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The association of contact lens solution use and *Acanthamoeba* keratitis

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Abstract

Purpose—Diagnosis of *Acanthamoeba* keratitis, a rare but serious corneal infection, has recently increased significantly at the University of Illinois at Chicago (UIC) Cornea Service. The purpose is to investigate *Acanthamoeba* keratitis risk factors.

Design—Retrospective case-control study.

Setting: University, tertiary care hospital.

Patients: Fifty-five *Acanthamoeba* keratitis cases with contact lens use were diagnosed between May 1, 2003 and September 15, 2006. Clinic-matched controls with contact lens use were recruited. Subjects completed surveys targeting lens hygiene, contact lens solution use, and water exposure.

Main Outcome Measure: *Acanthamoeba* keratitis.

Results—Thirty-nine (73.6%) cases and 113 (65.3%) controls participated; 38 cases had complete contact lens data. Thirty-five of 38 cases (92.1%) and 47 of 100 controls (47.0%) used soft lenses. Analysis was performed on 30 cases and 39 controls with matched pairs with soft lens use. Exclusive use of AMO Complete MoisturePlus Multi-Purpose Solution was independently associated with *Acanthamoeba* keratitis in multivariable analysis (55.2% vs. 10.5%; OR, 16.67; 95% CI, 2.11–162.63; p = 0.008). However, 38.8% of cases reported no use of AMO Complete MoisturePlus Multi-Purpose Solution or used it in combination with other solutions. Although not statistically significant, additional hygiene-related variables (solution 'reuse', lack of 'rubbing', and showering with lenses) suggest a pattern of risk,.

Conclusions—AMO Complete MoisturePlus Multi-Purpose Solution use is independently associated with *Acanthamoeba* keratitis among soft contact lens users. However, it does not explain all cases, suggesting additional factors. Further research into environmental risk factors and hygiene

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practices is warranted, especially considering this is the second outbreak of an atypical, contact lens-related infection.

Introduction

Acanthamoeba keratitis (AK) is a severe, painful infection of the cornea that usually causes corneal scarring and sometimes blindness. The causative agent, *Acanthamoeba*, is a ubiquitous free-living amoeba that is believed to contaminate the cornea through exposure to contaminated water, often potentiated by contact lens wear.[1] The first published report of confirmed AK was in 1974,[2] and through the next decade the infection was considered extremely rare. Disease frequency increased during the 1980's and temporally paralleled the widespread introduction of soft contact lenses. A 1985 AK outbreak investigation by the Center for Disease Control and Prevention implicated contact lens use as a primary cause,[3] and more than 85% of AK cases reported to the CDC between 1973 and 1988 were in contact lens wearers, suggesting that contact lens use is a significant risk factor.[4, 5] As further evidence, *Acanthamoeba* cysts and trophozoites have been shown to adhere to all types of contact lenses,[1, 6–12] suggesting that contact lenses may serve as a vector for disease transmission.[1] Other well-known risk factors include poor lens hygiene, contact lens use while swimming, use of certain contact lens disinfection products, and source water contamination.[13, 14] Genetic typing of *Acanthamoeba* isolates from the cornea in previous UK reports has matched *Acanthamoeba* isolates from the water supply in homes of AK patients.[15]

Because AK is rare, the epidemiology in the United States is poorly understood. The U.S. annualized incidence has been conservatively estimated to range from 1.65 to 2.01 cases per million contact lens wearers however[16] it may be as much as 15 times more common in the UK, Europe and Hong Kong.[13, 17, 18]

A statistically significant increase in AK cases occurred in the Chicago-area beginning in June 2003,[19] with a total of 63 incident cases identified through the end of 2006. This increase is inconsistent with previously understood risk factors, which to our knowledge, are unchanged in frequency.

Acanthamoeba species are largely resistant to most contact lens solutions.[22–29] Contact lens solutions in 2006 were independently associated with *Fusarium* keratitis, another rare and serious eye infection that is not normally associated with contact lens use.[20]

It is important to investigate the potential role of contact lens solutions in AK diagnosis because: 1) questions exists over contact lens solution effectiveness against AK; 2) solution companies are not required to demonstrate effectiveness against *Acanthamoeba* nor potential interactions between contact lens FDA Lens Group and solutions for FDA approval; and, 3) a specific contact lens solution was independently identified as a risk factor in the *Fusarium* outbreak. We have previously hypothesized that recently implemented U.S. Environmental Protection Agency (EPA) regulations reducing the allowable amount of carcinogenic disinfection byproducts in the water supply may have shifted the microbial risk balance and increased the risk of AK from tap water exposure.[19, 21] This solution risk factor analysis was conducted in conjunction with our ongoing case-control study investigating AK risk factors involving individual surveys and conducting water sampling of homes with laboratory and molecular analysis of identified corneal and environmental *Acanthamoeba* isolates. The purpose of this analysis is to investigate if use of certain contact lens solutions are associated with AK.

Methods

The University of Illinois at Chicago (UIC) Institutional Review Board reviewed and approved this research.

Disease Definition

Patients with atypical keratitis were defined as AK cases if they had disease resolution with anti-acanthamoebal treatment and at least one or more of the following conditions: 1) identification of trophozoites or cysts on confocal microscopy; 2) identification of trophozoites or cysts through smears when specimens were stained with Diff-Quick stain; 3) positive *Acanthamoeba* cultures; or, 4) pathology identification of AK on keratoplasty specimens. This definition was chosen based on 1) evaluation of the validity of diagnostic tests within our AK series; 2) confocal microscopy diagnostic sensitivity of 94.3% and specificity of 72% when compared against objective laboratory evidence of disease in a cohort of subjects who had confocal microscopy performed; and, 3) the fact that culture sensitivity in our series was only 51.3% (Tu EY et al. IOVS 2007;48:ARVO E-Abstract 753; AAO 2006:Abstract 455; Tu EY et al, under review, *American Journal of Ophthalmology*). This low culture positive rate is consistent with large-scale studies in the UK in which culture positive rates ranged from 43% – 54%,[13, 22] suggesting loss of cases if restricting to culture positive disease. All confocal microscopy images were re-reviewed at a single sitting prior to study initiation to minimize potential intra-observer variability.

Case Control Definition and Selection

All AK cases diagnosed at the UIC Cornea Service between May 1, 2003 and September 15, 2006 were included in analysis. Cases were restricted to contact lens wearers (n = 55). Potential cases were entered into an Excel-based tracking system and followed until pending diagnostic tests and clinical results confirmed AK status.

Controls were defined as contact lens-wearing patients from the UIC Cornea Service with all other conditions; patients with AK or diseases requiring use of soft bandage contact lenses were excluded as controls. Controls were selected according to patient census data. Controls were restricted to contact lens users and a 1:M variable-matching ratio plan was used to individually match cases to controls according to date of visit (± 1 month) and age (± 5 years). Matching factors were chosen as case age was somewhat bimodal in distribution and age-matching insured adequately-aged controls for analysis; as well, date-of-service was selected to control for potential seasonal variability in exposure to *Acanthamoeba*-contaminated water (ie, variability in recreational water activities or thermal variability in the water distribution system influencing microbial load due to organism thermotolerance, etc.). Both soft and rigid lens users were eligible.

Data Collection

All subjects were telephoned and invited to participate, and study packets consisting of a survey, water sampling kit and postage-paid return envelope were mailed to subjects who agreed to participate. All subjects signed informed consent documents and returned signed documents through the mail with survey and water sampling packets. Subjects were categorized ‘unable to contact’ if existing home and work telephone numbers were incorrect, or if five or more calls at different times and days of the week did not result in contact. Survey questions were focused on the six-month time period prior to symptom development and targeted three main categories of variables: 1) water exposure; 2) contact lens hygiene (including solutions and lens types); and, 3) habits associated with contact lens use. Color images of all contact lens solution products were included within the survey to assist in memory recall. The six-month time period was assigned for controls, starting from the date of symptom onset in matched cases.

Determination of Contact Lens Solution Product Formulations

Product formulations in solutions common to AK cases were reviewed to determine equivalency within a brand through the FDA 510(k) Premarket Notification Database Search accessed at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Findings were reviewed with James Saviola, OD, Chief, Vitreoretinal and Extraocular Devices Branch, Ophthalmic Device Panel, U.S. FDA (personal communication, March 12, 2007). The most recent AMO Complete Multi-Purpose Solution formulation change, 'Upgrade C' was approved by the FDA on December 10, 2002 (K023226), and was launched on August 18, 2003 according to the corporate website[23] (Advanced Medical Optics, Santa Ana, CA). The present formulation remains the same as the December 2002 formulation, and subsequent approvals have been labeling changes. All AMO Complete multipurpose solutions were treated as the newest formulation for analyses, AMO Complete MoisturePlus Multi-Purpose Solution (hereafter referred to as Complete MoisturePlus) because: 1) most subjects probably used Complete MoisturePlus based on the FDA approval date and market availability; and 2) the product names and images were nearly identical making discrimination between products difficult (AMO Complete MoisturePlus Multi-Purpose Solution vs. AMO Complete Multi-Purpose Solution). Differential reponses were compared over time to determine if they suggested changing market shares over time, and this was not evident.

Statistical Analysis

All statistical analyses were performed using SAS (v. 9.1.3; SAS Institutes, Cary, NC). Analyses were performed on all subjects unless either they or their matched case had missing data on contact lens use or reported no contact lens use during the assigned time period (n: cases = 1, controls = 13; Table 1), in which case they were dropped from further analysis. Descriptive analysis was conducted on all subjects currently enrolled in the case-control study. Analyses were restricted to subjects that used soft contact lenses because soft contact lens use was different between cases and controls. Univariate analysis was performed on this subset of complete matched case-control pairs using exact conditional logistic regression to estimate the odds ratio and 95% confidence intervals; cases or controls without matched pairs were dropped from analyses (Table 3). Exact conditional multivariable logistic regression was performed using forward stepwise addition to assess whether exclusive use of Complete MoisturePlus was associated with AK as compared to use of all other soft contact lens solution products after controlling for confounding variables. Exact unconditional logistic regression was also performed using the same subset of soft lens subjects and compared against exact conditional logistic regression results after controlling for confounding and matching variables, since use of conditional logistic regression in small data sets can produce biased estimates of effects and unconditional methods may yield more stable risk estimates.[24, 25] Exclusive use of Complete MoisturePlus was compared to use of all other soft lens solutions including use of multiple solutions because if Complete MoisturePlus was the greatest risk factor, then addition of other solutions to the exposed category would dilute risk compared to exclusive use of Complete MoisturePlus. A sensitivity analysis was performed to address the effects of missing data in regards to use of Complete MoisturePlus in which cases were classified as either exposed or unexposed, and controls were classified oppositely. Analysis was performed on the subset of culture positive cases to similarly confirm the robustness of results.

Results

Between May 1, 2003 and September 15, 2006, 55 AK cases were identified. Two hundred sixteen contact lens-wearing controls matched on age and date-of-service were identified through clinic census data and medical record reviews to determine contact lens use status. Of these, 152 subjects agreed to participate and completed survey and water sampling packets, resulting in cooperation rates[26] of 65.3% for controls and 73.6% for cases (Table 1). Of these, 38 cases and 100 controls were eligible based on complete data on contact lens use and use of contact lenses during the study period.

Thirty-five of 38 AK cases (92.1%) used soft contact lenses, as compared to only 47 of 100 (47%) controls (Table 2). Anecdotally, many soft contact lens controls were diagnosed with microbial keratitis, although this was not formally tracked. Of the 36 cases with complete data on solution use, 19 (52.8%) reported exclusive use of Complete MoisturePlus, as compared to only 7 of 100 (7.3%) unmatched controls and 4 of 39 (10.5%) matched soft contact lens controls (Tables 2 and 3; $p < 0.0001$).

Matched analysis was limited to soft contact lens users because soft contact lens use between cases and controls was statistically different and solutions are unique to soft and rigid lenses. Matched analysis included 30 cases and 39 matched controls because 30 of 35 cases had matched controls and 39 of 47 controls had matched cases currently participating in the study. There were no statistically significant differences between cases and controls in demographic variables, suggesting soft contact lens controls were similar to cases. There was no statistically significant difference in overnight contact lens use, which is a known risk factor for general microbial keratitis (Table 3).[27–29]

Cases were significantly more likely to report exclusive use of Complete MoisturePlus than controls (55.2% vs. 10.5%, respectively; OR, 17.76; 95% CI, 2.23 – 141.22; Table 3, Dichotomous solution use). Cases were also statistically more likely to report solution reuse or ‘topping off’ more than five times a month compared to five or fewer times per month (58.6% vs. 25.6%; OR, 3.19; 95% CI, 1.10 – 9.27; Table 3, Reuse solution).

Four hygiene-related variables demonstrated relatively strong measures of effect despite imprecise confidence intervals, including frequency of lens replacement, age of case at replacement, rubbing lenses while cleaning, and showering while wearing contact lenses (Table 3); the remaining variables resulted in non-statistically significant results. As such, multivariable analysis results adjusting for Complete MoisturePlus solution use and solution reuse or ‘topping off’ are presented in Table 4 and include these hygiene-related variables. Other variables with non-statistically significant results are excluded.

Self-reported use of Complete MoisturePlus was independently identified as a risk factor in multivariable analysis (OR, 16.67; 95% CI, 2.11 – 162.63; Table 4). The odds ratio for hygiene-related variables was strong despite imprecise confidence intervals (solution reuse more than five times per month compared to five or fewer times: OR, 3.17, 95% CI, 0.82 – 12.33; rubbing lenses ten or fewer times per month during cleaning compared to more than ten times: OR, 9.05, 95% CI, 0.82 – 100.19; shower with lenses more than five times per month compared to five or fewer times: OR, 9.07, 95% CI, 0.68 – 120.72).

Exact unconditional logistic multivariable regression demonstrated similar results in which exclusive use of Complete MoisturePlus was the strongest risk factor and a single hygiene-related variable became statistically significant while the rest remained non-significant (Complete MoisturePlus use: OR, 9.36, 95%CI, 2.42 – 36.21; solution reuse more than five times per month compared to five or fewer times: OR, 4.20, 95% CI, 1.25 – 14.10; Table 4).

Analyses performed with different dichotomous classifications of Complete MoisturePlus solution use, including restriction to single solution use and use of Complete MoisturePlus either alone or in combination with other solutions, resulted in consistent findings and identified Complete MoisturePlus use as independently associated with AK. The sensitivity analysis and also analysis of the subset of culture-positive cases (18 of 30 soft lens users) and their matched controls similarly identified Complete MoisturePlus use as independently associated with AK in multivariable analysis.

Discussion

These findings demonstrate that self-reported use of AMO Complete MoisturePlus Multi-Purpose Solution is an independent risk factor for AK among soft contact lens users. This is biologically plausible because *in vitro* studies demonstrate *Acanthamoeba* species are largely resistant to contact lens solutions in general,[30–39] and to Complete MoisturePlus in particular.[30, 31, 39] Although solutions have been largely effective enough to prevent AK through the 1990's[16] up until 2003 when our outbreak began[19] it is plausible that the recent AK outbreak may be due to a relative inability to withstand an *Acanthamoeba* challenge triggered by a higher microbial load related to potential outside issues, such as environmental- or hygiene-related factors.

A positive but statistically weak association was observed with conditional analysis between three hygiene-related variables (solution reuse, rubbing lenses, and showering with lenses) examined in our study; this association was consistent and strengthened in unconditional analysis. We did not find an association with overnight lens wear, however this may be artifactual due to the fact that we used a clinic-based control group and many had been diagnosed with microbial keratitis. The role that chance and various biases may play in these suggested associations needs to be clarified in larger studies; however, they are consistent with previous studies indicating poor hygiene in general as a risk factor.[13, 16, 18] These hygiene-related factors are important as they may help prevent disease, and although AK is still rare among contact lens users, contact lens use is common with an estimated 36 million people using contact lenses in the United States.[40] There have been published reports in the past year of increases in AK cases from multiple cities including Philadelphia,[30] Portland, [31] San Francisco (Sansanayudh et al. IOVS 2007;48:ARVO E-Abstract 756), and Boston (Tanhehco et al. IOVS 2007;48:ARVO E-Abstract 754), suggesting an AK increase elsewhere, too. Although this analysis is restricted to soft contact lens wearers seen in the UIC Cornea Service in Chicago, risk factors investigated and identified in this analysis are not unique to Chicago. Because this AK outbreak represents the second concurrent outbreak of a rare and serious eye infection,[19, 20] maintaining contact lens hygiene is prudent.

Additional risk factors beyond the identified solutions may be contributing to the dual increase in rare, contact-lens related keratitis caused by *Acanthamoeba* and *Fusarium* organisms. Complete MoisturePlus formulation changes in late 2002 roughly paralleled the onset of our outbreak; however, many cases did not use Complete MoisturePlus, suggesting inconsistencies in the simple assumption that the outbreak resulted from a product formulation change. In both the *Acanthamoeba* and *Fusarium* outbreaks, cases developing keratitis that did not use the affected solution exceeded the expected baseline occurrence of disease in contact lens wearers for each organism. Only 53% of AK cases used Complete MoisturePlus exclusively and 61% used Complete MoisturePlus either alone or in combination with other products; only 64% of *Fusarium* cases used Bausch & Lomb Renu MoistureLoc exclusively and 79% used MoistureLoc either alone or in combination with other products in the recent *Fusarium* keratitis outbreak investigation (Table 5; Bausch & Lomb, Rochester, NY).[20] In addition, cases of contact lens-related *Fusarium* keratitis that never used MoistureLoc solution have been reported after MoistureLoc removal from the market (Jeng et al. Federated Scientific Societies Session, 2006).

If suboptimal contact lens hygiene, such as reusing solution and not rubbing lenses during cleaning, contributes to increased biofilm on contact lenses, then *Acanthamoeba* exposure through shower aerosolization may contribute to disease, particularly if contact lens solutions are ineffective against *Acanthamoeba*. Showers have frequently been implicated as vectors in nosocomial infections through aerosolization of microbes,[41] and *Acanthamoeba* have been isolated from the air,[42, 43] making it plausible that exposure to *Acanthamoeba* organisms through showering while wearing contact lenses may contribute to AK disease. This possibility may be important if recent EPA regulations decreasing the allowable disinfection byproducts in the water supply have shifted the microbial risk,[19, 21] effectively increasing the load of microbes from general water exposure that contact lens solutions must kill in order to avoid disease. In addition, Complete multipurpose solution is less effective than other multipurpose solutions against cysts and trophozoites when tested using multiple *Acanthamoeba* genotypes,[39] as well as alternative amoebicidal efficacy testing techniques.[30, 31]

Analysis was restricted to soft contact lens use because the percentage of soft contact lens use between cases and controls was statistically different, reducing sample size. This differential soft lens use between cases and controls was unexpected based on previous AK series and laboratory studies, which suggest insufficient evidence to indicate differential AK risk among soft and rigid lens users. Control selection was not restricted to soft lenses as the percentage of soft lens use among contact lenses users in our AK series over time was between 85 – 95%, which approximates market shares[40, 44] and is similar to soft lenses use in other AK series.[3, 5, 13, 19, 22] Basic studies demonstrate nearly all U.S. rigid and soft contact lens solutions have at least some inadequacy in *Acanthamoeba* organism killing or inhibition.[8, 30–36] Results conflict as to whether *Acanthamoeba* organisms differentially adhere to soft and rigid lenses, although they appear to have greater adherence to newer silicone hydrogel lenses versus traditional soft hydrogel lenses.[1, 6–12, 45] Because there was insufficient evidence to suggest differential AK risk among soft and rigid lens users, controls were recruited that used any contact lens type. Results from our case-control study seem to imply that soft contact lens use may increase AK risk; however, this likely represents an artifact of excessive rigid lens use among controls as soft lens use in 92% of contact lens-wearing AK cases is more consistent with market shares. Rigid lens use among patients seen in a cornea clinic may be higher than the general population due to the beneficial optical properties of rigid over soft lenses for certain corneal disorders.

The frequency of contact lens replacement may be important in AK disease, as worn lenses increase *Acanthamoeba* attachment, presumably from biofilms that develop as a result of tear film deposits.[9, 10, 46] Our crude results based on the frequency of actual lens replacement (quarterly or more frequent vs. less frequent) did not demonstrate an effect between lens replacement and AK risk, however this result is likely confounded by many variables. It is plausible that older lenses may have a more highly developed biofilm than newer lenses, although the relationship is likely complex and may represent the culmination of all issues related to lens cleanliness if biofilm development is influenced by contact lens and tear film deposits, such as: individual tear film factors, lens material factors, solution efficacy factors, hygiene factors and lens age. Of these variables, the contact lens material FDA Lens Group appears to be more important than lens age or intersubject variability in predicting lens deposition,[47, 48] and this FDA Lens Group is also critical in predicting *Acanthamoeba* adherence.[11, 46, 49–51] This suggests that lens material may actually confound our lack of association between the frequency of lens replacement and AK risk. Even so, as we had considerable survey item non-response to contact lens product manufacturer and brand name, we were unable to further investigate FDA lens material grouping (Table 2).

Another large category in soft lenses includes silicone hydrogel lenses, which represent significant advancements in soft contact lens technology that allows substantially more oxygen to the eye. This increased oxygen is believed to reduce the risk of severe adverse events,[52–55] although this effect has not definitively been confirmed through population-based studies.

[56–58] On the other hand, *Acanthamoeba* appear to differentially adhere more strongly to silicone hydrogel lenses,[9, 10, 45] but our results did not show an increase in AK risk with silicone hydrogel lens use. Within this analysis, no cases and only 25% of soft lens-wearing controls reported silicone hydrogel lens use, yet silicone hydrogel lenses accounted for 37% of 2006 U.S. retail contact lens sales.[59] There was survey item non-response to contact lens product manufacturer and brand name, so misclassification potential for silicone hydrogel lens use exists (Table 2).

Potential misclassification effects resulting from analysis of all AMO Complete multipurpose solutions together are minimal. The outbreak continues unabated, and if related to the older formulation, the outbreak would have diminished, which is not the case. In addition, all cases reporting use of Complete multipurpose solutions were diagnosed after product launch of the newest formulation, AMO Complete MoisturePlus Multi-Purpose Solution. Based on a recent voluntary solution recall,[60] most old branded formulations remain on the market a maximum of approximately 12 months until supplies are used (James Saviola, OD, FDA, personal communication, March 12, 2006); if this were the case then only five cases reporting use of the previous Complete formulation may be misclassified, which still would result in more than twice as many AK cases using Complete MoisturePlus compared to any other brand. With current classifications, there are three-times more AK cases using Complete MoisturePlus compared to any other solution brand. Finally, AC Nielsen reports that contact lens solution market shares for the entire AMO brand approximated only 10% of the contact lens solution business between April and June 2006.[61] This suggests, strictly by crude analysis of market share, that only 10% of cases should be expected to report AMO use compared to other solutions, not the two- or three-fold increased reporting we find in our series. In comparison, only 10.5% of our soft lens controls reported Complete MoisturePlus use.

Several potential limitations exist within the study. First, clinic-based controls were used in order to further investigate the potential association between domestic water exposure and *Acanthamoeba* keratitis. Clinic-based controls are rarely considered either healthy or a random sample but simply ‘a sample’ of the source population, in part due to referral patterns.[62, 63] Clinic-based controls should represent many diseases and no association should exist between the study exposure and the disease causing the clinic visit to prevent underestimation of the disease association;[64] our controls included multiple diseases and there is no reason why study exposure, or use of Complete MoisturePlus, may result in controls requiring treatment at the UIC Cornea Service, hence our clinic-based control selection should lead to an appropriate effect measure (no fungal keratitis patients from the MoistureLoc outbreak[20] were among controls). Furthermore, reported use of Complete MoisturePlus among controls closely mirrored market shares of AMO in the general population, supporting our selection of controls and suggesting that results may be generalizable to the population. WhIle the use of clinic-based controls including microbial keratitis cases may have biased the association between overnight contact lens use and *Acanthamoeba* keratitis as overnight contact lens use is a known risk factor for microbial keratitis, it is unlikely to have changed the associaiton between Complete MoisturePlus use and *Acanthamoeba* keratitis as reported use of Complete MoisturePlus among controls mirrored market shares.[28, 56]

In addition, as with any retrospective study of self-reported data, potential recall bias exists that may affect the association between *Acanthamoeba* keratitis and Complete MoisturePlus use. Because previous associations between Complete MoisturePlus and *Acanthamoeba* keratitis have not been reported, the likelihood of differential recall between cases and controls is small, minimizing the potential effect of recall bias. As well, images of solution bottles were incorporated into the questionnaire to assist all subjects in memory and minimize potential recall bias.

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Finally, an oubtreak investigation of an extremely rare disease with limited cases may not have the statistical power to examine weaker disease associations. We attempted to mitigate this effect by including all cases of disease as defined by a very rigorous definition using multiple ancillary diagnositics tests, albeit a defintion not restricted exclusively to culture-positive cases. We think this is reasonable as *Acanthamoeba* culture positive rates are historically poor; for instance, Radford and Dart reported culture positive rates of 54% among 234 AK cases in 1992–96 and 43% among 106 AK cases in 1997–99 in an United Kingdom national survey.[13, 22] Critical to this study, there was no inter-observer variability: all diagnostic tests and the clinical evaluation were performed by a single individual, who – by virtue of our AK outbreak with more than 60 cases to date and a culture isolation rate around 50% – has been trained on the execution and interpretation of these diagnostic tests with nearly immediate validation of interpretation. Although our choice of case definition may have resulted in potential disease misclassification and biased associations, we believe this is unlikely given our strict disease definitions, and actually preferential to more conservative culture-positive definitions that prevent exploration of valid secondary hypotheses. Furthermore, the association between *Acanthamoeba* keratitis and Complete MoisturePlus use persisted when analysis was restricted only to culture-positive cases, which demonstrates the robust nature of our results.

In summary, our findings identify self-reported AMO Complete MoisturePlus Multi-Purpose Solution among soft contact lens users as a risk factor for AK. This is evident not only when examining results from our case-control study, but also when crudely comparing solution market share to the percentage of AK cases using AMO Complete MoisturePlus. While the underlying mechanism for this risk remains unknown, none of the widely-used multipurpose solutions have been shown to be highly efficacious against *Acanthamoeba*; however they have generally been adequate to suppress large AK outbreaks in the past.[8, 30–36] This suggests the risk presented by use of Complete MoisturePlus may be a relative inability to withstand an *Acanthamoeba* challenge compared to that of other solutions. Results similarly demonstrate non-statistically significant patterns of risk suggesting hygiene- and potentially water-related factors such as showering with contact lenses may contribute to AK. Despite the weak statistical association, these patterns may be important when taken into the context of a second unique outbreak of an extremely rare eye infection occuring in the same general time frame. In conclusion, our results demonstrate that use of AMO Complete MoisturePlus Multi-Purpose Solution is strongly associated with AK disease, but they also indicate that its use is not the only risk factor for disease. Continued research is warranted and ongoing to determine additional causes behind this AK outbreak and to evaluate whether potential shifts in the overall microbial load of the water supply may be contributing to this increase in disease.

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Table 1

Acanthamoeba keratitis case-control study participation response and cooperation rates. Response rates include all subjects including those who could not be contacted,* while cooperation rates reflect participation among contacted subjects.

Response Rates						**Cooperation Rates**†					
	Cases: *Acanthamoeba* keratitis		**Controls: No *Acanthamoeba* keratitis**				**Cases: *Acanthamoeba* keratitis**		**Controls: No *Acanthamoeba* keratitis**		
	n	**%**	**n**	**%**	**Total**		**n**	**%**	**n**	**%**	**Total**
'Unable to contact'*	2	3.6	43	19.9	45						
No	14	25.5	60	27.8	74	No	14	26.4	60	34.7	74
Yes	39	70.1	113	52.3	152	Yes	39	73.6	113	65.3	152
Total	55		216		271	Total	53		173		226

*Subjects were considered 'unable to contact' if existing home and work telephone numbers were incorrect, or if five or more calls at different times and days of the week did not result in contact.

†152 subjects agreed to participate; subjects were dropped if either they or their matched case had missing data on contact lens use or reported no contact lens use during the assigned time period (n: cases = 1, controls = 13), resulting in a total of 138 subjects (Table 2).

Table 2

Clinical characteristics of all enrolled *Acanthamoeba* keratitis cases and controls; all subjects used contact lenses.

	Cases: *Acanthamoeba* keratitis		Controls: No *Acanthamoeba* keratitis		Chi-square p-value
	Total n = 38	%	Total n = 100	%	Total n = 138
Use of soft contact lenses					
Yes	35	92.1	47	47.0	
No	3	7.9	53	53.0	p = <0.0001
Contact lens solution use					
Soft contact lens solutions					
AMO Complete MoisturePlus product[*]	19	52.8	7	7.3	
B&L ReNu products[†]	6	16.7	14	14.6	
Alcon Optifree products[‡]	0	0.0	9	9.4	
Hydrogen peroxide disinfectants	0	0.0	4	4.2	
Generic products	4	11.1	4	4.2	
Other soft contact lens solution products	1	2.8	1	1.0	
Multiple soft contact lens solutions	4	11.1	9	9.4	
AMO Complete MoisturePlus + additional soft contact lens solution	3 of 4		2 of 9		
B&L Renu + additional soft contact lens solution	1 of 4		6 of 9		
Alcon Optifree + additional soft contact lens solution	1 of 4		7 of 9		
Rigid contact lens solutions					
Boston RGP products[§]	0	0.0	36	37.5	
Lobob Optimum products[**]	0	0.0	9	9.4	
Other rigid contact lens solutions products	2	5.6	3	3.1	
Missing	2		6		p = <0.0001

[*] AMO; Advanced Medical Optics, Santa Ana, CA

[†] B&L; Bausch & Lomb, Rochester, NY

[‡] Alcon, Ft. Worth, TX

[§] Polymer Technology Corp, Menomonie, WI

[**] Lobob Laboratories, San Jose, CA

Table 3

Comparison of demographics and exposures of 30 *Acanthamoeba* keratitis cases and 39 clinic-matched controls wearing soft contact lenses.

	Matched Case-Control Pairs					Univariate Analysis			
	Cases:		Controls:				95% CI		
	Total N = 30	%	Total n = 39	%	Total n = 69	Conditional OR*			Chi-square p-value
Demographics									
Sex									
Male	16	53.33	18	46.15	69	1.04	0.26	4.13	0.953
Female	14	46.67	21	53.86					
Missing	0		0						
Age									
13 – <33	21	70.00	20	51.28	69		matching variable		
33 – <53	5	16.67	11	28.21					
53 – 74	4	13.33	8	20.51					
Missing	0		0						
General Health:									
Good, fair, poor	8	26.67	18	46.15	69	0.36	0.10	13.57	0.132
Excellent	22	73.33	21	53.85					
Missing	0		0						
Smoking Status:									
Yes	3	10.00	5	12.82	69	1.08	0.17	6.70	0.938
No	27	90.00	34	87.18					
Missing	0		0						
Contact Lens Use and Hygiene									
Use Contact Lens:									
>10 times per month	27	90.00	34	87.18	69	2.43	0.26	126.00	0.778
≤ 10 times per month	3	10.00	5	12.82					
Missing	0		0						
Silicone hydrogel contact lens use:									

	Matched Case-Control Pairs					Univariate Analysis			
	Cases:		Controls:				95% CI		
	Total N = 30	%	Total n = 39	%	Total n = 69	Conditional OR*			Chi-square p-value
Yes	0	0.00	6	28.57		1.04	0.89	2.11	0.812
No	25	100.00	15	71.43	46				
Missing	5		19						
Sleep with contact lens:									
≥ 1 time per month	7	24.14	11	28.21	68	0.42	0.09	2.07	0.286
0 times per month	22	75.86	28	71.79					
Missing	1		0						
Actual contact lens replacement:									
Quarterly or less frequently	7	25.93	17	50.00	63	0.418	0.13	1.43	0.164
More frequently than quarterly	20	74.07	17	50.00					
Missing	3		5						
Age of case at replacement:									
>3 months	21	70.00	21	53.85	68	2.34	0.74	7.41	0.149
≤ 3 months	8	30.00	18	46.15					
Missing	1		0						
Reuse solution:									
>5 times per month	17	58.62	10	25.64	68	3.19	1.10	9.27	0.033
0–5 times per month	12	41.38	29	74.36					
Missing	1		0						
Contact Lens Solutions									
Solution use									
AMO Complete MoisturePlus product	16	55.17	4	10.53					
B&L Renu Products	5	17.24	13	34.21					
Alcon Optifree Products	0	0.00	7	18.42					
Hydrogen peroxide disinfectants	0	0.00	4	10.53					
Generic	4	13.79	3	7.89					
Other Soft Contact Lens Solutions	0	0.00	1	2.63					

	Matched Case-Control Pairs					Univariate Analysis			
	Cases:		Controls:				95% CI		
	Total N = 30	%	Total n = 39	%	Total n = 69	Conditional OR*			Chi-square p-value
Multiple Soft Contact Lens solutions	4	13.79	6	15.79					
AMO Complete MoisturePlus + additional soft contact lens solution	3 of 4		1 of 6						
B&L Renu + additional soft contact lens solution	1 of 4		5 of 6						
Alcon Optifree + additional soft contact lens solution	1 of 4		5 of 6						
Missing	1		1						
Dichotomous solution use									
Exclusive use of AMO Complete MoisturePlus	16	55.17	4	10.53	67	17.76	2.23	141.22	0.007
All other soft contact lens solutions use†	13	44.83	34	89.47					
Missing	1		1						
Multipurpose Solution Use									
Yes	29	100.00	32	84.21	67	4.91	0.64	∞	0.139
No	0	0.00	6	15.79					
Missing	1		1						
Hydrogen Peroxide Use									
Yes	0	0.00	5	13.16	67	0.179	0	1.54	0.125
No	29	100.0	33	86.84					
Missing	1		1						
Saline Use									
Yes	2	6.90	5	13.16	67	0.58	0.01	8.36	p > 0.999
No	27	93.10	33	86.64					
Missing	1		1						
Daily Cleaner Use									
Yes	1	3.45	6	15.79	67	0.33	0.06	4.15	0.625
No	28	96.55	32	84.21					
Missing	1		1						
Enzyme Use									

	Matched Case-Control Pairs					Univariate Analysis			
	Cases:		Controls:				95% CI		
	Total N = 30	%	Total n = 39	%	Total n = 69	Conditional OR*			Chi-square p-value
Yes	1	3.45	3	7.89	67	1.41	0.02	117.66	p > 0.999
No	28	96.55	35	92.11					
Missing	1		1						
Lens-Handling Hygiene									
Rub lenses when cleaning									
≤ 10 times per month	20	76.67	20	53.85	65	2.54	0.61	10.56	0.200
>10 times per month	7	23.33	18	46.15					
Missing	3		1						
Wet hands while cleaning lenses									
>1 time per month	21	72.41	31	79.49	68	0.60	0.17	2.15	0.428
0 times per month	8	27.59	8	20.51					
Missing	1		0						
Rinse case with tap water									
>1 time per month	22	75.86	28	73.68	67	1.07	0.32	3.57	0.918
0 times per month	7	24.14	10	26.32					
Missing	1		1						
Shower with lenses									
>5 times per month	21	70.00	21	53.85	69	2.91	0.77	11.06	0.117
0–5 times per month	9	30.00	18	46.15					
Missing	0		0						

* Exact conditional logistic regression used when necessary

† Includes single use of all other products and also use of two or more products, including Complete MoisturePlus

Table 4

Conditional and Unconditional Multivariable* Odds Ratios and 95% Confidence Intervals for the Development of *Acanthamoeba* Keratitis among 30 *Acanthamoeba* keratitis cases and 39 clinic-matched controls wearing soft contact lenses.*

	Conditional Multivariable Analysis*†				Unconditional Multivariable Analysis*†‡			
	Conditional OR§	95% CI		Chi-square p-value	Unconditional OR**	95% CI		Chi-square p-value
Exclusive use of Complete MoisturePlus solution (compared to all other solutions)	18.51	2.11	162.63	0.008	9.36	2.42	36.21	0.001
Reuse of solution >5 times per month (compared to 0–5 times per month)	3.17	0.82	12.33	0.096	4.20	1.25	14.10	0.020
"Rub" while cleaning lenses ≤ 10 times per month (compared to >10 times per month)	9.05	0.82	100.19	0.073	3.76	0.93	15.15	0.063
Shower while wearing lenses >5 per month (compared to 0–5 times per month)	9.07	0.68	120.72	0.095	2.36	0.64	8.71	0.198
Actual contact lens replacement quarterly or more frequent (compared to less frequent than quarterly)	0.42	0.07	2.61	0.348	0.60	0.16	2.30	0.456
Age of case at replacement >3 months (compared to ≤ 3 months)	2.79	0.56	13.98	0.212	1.97	0.52	7.46	0.318

*The same subset of complete matched case-control pairs was used in each analysis

†Both conditional and unconditional multivariable analysis results adjusted for significant variables in univariate analysis, including exclusive use of Complete MoisturePlus solution and reuse of solution >5 times per month

‡Unconditional analysis also adjusted for matching variables, including age (continuous) and date-of-service

§Exact conditional logistic regression used when necessary

**Exact unconditional logistic regression used when necessary

Table 5

Percentage of cases among contact lens users in either the *Acanthamoeba* or *Fusarium* keratitis outbreak investigations attributable to the specific solution independently identified as associated with keratitis. Analysis is restricted to soft contact lens users.

	Fusarium Keratitis Outbreak 2006*		*Acanthamoeba* Keratitis Outbreak 2003 – 2006†	
	n	%	n	%
Single solution use				
Use of solution that statistically significantly increased risk of disease,‡§ single solution use only	94	64.4	19	52.8
Use of other contact lens solutions, including use of multiple solutions	52	35.6	17	47.2
Missing solution information	12		2	
Total	158		38	
Multiple solution use				
Use of solution that statistically significantly increased risk of disease,‡§ either alone or in combination with other solutions	115	78.8	22	61.1
Use of other contact lens solutions, excluding use of affected solutions	31	21.2	14	38.8
Missing solution information	12		2	
Total	158		38	

* Chang et al., 2006

† Current results from case-control study

‡ Bausch & Lomb ReNu MoistureLoc for *Fusarium* keratitis outbreak

§ AMO Complete MoisturePlus MultiPurpose for *Acanthamoeba* keratitis outbreak