A multi-country outbreak of fungal keratitis associated with a brand of contact lens solution: the Hong Kong experience

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Summary

Objectives: Starting in mid-2005, an increase in fungal keratitis caused by Fusarium spp was observed among contact lens wearers in Hong Kong, Singapore, and the USA. The objective of this study was to describe the outbreak and to determine any association with the use of Bausch & Lomb (B&L) ReNu® contact lens solution.

Methods: We defined a case as a disposable contact lens user with ophthalmologist-diagnosed keratitis and a positive culture of Fusarium spp reported to the Department of Health from January 1, 2005 to May 31, 2006. We identified cases through inpatient discharge data and the electronic laboratory databases of all public hospitals, and from physician reporting. Controls were recruited from three outpatient clinics. Risk factors were collected using a standardized questionnaire and analyzed by univariate analysis and binary logistic regression.

Results: From January 2005 through May 2006, we identified 33 cases of Fusarium keratitis. Most were in young adults (mean age 28 years) who presented with eye pain (100%), redness (84%), photophobia (41%), and tearing (34%). Twenty-four cases and 86 controls were recruited in the case-control study. By logistic regression, B&L ReNu solution showed the strongest association with being a case (adjusted odds ratio 26.1, 95% confidence interval 3.0—225.3) after adjusting for potential confounders.

Conclusion: Using B&L ReNu contact lens solution was strongly associated with Fusarium keratitis among disposable contact lens users in Hong Kong. B&L ReNu with MoistureLoc® was permanently withdrawn from the market globally in May 2006.

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Introduction

Microbial keratitis is the most devastating complication of contact lens wearing and may result in permanent vision loss from corneal scarring or perforation. Contact lens-related fungal keratitis is a severe corneal infection caused by fungi such as *Fusarium spp*, *Aspergillus spp*, and *Acremonium spp*. It has rarely been reported in the healthy soft contact lens wearing population. Patients may require corneal transplantation if anti-fungal medication fails. Risk factors associated with microbial keratitis in contact lens wearers include overnight wear, duration of continuous overnight wear, lower socio-economic class, smoking, and poor lens hygiene practice, specifically in daily wear lenses.

In late August 2005, the Centre for Health Protection (CHP), Department of Health of Hong Kong, became aware of an apparent increase in the number of cases of contact lens-related microbial keratitis among patients who attended public hospitals in one region of Hong Kong. Following this, the CHP initiated an investigation along with the doctors in public hospitals to determine whether there were any similar cases of contact lens-related microbial keratitis in other hospitals, and started monitoring the inpatient hospital discharge trend of contact lens-related microbial keratitis. The initial investigation suggested that many patients with fungal keratitis caused by *Fusarium spp* were disposable contact lens users and had reported a history of using a commercial contact lens solution, namely Bausch & Lomb (B&L) ReNu.

We describe herein the epidemiological details of the cases, and we present the findings of a case-control study conducted in February–March 2006 in Hong Kong, which helped to ascertain the risk factors associated with the development of Fusarium keratitis among disposable contact lens users.

Materials and methods

We actively identified patients having Fusarium keratitis from inpatient discharge diagnosis data and the electronic laboratory records of all the public hospitals in Hong Kong. We also received reports from both public and private ophthalmologists. A case was defined as a contact lens user who had clinical features compatible with fungal keratitis diagnosed by an ophthalmologist, with a positive culture of *Fusarium spp* obtained from corneal scraping, reported to the Department of Health from January 1, 2005 to May 31, 2006. We interviewed the cases by telephone using a standardized questionnaire to collect epidemiological and clinical information.

A retrospective unmatched case-control study was conducted in February–March 2006. To focus our investigation on the risk factors for the development of Fusarium keratitis among disposable soft contact lens users, our case definition was restricted to those cases of contact lens-related Fusarium keratitis reported to the CHP who were using disposable soft contact lenses (7-day, 2-weekly, or monthly). In March, urgent epidemiological information was needed to assist in making a public health decision and hence only cases reported from January 1, 2005 to March 31, 2006 were included in the case-control study. Controls were recruited from the attendees of the three family clinics of the Department of Health from February to March 2006. The Department of Health family clinics are general outpatient clinics for civil servants and their family members. We invited attendees who used disposable soft lenses (7-day, 2-weekly, or monthly) in the past 1 year to be controls; they had to have used the same brand of contact lens disinfectant solution over the past 6 months, before the voluntary suspension of B&L ReNu solution by the company. We excluded attendees who had had eye diseases related to the wearing of contact lenses in the past 1 year.

A standardized questionnaire was developed taking reference from a similar study in Singapore. Information concerning demographics, the choice and usage of contact lenses, the choice and usage of contact lens solution, and lens hygiene practice before onset of symptoms were elicited. Trained public health nurses administered the questionnaire to the cases by telephone interview. Two medical officers and five trained public health nurses approached potential controls in the waiting halls of the three family clinics and obtained verbal consent from them before administering the questionnaire through face-to-face interview. Issues of voluntary participation, confidentiality, and anonymity were emphasized before the interview. No clinical specimen was taken from the controls.

Data analysis was performed using SPSS version 13.0 and SAS Enterprise Guide 2.0. Univariate analysis (t-tests, Pearson Chi-square tests, or Fisher’s exact tests) was used to assess the variation/association of predictive values with case status. Selected variables that demonstrated variation/association with a p-value of less than 0.2 were entered into a binary logistic regression model. In selecting variables into the regression model, forward selection (likelihood ratio) was used. Adjusted odds ratios (AOR) and their 95% confidence intervals (95% CI) were estimated. For all statistical tests, association was considered statistically significant at p < 0.05.

A hygiene score (11–50) was developed in collaboration with the Singapore Ministry of Health, based on 10 questions (available on request) concerning lens hygiene practice, with a higher score signifying better hygiene practice. The score was analyzed as a continuous variable.

Results

Up until May 31, 2006, a total of 33 cases of contact lens-related Fusarium keratitis were reported to the CHP. Sixty-four percent (21/33) were female, and the age range of all cases was 16–51 years (mean 28 years). Twenty-five (75.8%) required hospital admission and at least two cases required corneal transplantation. Figure 1 shows the number of case hospital admissions/consultations by month. Thirty-two of these patients were successfully interviewed. They presented with eye pain (100%), redness (84%), photophobia (41%), tearing (34%), foreign body sensation (31%), and blurring of vision (28%). Among these 32 patients, 30 patients were disposable contact lens users (7-day, 2-weekly, or monthly), while two patients used conventional soft lens. Twenty-nine out of 32 (90.6%) patients recalled that they solely used B&L ReNu contact lens solution before the onset of their symptoms. The patients were using different batches of B&L ReNu solution, as evidenced by the different lot numbers of the solution. Among them, 27 (93.1%) patients could specify the product line to be B&L ReNu with MoistureLoc on repeated
enquiries, while the other two patients had forgotten the exact B&L ReNu product line they had used.

A total of 26 cases were identified for the period from January 2005 through March 2006. Twenty-four cases were included in the case–control study. One patient who was using conventional soft contact lens and another one who could not be contacted were excluded. The mean age of the cases was 30.3 years (range 16–51 years); 62.5% (15/24) were younger than 35 years of age and 29.2% (7/24) were male. A total of 86 controls were recruited for the study, 18 from clinic A, 26 from clinic B, and 42 from clinic C. The response rate was 98.9% (86/87).

Table 1 shows the baseline characteristics of the cases and controls. The control group had a significantly higher mean age than the cases, a lower prevalence of smokers, and a smaller proportion with contact lens use of less than 2 years. They showed comparable gender distribution, education level, type of disposable contact lens usage, and duration of wearing contact lenses each time. There was no statistical difference in pre-existing immunodeficiency or diabetes mellitus.

The results of the univariate analysis are summarized in Table 2. The crude odds ratio (OR) for using B&L ReNu solution was found to be 16.56, 95% CI 2.69–99.93, \( p < 0.001 \). The mean hygiene score of cases was 36.67, slightly lower than that for controls, 40.17 (\( p = 0.001 \)). Univariate analysis of the 10 individual factors of hygiene score showed that overnight wearing was a significant risk factor, whereas rubbing the lens while cleaning and recapping the contact lens case during storage of the contact lenses were protective factors.
Smoking was also found to be significantly associated with being a case (crude OR 5.40, 95% CI 1.42—20.48, \(p = 0.01\)). Other significant factors included using B&L contact lenses (crude OR 3.00, 95% CI 1.11—8.04) and using cleaning solution to clean disposable contact lenses before storage (\(p = 0.02\) by Fisher’s exact test). Storage place of contact lens case, storage place of contact lens solution, construction sites near residence, and participating in outdoor activities were not found to be significant risk factors.

All variables that were statistically significant in the univariate analysis were examined, and selected variables were analyzed using logistic regression. In the binary logistic regression model, we included sex, brand of contact lens solution used, less than 2 years of contact lens use, brand of contact lens used, and type of cleaning solution, as independent categorical variables. Age and hygiene score were included as continuous variables. The proportions of smokers among cases and controls were small and so smoking was not included in the multivariate analysis.

The results of the final logistic regression model are shown in Table 3. The \(R^2\) of our model was 0.42, explaining about 42% of the outcome. Using B&L ReNu solution was found to be a statistically significant risk factor for being a case (AOR 26.12, 95% CI 3.03—225.3) after adjusting for other risk factors, which included hygiene score and less than 2 years of contact lens use.

As an alternative, we replaced the mean hygiene score with the three significant hygiene factors identified in the univariate analysis, namely overnight use, rubbing of the lens, and recapping of the contact lens case, in the logistic regression model. Using B&L ReNu solution was still strongly associated with being a case (AOR 13.46, 95% CI 1.55—116.6).

### Table 2 Results of univariate analyses showing crude odds ratios for variables associated with being a case.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases ((N=24)) Number (%)</th>
<th>Controls ((N=86)) Number (%)</th>
<th>OR (95% CI)</th>
<th>(p)-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using B&amp;L contact lens solution</td>
<td>23 (95.8)</td>
<td>50 (58.1)</td>
<td>16.56 (2.69—99.93)</td>
<td>&lt;0.001 (^a)</td>
</tr>
<tr>
<td>Mean hygiene score (SD)</td>
<td>36.67 (4.93)</td>
<td>40.17 (4.16)</td>
<td>0.84 (0.75—0.94)</td>
<td>0.001 (^a)</td>
</tr>
<tr>
<td>Overnight wear</td>
<td>9 (37.5)</td>
<td>6 (7.0)</td>
<td>8.00 (2.56—24.99)</td>
<td>0.001 (^a)</td>
</tr>
<tr>
<td>Rubbing the lens while cleaning</td>
<td>7 (29.2)</td>
<td>61 (70.9)</td>
<td>0.17 (0.06—0.45)</td>
<td>&lt;0.0001 (^a)</td>
</tr>
<tr>
<td>Recapping the contact lens case after putting</td>
<td>14 (82.4)</td>
<td>84 (97.7)</td>
<td>0.11 (0.02—0.614)</td>
<td>0.031 (^a)</td>
</tr>
<tr>
<td>the contact lenses into the case(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (20.8)</td>
<td>4 (4.7)</td>
<td>5.40 (1.42—20.48)</td>
<td>0.01 (^a)</td>
</tr>
<tr>
<td>Brand of contact lens used</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&amp;L lenses</td>
<td>18 (75)</td>
<td>43 (50)</td>
<td>3.00 (1.11—8.04)</td>
<td>0.03 (^a)</td>
</tr>
<tr>
<td>Other brand</td>
<td>6 (25)</td>
<td>43 (50)</td>
<td>1.00, reference</td>
<td></td>
</tr>
<tr>
<td>Type of solution for cleaning disposable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>contact lenses before storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleaning solution</td>
<td>0 (0)</td>
<td>17 (19.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other solution (multipurpose solution, saline,</td>
<td>24 (100)</td>
<td>69 (80.2)</td>
<td></td>
<td>0.02 (^a)</td>
</tr>
<tr>
<td>distilled water, tap water, boiled water)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place of contact lens solution storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bathroom/kitchen</td>
<td>22 (91.7)</td>
<td>72 (83.7)</td>
<td>2.14 (0.50—9.00)</td>
<td>0.33</td>
</tr>
<tr>
<td>Bedroom/living room/other</td>
<td>2 (8.3)</td>
<td>14 (16.3)</td>
<td>1.00, reference</td>
<td></td>
</tr>
<tr>
<td>Place of contact lens case storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bathroom/kitchen</td>
<td>21 (87.5)</td>
<td>66 (76.7)</td>
<td>2.12 (0.61—7.30)</td>
<td>0.25</td>
</tr>
<tr>
<td>Bedroom/living room/other</td>
<td>3 (12.5)</td>
<td>20 (23.3)</td>
<td>1.00, reference</td>
<td></td>
</tr>
<tr>
<td>Construction site(^c)</td>
<td>2 (8.7)</td>
<td>13 (15.1)</td>
<td>0.54 (0.13—2.32)</td>
<td>0.43</td>
</tr>
<tr>
<td>Outdoor activity(^c)</td>
<td>10 (43.5)</td>
<td>29 (33.7)</td>
<td>1.51 (0.60—3.80)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
\(^a\) Statistically significant.
\(^b\) Seven missing values in the case group.
\(^c\) One missing value in the case group.

### Table 3 Results of binary logistic regression analyses showing adjusted odds ratios for variables associated with being a case.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases ((N=24)) Number (%)</th>
<th>Controls ((N=86)) Number (%)</th>
<th>Adjusted OR (95% CI)</th>
<th>(p)-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using B&amp;L contact lens solution</td>
<td>23 (95.8)</td>
<td>50 (58.1)</td>
<td>26.12 (3.03—225.3)</td>
<td>0.001 (^a)</td>
</tr>
<tr>
<td>Mean hygiene score (SD)</td>
<td>36.67 (4.93)</td>
<td>40.17 (4.16)</td>
<td>0.80 (0.70—0.91)</td>
<td>0.001 (^a)</td>
</tr>
<tr>
<td>Less than 2 years history of wearing contact</td>
<td>6 (25)</td>
<td>6 (7.0)</td>
<td>8.77 (1.69—45.46)</td>
<td>0.010 (^a)</td>
</tr>
<tr>
<td>lenses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
\(^a\) Statistically significant.
Fusarium spp fungal keratitis due to Fusarium spp in Singapore had detected 75 cases of contact lens-related with a spike of cases in January 2006. As of April 12, 2006, Singapore had detected 75 cases of contact lens-related fungal keratitis due to Fusarium spp. As of May 18, 2006 the Centers for Disease Control and Prevention (CDC) in the USA had received reports of 130 patients with confirmed Fusarium keratitis with onset of symptoms from June 1, 2005. The majority of patients in the two countries used the B&L ReNu product.

Our case–control study suggests that the development of Fusarium keratitis among disposable contact lens users in Hong Kong in the 2005–2006 series was strongly associated with the use of B&L ReNu solution. The AOR was found to be 26.12 after adjusting for other possible risk factors such as poor lens hygiene practice and years of wearing contact lenses. Similar observations found in case–control studies conducted in Singapore and the USA further support the findings of our study. A matched case–control study conducted by the CDC, USA, showed a significant association between using B&L ReNu with MoistureLoc solution and developing Fusarium keratitis, with a similar AOR (19.0). In our study, we could not differentiate the risk between ReNu MoistureLoc and ReNu MultiPlus because of the very similar packaging of these two solutions. However, among our case series, the majority (87.5%, 21 out of 24) of the patients could specify the product line to be B&L ReNu with MoistureLoc or ReNu MultiPlus. According to Bausch & Lomb (Hong Kong) Ltd, the new product ReNu MoistureLoc was introduced in Hong Kong replacing the previous ReNu MultiPlus contact lens solution in September 2004.

Another potential bias is recall bias. The study was conducted after the public announcement of an apparent increase in fungal keratitis among users of B&L solution, which may possibly have affected recall of the brand of contact lens solution used. Of the control group, 57.6% claimed to have used B&L ReNu solution, quite comparable to the market share figures (about 60%) as supplied by the B&L Company. Therefore, we believe that recall bias among the controls was minimal. In most of the cases, information on the brand of contact lens solution used was obtained before the media announcement in February, and about half of these patients could provide the lot number of the solution they had been using. Hence, recall bias among the cases should also have been minimal.

The underlying cause of the association between the solution and the development of Fusarium keratitis among disposable contact lens users still remains to be determined. The patients were using different batches of B&L ReNu solution and sterility tests for a few commercially bought samples were negative. This makes the possibility of batch contamination of the solution itself less likely. On the other hand, if there was really batch contamination, the contamination had to be at a very low level or intermittent, otherwise we would have expected a larger number of patients to be affected.

Although the B&L ReNu with MoistureLoc solution had satisfied all the standard tests and requirements of the US Food and Drug Administration before launching, it is possible that the potency of this solution might have been affected under certain extreme environmental conditions, such as extreme humidity and temperature, which are common in Hong Kong and Singapore. Combined with poor hygiene practice and contamination during cleaning and general lens manipulation, growth of Fusarium spp in the contact lens solution is possible. A study in the USA reported that fungal contamination was present in the contact lens care systems of seven out of 50 asymptomatic daily soft contact lens wearers. A previous local study demonstrated that the performance of multipurpose solutions is affected by time and temperature of storage, and that the efficacy of opened solution may not be sustained for as long as the 3 months recommended by the manufacturers. Potency tests simulating real life situations under extreme conditions would be useful. Genotyping of clinical isolates of patients, which is ongoing, may shed light on the possible source of contamination, whether at the supplier level or at the consumer level.

The reason why the majority of cases occurred in disposable contact lens users is uncertain. An increased incidence of microbial keratitis among disposable contact lens users has been reported before. There has been no sudden increase in users of disposable contact lenses in Hong Kong. According to the B&L Company, the proportion of disposable contact lens users (7-day, 2-weekly, and monthly) among all contact lens users in Hong Kong in the years 2004 and 2005 was stable at 38%. Several hypotheses have been proposed to explain this observation. First, it is possible that disposable contact lens users may be less vigilant in following strict hygiene practices. However, we have used the same questionnaire to interview 35 patients who were using conventional soft contact lenses. It was found that the mean hygiene score among these soft lens users was 39.75 (SD 5.64), similar to the hygiene score (40.17, SD 4.16) in all our control groups using disposable lenses (p = 0.65 by \( t \)-test). This result makes this hypothesis less likely. Secondly, it was found that the use of a separate cleaner to clean the lenses before storage was higher among conventional soft contact lens users (13/34 vs. 3/86). Using a separate cleaner might be a protective factor for microbial keratitis. Thirdly, there might be an interaction between the solution and the material used to make disposable contact lenses, which in turn could reduce the potency of the solution. This is supported by the evidence of inactivation or absorption of the active ingredients of solution into the lens after storage. Potency tests after incubation with different disposable lenses would probably...
answer this question. It has been reported in previous studies that fungi may penetrate and grow in certain lens material once contaminated. There appears to be a tendency towards deeper fungus penetration in the matrix of higher water-content contact lenses.

Apart from using B&L ReNu solution, hygiene score and history of wearing contact lens for less than 2 years were also found to be significantly associated with Fusarium keratitis. This is not unexpected, since a study in Singapore in 1989 found a general decline in the number of cases presenting with complications with respect to the number of years wearing daily wear lenses, which probably reflects the normal drop-out rate in the number of people wearing contact lenses.

It was estimated in 1994 that the number of contact lens wearers in Hong Kong was around 350,000 and that about 87% were soft lens wearers. The current figure is expected to be much higher than this, since 80% of the population are myopic and contact lens wear is a relatively cheap and effective means of visual correction for those living the demanding lifestyle of Hong Kong. With such a large number of soft contact lens users in Hong Kong as well as worldwide and the increasing trend towards the use of soft contact lenses in modern societies, it is imperative that the disinfectants are safe and potent to prevent this devastating condition, which can lead to loss of vision.

In late February 2006, the B&L Company voluntarily suspended sales of ReNu solution from the markets in Hong Kong and Singapore as a precautionary measure. On April 13, 2006, the Company suspended sales of ReNu with MoistureLoc in the USA. A global recall and permanent withdrawal of B&L ReNu with MoistureLoc solution was initiated on May 15, 2006.

Conclusion

We identified an upsurge in cases of Fusarium keratitis in Hong Kong affecting 33 patients since mid-2005. Our case-control study shows that the use of B&L ReNu contact lens solution had a strong and statistically significant association with the development of Fusarium keratitis among disposable contact lens users, after adjusting for other risk factors including poor hygiene practice and duration of contact lens wearing. To prevent recurrence of similar incidents in the future, it is important to determine the underlying cause and institute appropriate preventive measures.

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Conflict of interest: No conflict of interest to declare.

References