Risk Factors for Moderate and Severe Microbial Keratitis in Daily Wear Contact Lens Users

Fiona Stapleton, PhD,1,2,3 Katie Edwards, PhD,2,3 Lisa Keay, PhD,2,3,4 Thomas Naduvilath, PhD,1,2 John K. G. Dart, DM,5 Garry Brian, FRANZCO,3,6 Brien Holden, DSc1,2,3,6

Objective: To establish risk factors for moderate and severe microbial keratitis among daily contact lens (CL) wearers in Australia.

Design: A prospective, 12-month, population-based, case-control study.

Participants: New cases of moderate and severe microbial keratitis in daily wear CL users presenting in Australia over a 12-month period were identified through surveillance of all ophthalmic practitioners. Case detection was augmented by record audits at major ophthalmic centers. Controls were users of daily wear CLs in the community identified using a national telephone survey.

Testing: Cases and controls were interviewed by telephone to determine subject demographics and CL wear history. Multiple binary logistic regression was used to determine independent risk factors and univariate population attributable risk percentage (PAR%) was estimated for each risk factor.

Main Outcome Measures: Independent risk factors, relative risk (with 95% confidence intervals [CIs]), and PAR%.

Results: There were 90 eligible moderate and severe cases related to daily wear of CLs reported during the study period. We identified 1090 community controls using daily wear CLs. Independent risk factors for moderate and severe keratitis while adjusting for age, gender, and lens material type included poor storage case hygiene 6.4 × (95% CI, 1.9–21.8: PAR, 49%), infrequent storage case replacement 5.4 × (95% CI, 1.5–18.9: PAR, 27%), solution type 7.2 × (95% CI, 2.3–22.5: PAR, 35%), occasional overnight lens use (<1 night per week) 6.5 × (95% CI, 1.3–31.7: PAR, 23%), high socioeconomic status 4.1 × (95% CI, 1.2–14.4: PAR, 31%), and smoking 3.7 × (95% CI, 1.1–12.8: PAR, 31%).

Conclusions: Moderate and severe microbial keratitis associated with daily use of CLs was independently associated with factors likely to cause contamination of CL storage cases (frequency of storage case replacement, hygiene, and solution type). Other factors included occasional overnight use of CLs, smoking, and socioeconomic class. Disease load may be considerably reduced by attention to modifiable risk factors related to CL storage case practice.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. Ophthalmology 2012;119:1516–1521 © 2012 by the American Academy of Ophthalmology.
etritists were identified through the state registration boards and professional associations, and were similarly contacted at the start of the study. Active follow-up was carried out for therapeutically licensed optometrists and members of regional CL societies. Case detection was augmented by retrospective inpatient and casualty (where available) record audits at ophthalmic centers with a catchment population of >200,000 individuals (n = 11). Detailed methods have been reported elsewhere.5,12,13

Microbial keratitis was defined by either a positive corneal culture or a corneal infiltrate and overlying epithelial defect with ≥1 of the following characteristics:

- Any part of the lesion within or overlapping the central 4 mm of the cornea;
- Uveitis; or
- Pain.

Eligible cases were stratified by severity according to the disease characteristics as stated in Table 1. Vision loss was defined as a loss of 2 or more lines of best-corrected spectacle acuity compared with pre-event acuity (where available) or with fellow eye acuity (where available) or compared with 20/20. Written consent was obtained from patients to allow access to medical records, and consent was sought to perform a telephone interview and to collect pre-event data from the CL practitioner. Human research ethics approval was obtained from the University of New South Wales Human Research Ethics Committee and 51 regional area health services in Australia.

Identification of Controls and Eligibility

Contact lens–wearing controls were identified using a population-based telephone survey based on the population distribution of Australia. Cases and controls were interviewed by phone to determine CL type, wear habits, hygiene compliance and history, and demographics. Risk factors considered in the analysis are shown in Table 2.

Table 1. Criteria Used to Grade Severity of Microbial Keratitis Cases

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe keratitis</td>
</tr>
<tr>
<td>Moderate keratitis</td>
</tr>
<tr>
<td>Mild keratitis</td>
</tr>
</tbody>
</table>

*Report from practitioner or laboratory. 3+ colonies on ≥1 solid medium; 3+ on 1 solid and growth in broth; growth in 2 broth + similar morphology to organisms on smear. This grade allows for some variability between laboratory and practitioner criteria and their interpretation of the test result. Generally if the organism was only found on one medium, and/or after long periods of incubation, the result was considered negative.

†Dimension in the longest meridian.

Eligible CL wearers were individuals aged 15 to 64 years wearing lenses for the correction of low refractive errors (keratoconic, aphakic, and bandage CL wearers were excluded), who had worn their lenses in the 4 weeks before the event (cases) or before the survey phone call (controls). Definitions for mode of lens wear and lens hygiene have been reported elsewhere.14 Regular overnight use of CLs, sleeping in lenses overnight once per week or more, was classified as overnight wear (also known as extended wear). Cases and controls using lenses on this schedule were excluded from the analysis. Cases and controls using CLs overnight but less often than once per week were classified as occasional overnight wearers and included in the analysis. Strict daily wear was defined as no overnight use ever admitted.

Data Analysis

Univariate analysis initially determined the significance of all possible risk factors using the chi-square/Fisher exact tests for categorical risk factors and the t test for those measured on an interval scale. Factors that were significant at P<0.2 were considered for multivariate testing using binary logistic regression. Multiple binary logistic regression estimated determinants of risk of infection for both all keratitis and moderate and severe keratitis, as defined in Table 1. The goodness of fit of the final model was assessed using the Hosmer–Lemeshow test and discriminatory ability.
using the area under the receiver operating characteristic curve. Both models included age, gender, socioeconomic class, lens material type, and mode of lens use. A factor was retained in the final model if either there was a significant improvement in chi-square value or if confounding occurred. Interactions were explored and included in the model where statistically significant. Significance was set at 5%. The strength of association for significant factors was summarized using odds ratios and confidence intervals.

Univariate and combined PAR% were calculated to estimate the proportion of total cases that would be reduced by removing the risk factor from the population. Population attributable risk percentage is the rate of occurrence of the condition that can be attributed to the risk factor. Combined PAR% was estimated as follows:

\[
\text{Combined PAR\%} = \left(1 - \left(1 - \text{PAR}_{\text{risk factor 1}}\right)\right) \times 100
\]

Results

There were 125 eligible daily wear cases reported during the 12-month study period, including a subgroup of 90 cases of moderate or severe keratitis. Of the 90 cases, 63 were scraped for smear and culture and 41 of 63 (65%) were culture proven. Environmental organisms (Gram-negative bacteria, fungi, and Acanthamoeba) caused severe disease in 32 of 41 (78%) of culture proven cases, with 2 cases (5%) attributed to Acanthamoeba spp. There were no cases of fungal keratitis reported in this cohort. Corneal culture results are shown in Table 3.

We identified 1090 community controls using daily wear CLs during the telephone survey. Risk factors for moderate and severe microbial keratitis in daily wearers determined by multivariate analysis are shown in Table 4. Data for all keratitis from the same study dataset are shown for comparison, and only significant risk factors for each model are reported. Significant risk factors for moderate and severe disease in daily wear CL users included occasional overnight use of daily wear CLs (overnight use more often than once per month but less often than once per week), poor lens case hygiene (failure to air dry the storage case after use), smoking and high socioeconomic class, solution type (Multipurpose solution A, a no-rub multipurpose solution containing 0.0001% polyhexamethyl biguanide, polyoxam derivatives [Pluronic 87] and ethylidihyde tetra-acetic acid), infrequent case replacement (less frequently than every 6 months). The receiver operating characteristic curve statistic indicates an excellent model fit with these factors accounting for 90% of the variance in the model.

Univariate PAR% for all independent risk factors in severe disease are shown in Table 4. The combined PAR% for lens storage case replacement and storage case hygiene was 62%.

Discussion

The recent publication of incidence rates for all CL-related microbial keratitis has demonstrated that, despite the many advances in CL materials and solutions over the past 15 years, the incidence of infection has remained stable. One possible approach to limiting disease morbidity is to identify and address modifiable risk factors associated with moderate or severe microbial keratitis, a subset of microbial keratitis associated with greater morbidity in terms of vision loss, disease duration, and cost of disease.

The present study has applied sound population-based methodology to elicit risk factors and PAR% in a population using contemporary CLs prescribed for daily use, the most common CL modality prescribed in the community. Within the Australian population, 92% of wearers use CLs prescribed for daily use. Although lenses may be prescribed for daily wear, users may occasionally sleep in their CLs and this study establishes risks associated with the habitual wear of these products. Strengths and limitations of this study have previously been discussed, and it is possible that with changes to lens solutions and lens materials over time that the findings reported here may not be representative of all products currently in use. Notwithstanding this limitation, this study represents one of the most comprehensive evaluations of risk factors for CL-related infection, particularly moderate and severe disease, ever undertaken, both with regard to the sample size and the spectrum of risk factors considered.

Multivariable analysis for moderate and severe microbial keratitis has indicated an excellent model fit with those independent risk factors accounting for 90% of the variance in the data. Both poor CL case hygiene and infrequent replacement of the CL storage case were independently associated with a higher risk of moderate and severe keratitis. Almost 50% of all moderate and severe disease in daily wear could be eliminated by better attention to lens case hygiene and 27% by frequent storage case replacement alone. Attention to lens storage case hygiene and replacement practice combined would remove 62% of the disease load.

Poor storage case hygiene, namely, failure to air dry storage cases, has been identified as a risk factor in a study of all CL-related presumed microbial keratitis. These new data confirm the importance of the CL storage case in moderate and severe keratitis in daily wear CL users, possibly because the case may act as the source of causative organisms. Identical organisms have been previously recov-
Table 4. Risk Factors and Univariate Population Attributable Risk Percent for All Microbial Keratitis and Moderate and Severe Microbial Keratitis

<table>
<thead>
<tr>
<th>Factor</th>
<th>All Keratitis*</th>
<th>Moderate and Severe Keratitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P Value</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Ages (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid (25–54)</td>
<td>0.855</td>
<td>0.92</td>
</tr>
<tr>
<td>Young (15–24)</td>
<td>0.660</td>
<td>1.34</td>
</tr>
<tr>
<td>Old (55–64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.384</td>
<td>0.70</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lens material</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft hydrogel</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Daily disposable</td>
<td>0.499</td>
<td>1.49</td>
</tr>
<tr>
<td>Silicone hydrogel</td>
<td>0.058</td>
<td>2.62</td>
</tr>
<tr>
<td>Rigid</td>
<td>0.210</td>
<td>0.27</td>
</tr>
<tr>
<td>Mode of use&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strict DW</td>
<td>0.788</td>
<td>0.88</td>
</tr>
<tr>
<td>DW w o’night of 1/month or less</td>
<td>0.014</td>
<td>3.96</td>
</tr>
<tr>
<td>DW w o’night of 1/month to less than 1/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lens case hygiene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>0.001</td>
<td>3.70</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.007</td>
<td>2.96</td>
</tr>
<tr>
<td>No</td>
<td>0.013</td>
<td>2.66</td>
</tr>
<tr>
<td>Socioeconomic class&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQR 1 and 2 (low)</td>
<td>0.013</td>
<td>2.66</td>
</tr>
<tr>
<td>IQR 3 and 4 (high)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place of lens purchase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optometrist</td>
<td>0.031</td>
<td>4.76</td>
</tr>
<tr>
<td>Care solution type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other brands</td>
<td>0.001</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Multipurpose solution A&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of case replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least every 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least every 6 months</td>
<td>0.685</td>
<td>1.47</td>
</tr>
<tr>
<td>Less than every 6 months</td>
<td>0.009</td>
<td>5.39</td>
</tr>
<tr>
<td>Area under the ROC curve</td>
<td>79.1%</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; DW = daily wear; ROC = receiver operator curve; w o’night = with overnight.

*Data for all keratitis are shown for comparison. Only factors significant in the final model are shown for both analyses. Blank entries indicate factors not significant in the final model for either analysis.

<sup>a</sup>Individual univariate population attributable risk percent (PAR%) add up to >100% because exposures are not mutually exclusive. The combined PAR% for lens storage case replacement and storage case hygiene was 62%.

<sup>b</sup>Mode of use is defined as strict DW, daily use of lenses with no overnight use admitted; occasional overnight use defined as DW with overnight wear less often than once per week. Occasional overnight use has been further stratified into DW with occasional overnight use of less than once per month and DW with occasional overnight use between once per month but less often than once per week.

<sup>c</sup>Socioeconomic class was classified using the Socio-Economic Indexes for Areas based on the 2001 Australian Census. Scores were divided into quartiles and grouped as low and high interquartile ranges (IQRs). IQRs 3 and 4 (high) were compared with IQRs 1 and 2 (low, referent).

<sup>d</sup>Multipurpose Solution A; Complete Comfort Plus (Advanced Medical Optics, Inc; Santa Ana, CA), a no-rub solution containing 0.0001% PHMB, Poloxamer 237 (Pluronic 87), ethylene diamine tetra-acetic acid.

Eroded from the storage case and the corneal ulcer in bacterial and amoebic disease. Notwithstanding this association, good compliance with hygiene recommendations does not guarantee contamination-free storage cases, and microbial biofilms form on CL cases, irrespective of compliance with lens cleaning and disinfection instructions. The present study has confirmed that additional case hygiene factors are important for moderate and severe keratitis compared with all keratitis. More severe disease is typically associated with environmental pathogens, rather than commensal or skin biota. The storage case seems to provide an environment that supports the growth of environmental organisms. This hypothesis is also supported by the observation that the compliant use of daily disposable CLs in the absence of a storage case is associated with a low risk of moderate or severe keratitis, and shows a greater predisposition for commensal organisms as causative agents. Within this dataset, 6% of cases and 12% of controls used daily disposable CLs. Eliminating the need to use a CL storage case through the use of daily disposable CLs may
reduce the likelihood of lens contamination by environmental microorganisms.\textsuperscript{10}

Poor lens hygiene has consistently been associated with all presumed microbial keratitis\textsuperscript{6,7,9} and with sterile keratitis.\textsuperscript{22} However, other than storage case hygiene practice, compliance with other lens hygiene recommendations, including use of lubricants, lens cleaning instructions, storing lenses in saline, lens disposal, and replacement routine, was not associated with moderate and severe keratitis in daily lens wearers.

Occasional overnight use of daily-wear CLs results in a higher risk of moderate and severe keratitis than does strict daily wear. In this analysis, the frequency of occasional overnight use was a major determinant of risk; use of up to once per month was indistinguishable in risk from strict daily use. However, more frequent occasional overnight use (more often than once per month but less than once per week) increased the risk of disease by 6.5× and accounted for 23% of the disease load. It is possible that this is because of more “risk” behaviors or attitudes to CL wear in an individual who chooses to wear lenses more frequently overnight rather than the physiologic impact on the cornea of increased overnight use.

Solution type was identified as an independent risk factor for moderate and severe keratitis and accounted for 35% of the disease load. Associations between solution type and more severe disease have previously been shown for \textit{Acanthamoeba}\textsuperscript{23} and \textit{Fusarium} keratitis.\textsuperscript{24,25} The higher risk associated with the solution identified in this study, independent of lens type and self-reported hygiene compliance, including both rubbing and rinsing CLs and storage case hygiene, may suggest some failure of the product in use, which allows microorganisms to survive in the storage case. This result is supported by several laboratory studies that are summarized as follows. Reduced antimicrobial activity against clinical and tap water isolates of \textit{Acanthamoeba}, has been reported for this product compared with other multipurpose solutions.\textsuperscript{26} However, when used with a rub and rinse regimen, its activity against the International Standards Organisation panel of microorganisms was comparable to other, multipurpose solutions.\textsuperscript{27} During periods of extended storage in the presence of a CL, a reduction in the antimicrobial efficacy of this product has been demonstrated.\textsuperscript{28} Recently, biofilms formed on CLs by both International Standards Organisation panel bacteria and clinical bacterial isolates have been shown to be more resistant to polymeric biguanide–based care systems compared with hydrogen peroxide or polyquaternium–based care systems.\textsuperscript{29}

Other independent risk factors reported here have been previously associated with presumed microbial keratitis, irrespective of disease severity. Smoking has previously been associated with an increased risk of infection and has been considered a possible proxy for other types of risky behaviors.\textsuperscript{6} Lower socioeconomic status has been associated with an increased risk of presumed microbial keratitis.\textsuperscript{6,7} The association between higher socioeconomic class and moderate and severe microbial keratitis in the present study was unexpected and remains unexplained. Perhaps this is attributable to some attitude or behavior to lens wear not examined in this study. Interestingly, a recent case-control study of \textit{Fusarium} keratitis\textsuperscript{30} showed that, based on monthly household income, those of higher socioeconomic status had a greater risk of infection than those of lower status.

There were differences in the risk factors between all microbial keratitis and moderate and severe disease only. These differences may be because of the smaller sample size and reduced power for the more severe phenotype. For example, the place of CL purchase was a significant factor for all disease, but not for moderate or severe disease. The greater impact of solution type and storage case hygiene/ replacement in moderate and severe disease may suggest that the mechanisms of disease differ.

In conclusion, moderate and severe microbial keratitis in daily CL users was associated with occasional overnight use of CLs, poor storage case hygiene, smoking, solution type, and infrequent storage case replacement. Contact lens material type and wearer age and gender were not associated with moderate and severe disease. These data support the importance of the CL storage case in moderate and severe disease, with almost 50% of the disease load attributable to poor case hygiene. Attention to modifiable risk factors, specifically to CL storage case practice, may reduce disease severity and possibly the incidence of microbial keratitis in CL users. These findings imply that there is a continuing need for education among CL users in safe CL practice.

References


Footnotes and Financial Disclosures


Available online: April 21, 2012. Manuscript no. 2011-1147

1 Brien Holden Vision Institute, Sydney, Australia.
2 School of Optometry & Vision Science, University of New South Wales, Sydney, Australia.
3 Vision CRC, Sydney, Australia.
4 The George Institute for Global Health, University of Sydney, Sydney, Australia.
5 NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and the University College London, Institute of Ophthalmology, London, United Kingdom.
6 International Centre for Eyecare Education, Sydney, Australia.

Financial Disclosure(s):
The authors have no proprietary or commercial interest in any of the materials discussed in this article.

This study was supported by the Brien Holden Vision Institute (F.S., T.N.), CIBA Vision (all authors), the University of New South Wales (F.S.), the Vision Cooperative Research Centre (K.E., L.K.), the National Health and Medical Research Council (L.K.). The authors were responsible for design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. A draft of the manuscript was provided to the Brien Holden Vision Institute and CIBA Vision before publication, and modifications were limited to clarification and editorial changes.

The Vision CRC and Brien Holden Vision Institute receive a royalty on the sales of certain contact lenses.

Correspondence:
Professor Fiona Stapleton, Brien Holden Vision Institute, University of New South Wales, Sydney, New South Wales, 2052, Australia. E-mail: