction is differentiated from CLARE because subjects may be asymptomatic and the condition is not restricted to the overnight use of contact lenses or the ocular surface.

Here we report on the finding that at the time of acute inflammatory events in the cornea, either a contact lens-induced red eye or corneal infiltration, *H. influenzae* can be isolated in large numbers from the contact lens.

MATERIALS AND METHODS

The contact lens wearing populations. Two hundred forty-one neophyte contact lens wearers were enrolled in the study, prescribed to wear soft contact lenses on a daily basis for a 2-week adaptation period, and then moved into an extended-wear modality (6 nights of wear). All subjects were free of ocular and systemic disease, had no previous ocular surgery, and required visual correction for low refractive errors only. Informed consent was obtained, and subjects underwent ocular examination, including a detailed history and slit-lamp biomicroscope examination prior to lens fitting. All subjects underwent routine ocular examinations, including slit-lamp biomicroscopy and fluorescein staining, at the baseline, after 2 weeks of daily wear of lenses, and subsequently, after 1, 3, 6, 9, and 12 months of wear. Also at these visits, the subjects' contact lenses and ocular swabs (see below) were sent for routine microbiological analysis.

Subjects presented at the clinics at the time of a CLARE or infiltrative reaction. Prior to ocular examination, the contact lenses were removed and sent for microbiological analysis. The patients' eyes were examined with a slit-lamp biomicroscope with fluorescein instillation. The patients also completed a detailed questionnaire, in which questions regarding predisposing factors that may have contributed to the production of CLARE were asked. Such questions

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TABLE 1. Clinical details of patients at the time of the inflammatory reaction

Subject identification	Episode no.	Diagnosis	Length of contact lens wear prior to event (mo)	Eye affected[a]	Lens age at time of event (days)	Conjunctival injection	Extent and type of corneal infiltration	Conjunctival hemorrhage[b]	Time to resolution (days)	Associated symptoms
LVPEI 42	1	CLARE	12	OS	6	Bulbar and limbal; severe	11 to 2 o'clock; diffuse and focal (<0.5 mm in diameter)	N	6	*H. influenzae* isolated from conjunctiva 2 months prior[c]
	2	CLARE	13.75	OD	2	Bulbar and limbal; severe	3 to 8 o'clock; diffuse and focal (<0.5 mm)	N	5	Prior CLARE
	3	Infiltrates	14	OS	6	Bulbar and limbal; moderate	3 and 1 to 7 o'clock; diffuse and focal (<0.5 mm)	N	5	Prior CLARE
LVPEI 62	1	Infiltrates	17.75	OS	5	Limbal; slight	6 o'clock; diffuse	N	6	None
LVPEI 77	1	Infiltrates	15	OD	3	Bulbar and limbal; severe	10 to 12 o'clock; 4 to 7 o'clock; diffuse	Y	10	Fever and cough 7 days earlier
LVPEI 92	1	CLARE	5.75	OS	5	Bulbar and limbal; severe	360°; diffuse and focal	N	10	Conjunctivitis 18 days earlier
	2	CLARE	6.75	OS	2	Bulbar and limbal; severe	2 to 5 o'clock; diffuse and focal	Y	9	None
LVPEI 131	1	CLARE	3	OS	6	Bulbar and limbal; slight	10 to 12 o'clock; diffuse and focal	Y	30[d]	Fever and throat infection 3 days earlier
LVPEI 324	1	CLARE	0.07	OD	1	Bulbar and limbal; slight	3 to 11 o'clock; diffuse and focal	N	5	History of mild discomfort and lid swelling on awakening
CCLRU 4106	1	CLARE	13	OD	3	Bulbar and limbal; severe	360°; diffuse and focal	N	17	None

[a] OD, right eye; OS, left eye.
[b] N, no; Y, yes.
[c] The subject was asymptomatic at this time.
[d] Patient did not attend clinic until a month after the inflammatory episode.

included whether the subject had had any respiratory illness within the previous 2 months.

Contact lenses. The base materials of the contact lenses used were etafilcon A (Acuvue; Vistakon; Johnson & Johnson, Jacksonville, Fla.), an ionic hydrogel material with a 58% water content, and polymacon (SeeQuence 2; Bausch & Lomb, Rochester, N.Y.), a nonionic hydrogel material with a 38% water content. A different lens type was worn in each eye, and lenses were allocated randomly. Lenses were worn on a schedule of 6 continuous nights per week, with the lenses being replaced weekly.

Microbiological analysis of contact lenses and ocular sites. Calcium alginate swabs were used because these swabs have been shown to enable the good recovery of organisms from ocular sites (5). Samples were taken from the upper bulbar conjunctiva, avoiding contact with the lids, lashes, and tarsal conjunctiva. A second swab was passed along the lower lid margin, avoiding contact with the bulbar conjunctiva and lashes. The swabs were immediately placed into 3 ml of phosphate-buffered saline (PBS; NaCl, 8 g/liter; KCl, 0.2 g/liter; Na_2HPO_4, 1.15 g/liter; KH_2PO_4, 0.2 g/liter) containing 1% (wt/vol) $(NaPO_3)_6$, and the mixture was vortexed for 30 s. After removal of the swab, 0.4-ml aliquots were used to inoculate three chocolate agar plates and one Sabouraud agar plate (containing chloramphenicol). The Sabouraud agar plate and one chocolate agar plate were incubated aerobically at 35°C. The remaining chocolate agar plates were incubated at 35°C under conditions of increased carbon dioxide (5%; vol/vol) and anaerobically, respectively.

Contact lenses were removed aseptically from the eyes of the subjects with sterile gloves. The lenses were transported to the laboratory in 2 ml of PBS. At the laboratory, the lenses were vortexed for 1 min, removed aseptically, and cultured by an agar sandwich technique. We have previously found that vortex mixing of the lenses in saline aids in the dispersal of the bacteria that are loosely adhered to the lenses and allows for the more accurate quantification of the number of bacteria adherent to the lenses. The agar sandwich technique involves placing the lenses concave side up on a chocolate agar plate and flooding the plate with molten (56°C) agar (Oxoid Ltd.). The agar plates were then cultured by the methods described above for the swabs. After vortex mixing the lenses and incubating the agar plates, the bacteria were well dispersed from the contact lens and the numbers of CFU per lens could be easily read.

The subjects were routinely sampled during their contact lens wear at various time intervals. For determination of the contact lens contamination, lenses were sampled after 2 weeks of daily wear; after 1 night, 1 week, and 1 month of extended wear; and then at 3-month intervals. For determination of the ocular surface contamination (lower lid margin or upper bulbar conjunctiva), the sites were sampled at the baseline (prior to contact lens wear); after 1 night, 1 week, and 1 month of extended wear; and then at 3-month intervals until the subjects reached 2 years of extended wear. Their ocular sites were then sampled every year for microbiota. Contact lenses and ocular swabs were also taken at unscheduled visits at the time of an adverse response.

All agar plates were initially read after 48 h, and anaerobic plates were reincubated for up to 5 days at 35°C and Sabouraud agar plates were reincubated for 6 days at ambient temperature. The colonies were enumerated and identified by Gram staining, by standard biochemical methods (2), and by using API NH strips (Vitek BioMerieux, Sydney, Australia) and Biolog strips (Biolog, Hayward, Calif.) for gram-negative isolates. *H. influenzae* isolates were typed with commercially available antisera (Difco, Detroit, Mich.) and by a slide agglutination assay, and biotypes were determined with Biolog kits.

Microbiological analysis of subjects' fingers and throats. The fingers of subjects who presented with CLARE were sampled for culture by gently pressing all five fingers of each hand onto separate chocolate agar plates. The fingers were left in contact with the plates for 5 s, and the plates were then incubated at 35°C under conditions of increased carbon dioxide (5%; vol/vol). The colonies were then purified and identified as described above.

For analysis of subjects' throat microbiota, a calcium alginate swab was used to sample the microbiota of the back of the throat. The samples were then analyzed in the same manner as the ocular swabs (see above).

RESULTS

Patient and ocular characteristics at the time of an event. Table 1 gives the patient and ocular characteristics at the time of the events. No patient had altered visual acuity at the time of an event, and all lens fits were acceptable. Normally, treatment for the subjects involved removal of the contact lenses, discontinuation of contact lens wear until all signs of the inflammation had disappeared, and optometric monitoring on the day subsequent to the episode and then 6 days subsequent to the episode. For the second event, subject LVPEI 42 was prescribed topical betamethasone (0.1%) for use at a frequency of four times a day.

In total, seven subjects experienced a corneal inflammation associated with *H. influenzae*. One subject (subject LVPEI 42) had three episodes. Another subject (subject LVPEI 92) had a repeat episode of CLARE of uncertain etiology because no significant bacteria were isolated from the subject's contact lenses (because they were removed nonaseptically and so were not cultured) or ocular swabs. There was no association with the gender of the subjects or the lens power and the development of the corneal inflammatory response.

Microbiological analysis of contact lenses, ocular swabs, fingers, and throat. The microbiological results are presented in Table 2. Two subjects presented to the clinic without contact lenses because they had removed the lenses in the early morning because of ocular irritation and had discarded them; thus, no microbial analysis of these lenses could be performed. Occasionally, subjects reported that they had instilled sterile saline into their eyes at the time of the adverse event to alleviate their ocular discomfort. This may account for situations in which no growth from the ocular swabs was recorded. For most of the episodes (six of nine), moderate to high numbers of *H. influenzae* organisms were isolated from the contact lenses of eyes experiencing a reaction, with the numbers of *H. influenzae* organisms usually being higher on the contact lenses from eyes experiencing a corneal inflammation (CLARE or infiltrates) compared with the numbers on contact lenses from the contralateral eye. The *H. influenzae* organisms isolated from all episodes were nontypeable with commercially available antisera. Biolog kits biotyped all isolates as biotype A.

The other bacterial types isolated from contact lenses were *Staphylococcus aureus*, *Bacillus* spp., *Staphylococcus epidermidis*, *Corynebacterium* spp., and α-hemolytic streptococci. With the exception of α-hemolytic streptococci and one episode of *S. epidermidis* infection, bacteria other than *H. influenzae* were cultured in low numbers (<5 CFU).

The upper bulbar conjunctiva and lower lid margins of the subjects were contaminated with a greater number of types of bacteria than the contact lenses, and these bacteria were predominantly members of the normal ocular microbiota (16, 22). The conjunctiva and lid were contaminated with seven different bacterial types (Table 2) and two fungal genera, *Cladosporium* and *Aspergillus* spp. In general, the numbers of bacteria contaminating the conjunctiva and lids was much less than the numbers of *H. influenzae* organisms isolated from contact lenses. For the episodes in which the subjects had discarded their contact lenses, *H. influenzae* was isolated from the contralateral contact lens and/or the ocular swabs from either eye (Table 2).

The most common bacteria isolated from fingers was *S. epidermidis*, which was isolated 67% of the time that organisms were isolated in cultures of samples from fingers; this was followed by *S. aureus*, which was isolated from 33% of the episodes. The finger microbiota of two patients was not analyzed. *H. influenzae* was never isolated from the fingers. Only one patient's throat was swabbed at the time of presentation. For this patient (subject LVPEI 77) confluent growth of *H. influenzae* was found (>300 CFU).

The ocular and contact lens microbiota of the subjects were sampled on previous occasions during routine visits to the clinics. On average, the ocular and contact lens microbiota had been sampled seven times. *H. influenzae* was cultured from the upper bulbar conjunctiva of subject LVPEI 42 7 days prior to the subject's first CLARE event; at that time the patient was asymptomatic. *H. influenzae* was isolated from the upper bulbar conjunctiva of subject LVPEI 92 18 days prior to the CLARE event when a diagnosis of acute conjunctivitis was made. Once the inflammatory condition had subsided, with the exception of subjects LVPEI 92 and LVPEI 324, who discontinued contact lens wear, all subjects returned to extended

TABLE 2. Microbiological analysis of contact lenses, conjunctiva, and lids of subjects experiencing a CLARE reaction[a]

Subject identification	Eye	Lens microbiology		Upper bulbar conjunctiva microbiology		Lower lid margin microbiology	
		Organism	CFU/ml	Organism	CFU/ml	Organism	CFU/ml
LVPEI 42	Affected	*H. influenzae*	200	NG[b]	0	NG	0
		α-Hemolytic streptococci	2				
	Contralateral	*H. influenzae*	14	NG	0	NG	0
		Corynebacterium spp.	1				
LVPEI 42	Affected	NA[c]		NG	0	NG	0
	Contralateral	*H. influenzae*	>300	NG	0	*S. epidermidis*	3
LVPEI 42	Affected	NA		*S. epidermidis*	2	*H. influenzae*	28
	Contralateral	NA		*S. epidermidis*	1	*S. epidermidis*	1
LVPEI 62	Affected	*H. influenzae*	15	*H. influenzae*	1	NG	0
		S. aureus	2	*S. epidermidis*	1		
	Contralateral	*H. influenzae*	300	*S. aureus*	3	*H. influenzae*	2
						Neisseria spp.	1
LVPEI 77	Affected	*H. influenzae*	104	*H. influenzae*	1	*H. influenzae*	5
						Micrococcus spp.	4
		Bacillus spp.	1			*Aspergillus niger*	1
	Contralateral	*H. influenzae*	>300	*H. influenzae*	48	*H. influenzae*	16
		S. epidermidis	110	*S. epidermidis*	2	*S. aureus*	1
LVPEI 92	Affected	*H. influenzae*	>300	NG	0	NG	0
		S. epidermidis	3				
	Contralateral	NG	0	NG	0	NG	0
LVPEI 131	Affected	*H. influenzae*	177	*H. influenzae*	4	*S. epidermidis*	40
		S. epidermidis	4	*Micrococcus* spp.	1	*Bacillus* spp.	1
		Corynebacterium spp.	2	*Bacillus* spp.	3	*Corynebacterium* spp.	1
		α-Hemolytic streptococci	>300			*Propionibacterium* spp.	5
	Contralateral	*S. epidermidis*	1	*S. aureus*	4	*S. epidermidis*	7
		Corynebacterium spp.	1	*Bacillus* spp.	1	*Corynebacterium* spp.	1
LVPEI 324	Affected	*H. influenzae*	48	*Micrococcus* spp.	1	*S. epidermidis*	2
	Contralateral	NG	0	*Cladosporium* spp.	3	NG	0
CCLRU 4106	Affected	NA		NG	0	*Propionibacterium* spp.	3
	Contralateral	NA		*H. influenzae*	3	*H. influenzae*	3
				Propionibacterium spp.	3		

[a] Contact lenses and ocular swabs were cultured at 37°C under various atmospheric conditions. After incubation the different colonial types were identified by standard microbiological techniques.
[b] NG, no growth.
[c] NA, not cultured.

wear of contact lenses. For most of these subjects their contact lenses have been sampled since the inflammatory event and no *H. influenzae* isolate has been grown from the contact lenses.

During the study 8 of the 241 subjects experienced a CLARE event, giving a frequency for this condition of approximately 3%. The only subject who experienced a CLARE event in the absence of *H. influenzae* infection had >300 CFU of *Escherichia coli* adherent to the contact lenses at the time of the event (data not shown). The patients who did not have a CLARE or other adverse response to contact lens wear served as a control of contact lens wearers, and of these, the contact lenses, lids, or conjunctiva of six patients were colonized with *H. influenzae*. The contact lenses of these subjects were colonized at a frequency of 3% and with a range of *H. influenzae* of between 2 and >300 CFU per lens. The lids and conjunctiva of these subjects were colonized at a frequency of 1% each, with the range of CFU being 1 for the conjunctiva and 3 to 252 for the lids.

DISCUSSION

The present study has clearly demonstrated a link between the contamination of contact lenses with *H. influenzae* and the production of acute red eye reactions involving infiltration of the cornea. Previously, we and others have reported that *Pseudomonas* spp., particularly *P. aeruginosa* and *S. marcescens*, can produce CLARE (10) and keratitis (7, 13, 20) associated with contact lens wear. CLARE or infiltrates associated with *H. influenzae* sometimes show subconjunctival petechial hemorrhage, and patients have often complained of a sore throat or other upper respiratory tract symptoms in the period prior to the inflammatory event.

H. influenzae is a common bacterial cause of conjunctivitis, particularly in infants (12). One of the subjects in the present study was diagnosed as having acute conjunctivitis, with *H. influenzae* being isolated from the subject's conjunctiva prior to the adverse event during contact lens wear. However, the af-

fected eyes of most other patients were asymptomatic prior to the adverse event. The CLARE and infiltrative reactions are distinct from bacterial conjunctivitis in that there is no mucopurulent discharge, and commonly (56%) *H. influenzae* could not be cultured from the conjunctiva or lid of the CLARE subjects. The current and another study (10) indicate that it is the bacteria adherent to the contact lens rather than the bacteria present on the conjunctiva that lead to the production of CLARE. This is supported by the fact that symptoms rapidly disappear once the contact lenses are removed, with conjunctival redness commonly disappearing within 24 h, although corneal infiltration may take up to 1 month to clear. In addition, there was no persistent colonization of the ocular surface with *H. influenzae*. Subject LVPEI 42 had three inflammatory episodes, but *H. influenzae* was not cultured from the conjunctiva or lid margin prior to the third episode. It is likely that the bacteria colonize the contact lens after colonizing another body site. It is of interest that *H. influenzae* was isolated from the conjunctiva of subject LVPEI 42 prior to the first CLARE event, but the subject was asymptomatic at that time. This lends support to the observation that subjects can harbor *H. influenzae* in their conjunctival sacs (21) but be asymptomatic.

Six subjects were colonized with *H. influenzae* but did not show signs of an acute inflammatory response such as CLARE or infiltration. Usually, the contact lenses, lids, or conjunctiva of these subjects were colonized with low numbers of *H. influenzae*. Of the 13 subjects in total who were colonized with *H. influenzae*, 7 developed a CLARE or infiltrative response, for an incidence of 54%; of the 228 subjects who were not colonized with *H. influenzae*, 1 subject had a CLARE or infiltrative response, for an incidence of 0.4%. Therefore, subjects colonized with *H. influenzae* were 154 times as likely to have a CLARE or infiltrative response as subjects who did not carry *H. influenzae*, and this was significant ($P < 0.0001$). Two of the symptomatic subjects were infected with >300 CFU of *H. influenzae* per lens. We propose that these two subjects developed this level of *H. influenzae* on their lenses during the daily wear of the contact lenses, and since the subjects did not sleep with the contaminated lenses in place, they did not experience a CLARE. It has been shown previously that the closed-eye environment can be considered in a state of subclinical inflammation (18), and we propose that in order to develop a CLARE, subjects must sleep with their contact lenses that are colonized with large numbers of *H. influenzae*. Therefore, the presence of *H. influenzae* alone is not sufficient to induce a CLARE event. In addition, although the subjects who were colonized with *H. influenzae* may have been at risk of developing a CLARE or infiltrative reaction, three of them were permanently discontinued from the study because of non-lens-related phenomena and as such were lost to follow-up. It is possible that the other subjects may develop CLARE at some future time, and we are continuing to monitor them microbiologically and optometrically. We have previously reported that there is an approximately 50% chance that subjects who have had a CLARE will develop subsequent episodes while wearing extended-wear (sleep-in) hydrogel contact lenses (25). Another possible explanation is that there are some as yet undefined subject characteristics that predispose individuals to the CLARE response. Indirect evidence for this has been reported earlier during a study that measured the ocular responses of 12 subjects, all of whom were found to have large numbers of *P. aeruginosa* or *S. marcescens* isolates adherent to their contact lenses. After sleeping with these lenses in place, only 50% of the subjects had either a CLARE or an infiltrative response (10).

The source of the bacteria in the present study was believed to be the nasopharynges of the subjects, because 57% of the subjects had had cold-like symptoms within the preceding 2 months. The throat microbiota of one subject was cultured, and the subject was found to be colonized with large numbers of *H. influenzae*, which lends support to this hypothesis. Indeed, it has previously been shown by molecular epidemiological techniques that the same types of *H. influenzae* that cause acute purulent conjunctivitis in children can be isolated from the nasopharynx and the conjunctiva (23). Hart and Shih (9) have implicated the fingers as potential sites from which the eye can acquire its microbiota. The present study does not support this route of colonization for *H. influenzae* because this bacterium was never isolated from the fingers of the subjects at the time of an event.

In conclusion, *H. influenzae* is associated with the production of acute corneal and conjunctival inflammation. *H. influenzae* colonization of the contact lens and eye may be subsequent to colonization of the nasopharynx. Contact lens wearers should be made aware of the potential risk of CLARE or infiltrates associated with the wearing of contact lenses for extended periods during and subsequent to upper respiratory tract infection.

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