Case-Control Pilot Study of Soft Contact Lens Wearers With Corneal Infiltrative Events and Healthy Controls

Kathryn Richdale,[1] Dawn Y. Lam,[2] Heidi Wagner,[3,4] Aaron B. Zimmerman,[3] Beth T. Kinoshita,[5] Robin Chalmers,[6] Luigina Sorbara,[7] Loretta Szczotka-Flynn,[8] Usha Govindarajulu,[1] and G. Lynn Mitchell[3]

[1]College of Optometry, State University of New York, New York City, New York, United States
[2]Southern California College of Optometry, Marshall B. Ketchum University, Fullerton, California, United States
[3]College of Optometry, The Ohio State University, Columbus, Ohio, United States
[4]College of Optometry, Nova Southeastern University, Fort Lauderdale, Florida, United States
[5]College of Optometry, Pacific University, Forest Grove, Oregon, United States
[6]Clinical Trial Consultant, Atlanta, Georgia, United States
[7]School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada
[8]University Hospitals Case Medical Center and Case Western Reserve University, Cleveland, Ohio, United States

Correspondence: Kathryn Richdale, SUNY College of Optometry, 33 West 42nd Street, New York, NY 10036, USA;
KRichdale@SUNYopt.edu.

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Purpose. The purpose of this study was to assess risk factors associated with soft contact lens (SCL)-related corneal infiltrative events (CIEs).

Methods. This was a single-visit, case-control study conducted at five academic centers in North America. Cases were defined as current SCL wearers with a symptomatic CIE. For each case, three age- and sex-matched controls were enrolled. Subjects completed the Contact Lens Risk Survey (CLRS), a standardized scripted medical interview, supplied a recent health history, and underwent an ocular examination. Microbial culturing of the ocular surface, SCL, and lens storage case was conducted for all cases and one of the three matched controls. Univariate and multivariate logistic regression modeling were used to assess the risk of developing a CIE.

Results. Thirty cases and 90 controls 13 to 31 years of age completed the study. Corneal infiltrative event diagnosis included contact lens–associated red eye, infiltrative keratitis, and contact lens peripheral ulcer. Subjects with symptomatic CIEs were more likely to harbor substantial levels of gram-negative bioburden on the ocular surface and contact lens. Significant risk factors for developing a CIE were overnight wear of SCLs, use of multipurpose solution, rinsing SCLs with water, lens storage case older than 6 months, previous "red eye" event, use of ocular drops in the past week, and illness during the past week.

Conclusions. This pilot study demonstrated feasibility of enrolling a representative pool of SCL wearers with an untreated, symptomatic CIE and assessing CIE risk factors by using standardized methods. A larger sample size is needed to determine relationships between patient-reported behaviors and exposures, microbial bioburden, and CIE development.

Keywords: adverse events, contact lenses, corneal infiltrative events, microbial culturing

A recent report from the US Centers for Disease Control and Prevention (CDC) called to light the substantial burden associated with contact lens–related complications.[1] The CDC report estimated that contact lens–related keratitis results in nearly 1 million doctor visits each year and carries an associated cost of $175 million.[1] This estimate does not include the additional "costs" to the patient such as pain or discomfort, missed school or work, and potential for permanent loss of vision.

Approximately 37 million people in the United States currently wear contact lenses and, due to the increasing prevalence of myopia, more and younger patients are expected to begin wearing contact lenses to aid in its management.[2,3] Research has demonstrated that adult and pediatric patients can safely wear soft contact lenses (SCLs) within controlled trials, with relatively low rates of complications, especially for daily lens wear.[4,5] However, as with most medical devices, when contact lenses are used by the general population outside of controlled trials, the rate and types of complications increase.[1,6–8] The increased risk of complications is likely caused by poor wear and care behaviors, but the cause and effect relationships are not entirely clear, especially to patients.[9–12]

The Contact Lens Assessment in Youth (CLAY) group developed the Contact Lens Risk Survey (CLRS) to thoroughly and systematically evaluate patient-reported behaviors and exposures associated with contact lens wear. The CLAY Observations of Risks Associated with Contact Lenses (ORACL) study was designed to pilot methods for conducting a multicenter clinical study to explore relationships between patient-reported behaviors and exposures, microbial biobur-

den, and risk factors for developing contact lens–related corneal infiltrative events (CIEs).

Methods

Study Procedures

The ORACL study was a multicenter, single-visit, case-control pilot study conducted at five academic centers in North America (see Supplementary Appendix for sites). The study followed the tenets of the Declaration of Helsinki and was approved by each site's Institutional Review Board prior to recruitment. Current SCL wearers (defined as having worn SCLs in the last week) between 12 and 33 years of age were recruited. Case subjects were patients presenting with untreated, symptomatic CIEs. Control subjects were sex- and age-matched (±2 years), and three controls were enrolled for each CIE case. Control subjects were excluded if they had had an eye examination in the 3 months prior to the study visit in order to minimize the effects of recent patient education or change in SCL brand. Eye care providers (including residents or students), or patients related to eye care providers were not eligible to participate. Subjects who were enrolled in another clinical trial or subjects who were pregnant also were not eligible. After the purpose of the study was explained to the patients and a parent/guardian of minors, informed consent/assent was obtained from the patients and the parent/guardian of minors, as appropriate.

Subjects were asked to complete the CLAY CLRS and the CDC Healthy Days Core Module survey.[13–15] The CLRS tool was developed using patient-reported outcome methods and is briefly described below.

Initial survey items were derived from a review of published known and presumed risk factors for SCL-related complications. Many items were deemed amenable to self-report, but certain known risk factors which were thought to be difficult to accurately ascertain due to poor patient recall or knowledge (e.g., accurate refractive error, diagnosis, or severity of systemic disease) were not included. To elucidate other meaningful factors from clinical findings, the CLAY study team conducted a review of records from a previous study.[16,17] These items were used to create a bank of questions and response options. Questions were refined to use only non-leading lay-language and to avoid double-barrel question stems. Response options included: yes/no, Likert scales, and select one/mark all that apply. The 5-point Likert scale used the labels "always," "fairly often," "sometimes," "infrequently," and "never." Readability of the questions and responses was assessed at a fifth-grade level (average, 11 years of age), using Flesch-Kincaid statistics in Microsoft Word software (Microsoft, Redmond, WA, USA). Photos were used to improve the participant's ability to identify their SCL and lens care products.[18] Branching logic was incorporated (i.e., patients who reported not using a lens case were not asked how often they cleaned their lens case), and the survey was developed into an on-line (Web-based) instrument using Qualtrics software (Qualtrics Labs, Inc., Provo, UT, USA) so that it could be fielded with a desktop or portable computer.

Pilot testing of the CLRS was first conducted in healthy SCL wearers and was shown to be able to discriminate among differences in patient behaviors, environmental exposures, and health status by age.[19] The survey was also assessed for within-subject repeatability, by resurveying a group of 119 subjects 1 week after the initial survey. There was good agreement between the test and retest responses for most items on the CLRS (see Supplementary Appendix). Test–retest repeatability of contact lens care, hygiene, lens dependence, environmental exposure, and wellness were generally high, with most kappa values (κ_w) above 0.61 (agreement was substantial or better). Eight items had only moderate agreement (0.41–0.60), and none had less than moderate agreement. Most survey items also showed high symmetry, indicating only random disagreement, if any. The test of symmetry was below 0.5 for a few items. A nonrandom pattern to the observed disagreement occurred for sleeping in contact lenses, number of colds/influenza and stress level. It is reasonable to expect that these responses could change over time. Data from healthy and red-eye SCL wearers are being used to construct a scoring methodology for the CLRS tool for future use in research or clinical care.

After subjects completed the CLRS, investigators conducted a scripted medical interview with all case subjects and a health history with all subjects (cases and controls). The scripted medical interview included questions regarding the CIE subject's signs and symptoms, attempts at self-treatment, and access to care. The health history queried current (the previous week) SCL wear and care behaviors, as well as systemic and ocular health and medication histories. A standardized biomicroscopy examination was conducted, and the investigator cultured the ocular surface and contact lens and lens case for all CIE subjects and one matched control subject for each CIE case. In this pilot study, cultures were obtained only from the case subjects and one control subject per case due to costs associated with the microbiological procures (see Culturing Methods below). Following sample collection, sodium fluorescein (NaFl) was instilled to complete the anterior segment evaluation. No further study-related procedures or visits occurred, and the subject was treated and scheduled as was usual and customary for each site (see Supplementary Appendix for scripted interview, health history, biomicroscopy and culture collection forms).

Culturing Methods

All study investigators were trained in proper culturing methods based on previously reported techniques.[20,21] Investigators wore clean gloves and used separate swabs and agar plates for each culture location. The lower eyelid margin and superior bulbar conjunctiva of each eye were swabbed with a moistened calcium alginate swab and plated onto chocolate agar (Fisher Scientific, Hampton, NH, USA). If the subject was wearing SCLs, the lenses were aseptically removed from the eyes. If the SCLs were in lens storage cases, lenses were aseptically removed from the case and the duration since lens removal from the eye and type of lens care solution was recorded. Soft contact lenses were placed in a vial with 1 mL nonpreserved sterile saline. Contact lens storage cases were kept and a replacement case was provided to the subject.

Culture samples were maintained at 4°C to 8°C until they were shipped to the central laboratory (University Hospitals Case Medical Center, Cleveland, OH, USA). If culture samples were collected on Friday or Saturday, they were refrigerated and shipped Monday. Culture samples were shipped overnight with cool packs to avoid overgrowth of organisms in transit. All cultures were processed following previously described methods.[20,21] Inoculated plates were incubated in 5% CO_2 for 48 h at 35°C. All plates were read by masked examiners after 48 h and reincubated and examined for up to 5 d if no growth was seen initially. Upon arrival at the laboratory, contact lens specimens were aseptically removed and placed concave side down on a chocolate agar plate, covered with 10 mL molten agar, and incubated in 5% CO_2 for up to 5 d at 35°C. Storage cases were swabbed and plated on chocolate agar plates as well. Colony-forming units (CFUs) were enumerated and colonies identified by use of gram stain and standard

Table 1. Summary of CIE Cases

		Diagnosis		Resolution			Contact Lens		
Subject ID	Severity Score*	Adjudicated Diagnosis	Bilateral	Visual Acuity Loss	Days to Resolution	No. of Visits	Manufacturer Replacement Schedule	Material	Lens Care
1	14	CLARE w/CIE	Yes	None	12	3	2-wk	SiHy	MPS
2	7	CLARE w/CIE	No	None	4	1	Monthly	SiHy	MPS
3	11	CLARE w/CIE	No	None	3	3	Daily	Hydrogel	None
4	14	CLARE w/CIE	No	None	14	2	Daily	Unknown	None
5	18	CLPU	No	None	6	3	2-wk	SiHy	MPS
6	20	CLPU	No	None	7	4	Monthly	SiHy	None
7	14	CLARE w/CIE	Yes	None	5	3	2-wk	SiHy	H_2O_2
8	8	IK	Yes	None	8	2	2-wk	SiHy	MPS
9	17	IK	No	None	7	2	Monthly	Hydrogel	MPS
10	14	CLARE w/CIE	Yes	None	14	2	2-wk	Unknown	MPS
11	10	CLARE w/CIE	No	None	9	2	Monthly	SiHy	H_2O_2
12	12	IK	No	None	8	2	2-wk	SiHy	Unknown
13	16	IK	No	None	9	3	Monthly	SiHy	MPS
14	13	CLARE w/CIE	Yes	None	9	3	2-wk	SiHy	MPS
15	12	CLPU	No	None	16	5	2-wk	SiHy	MPS
16	20	CLPU	No	None	5	3	2-wk	SiHy	Unknown
17	15	CLPU	No	None	11	5	2-wk	SiHy	Unknown
18	13	CLARE w/CIE	Yes	None	5	3	Monthly	SiHy	Unknown
19	14	CLPU	No	None	4	3	2-wk	SiHy	Unknown
20	19	CLPU	No	None	4	3	2-wk	Hydrogel	MPS
21	16	CLPU	No	None	6	3	Daily	Hydrogel	None
22	14	CLPU	Yes	None	12	4	2-wk	SiHy	MPS
23	10	IK	No	None	3	3	Monthly	SiHy	MPS
24	10	CLARE w/CIE	No	None	5	2	Monthly	SiHy	None
25	13	IK	No	None	6	2	Monthly	Hydrogel	MPS
26	17	CLARE w/CIE	No	None	7	2	2-wk	SiHy	MPS
27	12	IK	No	None	14	2	Monthly	Hydrogel	MPS
28	13	CLARE w/CIE	No	None	7	2	2-wk	SiHy	MPS
29	7	IK	Yes	None	5	2	2-wk	Hydrogel	MPS
30	11	IK	Yes	Unknown	7	2	2-wk	SiHy	MPS

H_2O_2, hydrogen peroxide; MPS, multipurpose solution; SiHy, silicone hydrogel.

* Severity was scored according to Institute for Eye Research/L.V. Prasad Eye Institute *Guide to Corneal Infiltrative Conditions* criteria.[28,29]

identification methods.[21] Based on previous reports, "substantial microbial bioburden" was defined as ≥10 CFUs of any gram-negative bacteria or higher virulence gram-positive organisms or high levels (≥80 CFUs) of normal ocular biota (e.g., *Corynebacterium*, coagulase-negative staphylococci [CNS]).[20–27]

Adjudication of Cases

Subjects' clinical records were used to adjudicate the cases to a final diagnosis following previously described methods.[16] Each CIE case was scored for severity using Institute for Eye Research/L.V. Prasad Eye Institute *Guide to Corneal Infiltrative Conditions* criteria.[28,29] Scores were based on a 4-point scale for 10 items such that the final score could range from 0 to 40, with 40 being the most severe.

Statistical Methods

Conditional logistic regression with univariate and multivariate modeling was used to assess the effect of patient characteristics and behaviors as reported on the CLRS, scripted medical interview, and health history data on the risk of CIE. This analysis methodology, as opposed to simple logistic regression, was used due to the matching (3:1 ratio) of cases and controls. Based on previous research indicating directionality of risk factors, a one-sided *P* value and a 95% confidence interval upper limit are reported. Pilot data collected from microbial culturing (1:1 matching) were used to explore trends between microbial bioburden and behaviors or exposures using multiple logistic regression adjusted for confounding by age and sex. These data were also used to determine ranges of sample sizes needed for a full-scale study.

Results

Sample Population (Cases and Controls)

Thirty CIE cases and 90 matched controls were enrolled between November 2013 and June 2014. Enrolled subjects were between 13 and 31 years of age (mean: 27.7 years of age), and 57% were female. There was a broad distribution of racial groups (37% caucasian, 30% Asian, 16% Hispanic, 8% African American) represented in the study. The majority of subjects were full-time (86% wore SCLs ≥4 d/wk) planned-replacement (46% 2-weekly, 28% monthly) wearers. Most subjects wore lenses of silicone hydrogel (SiHy) material (66% SiHy), and 79% used multipurpose solution (MPS) to clean and store their SCLs.

The type and severity of CIE cases are presented in Table 1. Most CIEs were located in the peripheral or midperipheral cornea, were as deep as anterior stroma, and were 1.0 mm or less in diameter. The average severity score was 13.5 ± 3.5. Diagnoses of CIEs were almost evenly distributed among

Table 2. Univariate and Multivariate Models For Risk of Corneal Infiltrative Events From Health History

		Univariate Model*			Multivariate Model*		
Factor	**Response**	**OR**	**Upper 95% CI**	***P* Value†**	**aOR**	**Upper 95% CI**	***P* Value†**
Age of current CL storage case	>6 mo	4.86	15.07	**0.01**	7.69	31.57	**0.01**
	3–6 mo	–	–	**0.10**	–	–	0.24
	Do not use a case	–	–	0.22	–	–	0.47
	≤2 mo		Referent			Referent	
Used ocular drops in the last wk	Yes	3.53	7.31	**0.002**	4.53	10.92	**0.002**
	No		Referent			Referent	
Cold/influenza in the last wk	Yes	2.15	4.67	**0.052**	3.45	9.12	**0.02**
	No		Referent			Referent	
Overnight wear in the last wk	Yes	3.35	6.83	**0.003**	3.30	7.76	**0.01**
	No		Referent			Referent	
Slept away from home in the last wk	Yes	2.54	5.48	**0.023**			
	No		Referent				

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.
* Univariate, $P \leq 0.10$; multivariate, $P \leq 0.05$.
† *P* values in boldface indicate significance at the stated levels.

contact lens-associated red eye (CLARE) with infiltrates (11 subjects), infiltrative keratitis (IK) (10 subjects), and contact lens peripheral ulcer (CLPU) (9 subjects). The clinical treatment of CIEs varied somewhat by site and ranged from temporary discontinuation of SCL wear to prescribing antibiotic and/or steroid combination drops. The median time to resolution was 7 days (mean ± 7.7 ± 3.6 days), and required an average of 3 office visits (2.7 ± 0.9 visits). As expected, CIE cases were more likely to have bulbar redness, papillae or follicles, conjunctival and corneal edema, discharge, corneal scars, and corneal staining compared to controls (all $P < 0.05$).

Scripted Medical Interview (Cases Only)

The scripted medical interview of CIE subjects indicated that the average onset of symptoms occurred approximately 2.5 days prior to the appointment (2.44 ± 3.46 days; range, 2 hours to 14 days). The most common factors subjects reported for their delay in seeking care were that they "thought it would improve on its own" or were "too busy." Subjects reported typical symptoms of ocular redness, pain, burning, swelling, discharge, and decrease in vision. The most common attempts to alleviate symptoms were to "rinse and reinsert SCLs," "replace SCLs with a new pair," or "use eye drops."

Health History and CLRS (Cases and Controls)

The ocular and systemic health history revealed that the majority of subjects were not taking any oral medications beyond over the counter (OTC) vitamins and supplements. A few subjects reported taking oral medications for birth control (13%) and allergies (12%). The majority of subjects had medical insurance (65%), but less than half had vision insurance (45%). Forty percent reported seasonal and/or environmental allergies.

There were five significant risk factors identified from the univariate analysis of the health history data (Table 2). In the multivariate model (Table 2), subjects whose contact lens storage case was six months of age or older, were nearly eight times more likely to have had a CIE than those whose lens storage case was 2 months of age or newer ($P = 0.01$). Overnight wear, cold/influenza, and use of eye drops in the previous week were also related to the risk of developing a CIE (all $P \leq 0.02$). The ocular drops reported as being used by CIE subjects were most often an OTC vasoconstrictor indicated to "get the red out" and were likely associated with the subject's attempt to self-treat prior to seeking professional help.

Univariate analysis of the CLRS data identified 10 significant risk factors for developing a CIE (Table 3). In the multivariate model (Table 3), subjects who reported a previous red eye event, used MPS, slept overnight in their SCLs "always" or "fairly often," or who replaced their SCLs less often than daily were 3 to 10 times more likely to have experienced a CIE. As mentioned previously, biomicroscopy data indicated that CIE subjects were more likely to have a pre-existing corneal scar, which supports the patient-reported CLRS finding of previous red eye events. The remainder of the CLRS questions, including living environment, hand-washing behaviors, stress, and health status were not significant in this pilot study (all $P > 0.05$). Although not significantly related to risk of CIE, it was also noted from the CLRS tool that nearly half (43%) of subjects reported rinsing and/or storing their SCLs in water at least infrequently; a behavior that is associated with the risk of acanthamoeba keratitis, one of the most severe forms of microbial keratitis (MK).[30,31] None of the CDC Healthy Days Questions were significantly associated with the risk of developing a CIE (all $P > 0.05$, data not shown).

A multivariate model with data from both the CLRS and health history was explored to determine which information best predicted the risk of a CIE (Table 4). This final model included two factors from the health history (recent illness and self-treatment prior to the event), and four from the CLRS (overnight wear, previous red eye, use of MPS and rinsing SCLs with water) all of which were more likely to be associated with development of a CIE.

Microbial Cultures

Eyelid and conjunctival cultures were obtained from almost all the CIE cases and controls (Table 5). One subject declined bulbar conjunctival swabs due to discomfort. Many of the CIE subjects discarded their SCL at the onset of the event, so there were fewer SCL available for culturing from CIE subjects (17 of 30) compared to control subjects (27 of 30). Fewer than half of all subjects presented to the visit with their lens storage cases.

Corneal infiltrative event subjects were more likely to have substantial levels of bioburden on their eyelids, conjunctivas, and contact lenses (Table 5, all $P \leq 0.02$). The type of bacteria was generally consistent across the eyelid margin, conjunctiva, contact lenses, and storage case, where available (Table 6). Culture-positive CIE subjects harbored mostly gram-negative bacteria. The bacteria identified on the healthy control subjects were primarily normal commensal flora and did not reach the

Table 3. Univariate and Multivariate Models For Risk of Corneal Infiltrative Events From the CLRS

		Univariate Model*			Multivariate Model*		
Factor	**Response**	**OR**	**Upper 95% CI**	***P* Value†**	**aOR**	**Upper 95% CI**	***P* Value†**
SCL replacement	>Daily	6.76	39.75	**0.038**	9.51	92.20	**0.05**
	Daily		Referent			Referent	
Overnight wear of SCL	Always/fairly often	6.46	19.06	**0.002**	4.84	15.88	**0.02**
	Sometimes	2.58	7.58	0.075	–	–	0.16
	Infrequently/never		Referent			Referent	
Lens care product	MPS	3.80	13.76	**0.044**	4.62	18.26	**0.03**
	Hydrogen peroxide		Referent			Referent	
Previous red eye event	Yes	2.55	5.13	**0.014**	3.27	7.84	**0.01**
	No		Referent			Referent	
ECP recommends extended wear	Yes	18.00	106.40	**0.004**			
	No		Referent				
Showering in SCL	Always/fairly often	3.16	8.34	**0.026**			
	Sometimes	–	–	0.20			
	Infrequently/never		Referent				
>18 h of SCL wear/d	Always/fairly often	3.07	7.09	**0.014**			
	Sometimes	–	–	0.68			
	Infrequently/never		Referent				
Smoking	Yes	3.00	8.98	**0.050**			
	No		Referent				
Rinse SCL with tap water	Yes	2.39	5.00	**0.026**			
	No		Referent				
Other exposure of SCL to water	Yes	2.13	4.78	**0.063**			
	No		Referent				

ECP, eye care practitioner.
* Univariate, $P \leq 0.10$; multivariate, $P \leq 0.05$.
† *P* values in boldface indicate significance at the stated levels.

threshold of substantial levels of bioburden for most subjects; however two control subjects had substantial levels of CNS and one subject presented with *Escherichia coli* in their lens storage case.

Exploratory logistic regression analyses were conducted to determine if certain CLRS questions were associated with substantial levels of microbial bioburden. To avoid type II errors, only questions previously shown to be related to microbial bioburden or that were strongly biologically plausible were tested. The questions selected were overnight SCL wear, rinsing/storing SCLs in water, washing hands before inserting/removing SCLs, topping off contact lens solution, and use of and frequency of replacement of lens storage case. Due to the limited microbial cultures of SCLs and lens storage cases, only the culture result from the lid margin was used as the outcome variable. After adjusting for age and sex, none of the selected predictor variables were associated with substantial levels of microbial bioburden on the eyelid margin (all $P > 0.05$). Sample size calculations using the microbial culture and CLRS data assumed an expected odds ratio of 2 to 3 using a logistic regression to predict lid burden with a single categorical predictor. If 50% of outcome response is positive (i.e., 50% of participants experience significant bioburden), 50% R^2 between the main predictor and other predictor, and 50% at baseline have a positive outcome, we would need between 230 and 544 persons (total case and control subjects) to achieve at least 80% study power.

Discussion

The sample enrolled in the CLAY ORACL study was a good representation of the current SCL-wearing population in the

Table 4. Multivariate Model For Risk of Corneal Infiltrative Events Using Health History and CLRS Data

Source of Data	**Factor**	**Response**	**aOR**	**Upper 95% CI**	***P* Value***
CLRS	Lens care product	Multipurpose solution	**17.28**	107.7	**0.01**
		Hydrogen peroxide		Referent	
Health history	Ocular drops in last week	Yes	**7.72**	24.84	**<0.01**
		No		Referent	
CLRS	Overnight wear of CLs	Always/fairly often	**5.45**	21.46	**0.02**
		Sometimes	–	–	0.24
		Infrequently/never		Referent	
CLRS	Previous red eye	Yes	**4.16**	13.46	**0.02**
		No		Referent	
Health history	Cold/influenza in last week	Yes	**3.41**	9.68	**0.03**
		No		Referent	
CLRS	Rinse CLs with tap water	≥Infrequently	**2.85**	8.17	**0.05**
		Never		Referent	

* *P* values in boldface indicate $P \leq 0.05$ level.

Table 5. Cultures With Substantial Levels of Bioburden and Total Cultures Obtained For Cases and Controls

Location	Cases With Significant Bioburden/Total Cultured (%)	Controls With Significant Bioburden/Total Cultured (%)	*P* Value†
Eyelid margin	8/30 (26.7)	1/30 (3.3)	**0.01**
Bulbar conjunctiva	5/30 (16.7)	0/29 (0.0)	**0.02**
Contact lenses	6/17 (35.3)	0/27 (0.0)	**<0.001**
Lens storage case*	5/10 (50.0)	2/14 (14.3)	0.058

Chi-square tests were used for the proportion of substantial bioburden between cases and controls.
* Three case and 6 control subjects reported not using a lens storage case.
† *P* values in boldface indicate $P \leq 0.05$ level.

United States as the majority of subjects were full-time wearers using silicone hydrogel planned replacement SCLs and multipurpose care solutions.[2] The type and severity of CIEs were also representative of the typical "red eye" patient seen in general optometry or ophthalmology practice (i.e., not at a corneal specialist or tertiary referral site). The average event lasted approximately one week and required three doctor visits which supports the CDC's report that, although "mild to moderate" CIEs may not cause permanent visual loss, they can result in meaningful personal and financial burden.[1]

The scripted medical history revealed that subjects who experienced a CIE were more likely to have had an illness in the week prior to the event. Poor or compromised health has been established as a risk factor for CL-related complications.[32,33] These subjects were also more likely to have slept away from home prior to the event, which is a new finding and could be associated with patients not having their typical lens care products with them and thus over wearing lenses or using different lens care products.

A number of known and novel risk factors for developing a CIE were identified in the self-reported CLRS data. Not surprisingly, subjects with active infiltrative events were more likely to have slept overnight in their SCLs.[5,17,32,34–38] CIE case subjects had increased exposure to soiled contact lenses; both by extending their SCL daytime wearing hours and extending the replacement of their SCLs. Our and others' work has demonstrated that planned replacement SCLs are associated with higher risk of complications than daily disposable lenses,[16,17,39,40] but little has been reported regarding the effects of longer SCL wear hours. It could be hypothesized that the longer wear hours further compromise the ocular surface and allow adherence and colonization of bacteria and thus increase the likelihood of a CIE. Other established risk factors supported by this study were use of an older contact lens storage case,[41,42] and use of multipurpose solutions (versus hydrogen peroxide),[17,39,43] and smoking.[32,37,44–47]

Surprisingly, most subjects (both cases and controls) reported showering while wearing their lenses and/or exposing their lenses to other water sources (e.g., pools and hot tubs), and CIE cases in this study were significantly more likely to report rinsing their SCLs in tap water. Exposure of SCLs or lens storage cases to water is a well-established risk factor for the development of microbial keratitis, especially visually threatening *Acanthamoeba* keratitis.[31,42,48] Water exposure has also been associated with contamination of contact lenses with pathogenic gram-negative bacteria.[27]

In the multivariate analysis of the CLRS with the scripted history, most of the factors that remained significant were consistent with those previously reported in the literature (overnight wear of SCLs,[4,5,17,19,34,37,49] previous CL complication,[45] use of multipurpose solution,[17,43,48,50] SCL exposure to water,[30,31,42,48] and illness[33]). Some factors that dropped out of the multivariate analysis were closely linked with other factors (i.e., wearing SCLs greater than 18 h/d was highly associated with overnight wear).

Previous CLAY Study Group results have shown that there are significant differences in behaviors and environmental exposures by age.[51–53] Due to age matching and the relatively small sample in this study, it was not possible to examine differences in risks by age. Further research is warranted to examine the influence and interactions of the multiple known and presumed risk factors in younger and older populations of SCL wearers.

This study was also designed to pilot multisite collection and central processing of microbial cultures of clinical patients. A total of 14 of the 30 CIE subjects were shown to harbor substantial levels of bioburden on their ocular surface, contact lens, or lens case. It is a known limitation of standard culturing techniques that only "viable" bacteria can be detected even though dead bacteria, endotoxins, and exotoxins are able to trigger inflammatory events. There are also many bacteria that simply do not grow under standard laboratory conditions. It is therefore not surprising that some CIE subjects had low levels of detectable contamination.[22,54] As shown by other groups, significant levels of gram-negative bacteria were more common in subjects with active CIEs compared to healthy controls.[21,22,24,54] It is noteworthy that, while culturing is not the standard of care for CIEs considered to be low risk for MK, this study revealed that even mild to moderate case presentations harbored gram-negative bacteria known to be resistant to standard treatment regimens (e.g., *Achromobacter xylosoxidans* and *Elizabethkingia* and *Delftia* spp).[21,55] Consistent with previous findings, the bacteria identified on the majority of the healthy control subjects were normal commensal flora below our specified levels of substantial bioburden.[21,22,27] The control subject who showed substantial bioburden on the lens storage case but did not have an active CIE at the time of the study, could have been at risk of developing one in the future had he continued to use the same soiled lens storage case. One of the limitations of a cross-sectional study is that it is only a snapshot in time and cannot fully describe the subjects' exposures and risks.

There were some additional limitations to this study. There were fewer SCLs and lens storage cases available for culture than had been planned. The sites did their best to educate potential CIE and Control subjects to bring their SCLs and lens storage case to their appointments, but it was not realistic to expect that all patients would follow these instructions. Based on this and the aforementioned limitations of standard culturing techniques, future studies should enroll larger samples to allow for missing culture data or should consider other types of microbial assessment (i.e., RNA based analysis).[55,56] Because our study and those of others have shown that the bulbar conjunctiva generally harbors the same or fewer microbiota, future studies could consider forgoing conjunctival culturing to save costs and minimize time.[20,27] The relatively small sample of positive culture results limited

Table 6. Microbial Cultures Reaching Predefined Substantial Levels of Microbial Bioburden

Subject ID	Adjudicated Diagnosis	Lids	Conjunctiva	Contact Lens	Storage Case
1	CLARE	A. xylo	A. xylo	A. xylo	
2	CLARE	—	—	—	
3	CLARE	CNS	—		
4	CLARE	—	—	—	
7	CLARE	S. mar	S. mar		
10	CLARE	S. mar	S. mar/A. xylo	S. mar/A. xylo	S. mar/A. xylo
18	CLARE	—	—	—	—
26	CLARE	H. influ	H. influ	—	—
11	CLARE	—	—	—	
14	CLARE	—	—		—
24	CLARE	—	—		
28	CLARE	—	—		
5	CLPU	—	—	—	
6	CLPU	CNS	—		
16	CLPU	—	—		—
17	CLPU	—	—	—	—
19	CLPU	—	CNS		
20	CLPU	—	—	S. mar/A. xylo	S. mar/A. xylo
21	CLPU	—	—		
22	CLPU	Eliza/Delft	—	Eliza/Delft	Eliza/Delft
15	CLPU	—	—		
8	IK	—	—	—	
9	IK	—	—	—	
12	IK	—	—	A. xylo	A. xylo
13	IK	—	—	Gram− rods	
23	IK	Eliza	—	Eliza	Eliza
25	IK	—	—		
27	IK	—	—	—	
29	IK	—	—		
30	IK	—	—		
	Control	—	—	—	
	Control	—	—	—	—
	Control	—	—	—	
	Control	—	—		
	Control	—	—		
	Control	—	—	—	
	Control	CNS	—	—	
	Control	—	—		
	Control	—	—	—	
	Control	—	—	—	
	Control	—		—	CNS
	Control	—	—	—	—
	Control	—	—	—	—
	Control	—	—	—	—
	Control	—	—	—	
	Control	—	—	—	—
	Control	—	—	—	—
	Control	—	—	—	—
	Control	—	—	—	—
	Control	—	—	—	
	Control	—	—	—	
	Control	—	—	—	—
	Control	—	—	—	—
	Control	—	—	—	
	Control	—	—	—	
	Control	—	—	—	
	Control	—	—	—	

Gram-negative bacteria are indicated by hatched shading and gram-positive bacteria by solid gray shading. Black shading indicates when an item was not available for culture, and a dash, —, indicates the sample was negative or did not achieve substantial levels of bioburden. ID numbers correspond to those in Table 1. A. xylo, *Achromobacter xylosoxidans*; CNS, coagulase-negative staphylococci; Delft, *Delftia acidovorans*; E. coli, *Escherichia coli*; Eliza, *Elizabethkingia miricola*; H. influ, *Haemophilus influenza*; S. mar, *Serratia marcescens*.

the ability to assess relationship between CLRS patient-reported behaviors and exposures and microbial bioburden. And, while the study group has been making steps toward a broader assessment of the many known and presumed risk factors, the ORACL pilot study did not assess all of the known and presumed drivers of CL complications (i.e., genetic predisposition, ocular immune response).[57–59] Nevertheless, this study demonstrated that the use of standardized patient surveys and study procedures allowed systematic collection of detailed data that would not otherwise have been available from clinical records and can be used as a model for future studies.[51,52,60]

Conclusions

This pilot study demonstrated feasibility of enrolling a diverse and representative mix of active CIE and control subjects, and assessment of risk factors using a multipronged approach that included a self-administered patient survey, trained investigator examination, and microbial culturing. A larger study is needed to better understand relationships between microbial bioburden and behaviors and exposures of SCL wearers.

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