Epidemiology of Ulcerative Keratitis in Northern California

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Objective: To determine the incidence and associated risk factors for ulcerative keratitis in northern California.

Methods: In this large-population, retrospective, cohort study, all medical records with diagnosis coding for corneal ulcers during a consecutive 12-month period were reviewed. Incidence rates were calculated using a dynamic population model. Multivariate relative risk regression was conducted to evaluate potential risk factors for ulcerative keratitis.

Results: Within the target population of 1,093,210 patients, 302 developed ulcerative keratitis. The incidence of ulcerative keratitis was 27.6 per 100,000 person-years (95% confidence interval, 24.6-30.9). The incidence of corneal ulceration in contact lens wearers was 130.4 per 100,000 person-years (95% confidence interval, 111.3-151.7), with an adjusted relative risk of 9.31 (7.42-11.7; P < .001) compared with non–contact lens wearers, who had an incidence of ulcerative keratitis of 14.0 per 100,000 person-years (11.7-16.6). Seven of 2944 people known to be infected with human immunodeficiency virus developed ulcerative keratitis, with 5 being contact lens wearers. The incidence of ulcerative keratitis in human immunodeficiency virus–positive patients was 238.1 per 100,000 person-years (95% confidence interval, 95.7-490.5), with an odds ratio of 9.31 (7.42-11.7; P < .001) compared with human immunodeficiency virus–negative patients, who had an incidence of ulcerative keratitis of 27.1 per 100,000 person-years (24.1-30.3).

Conclusions: The incidence of ulcerative keratitis in this population is higher than previously reported. This may be owing to the increasing prevalence of contact lens wear.

A retrospective incidence cohort study using a dynamic population model for calculation of incidence was performed. Nine KP medical facilities in 8 KP communities in northern California were chosen for this study: Fremont, Hayward, Milpitas, Oakland, Redwood City, Richmond, San Francisco, Santa Clara, and South San Francisco. The size of each of the 9 medical facility study populations was defined by the KP Division of Health Statistics as the number of active KP Health Plan members who use each of these facilities as their site for outpatient clinical services. During the study period, the Northern California KP Health Care Program consisted of 35 medical facilities in 17 KP community service areas: 23 of the 35 medical facilities had ophthalmologists on site with at least 1 facility in each of the 17 KP communities providing ophthalmologic care.

The Outpatient Diagnostic Database of the Northern California KP Health Care Program was used to identify all patients coded with the diagnosis of corneal ulcer during a consecutive 12-month period from September 1, 1998, through August 31, 1999. All identified medical records were screened based on inclusion and exclusion criteria.

For inclusion, patients were required to have their initial visit for a newly diagnosed case of ulcerative keratitis during the study period and to have medical record–documented examinations meeting the clinical definition of ulcerative keratitis: the presence of a corneal epithelial defect with an underlying stromal infiltrate and inflammation attributed to bacterial, fungal, or parasitic infection. Patients with culture-positive and culture-negative results were included. Excluded were patients with epithelial breakdown or stromal infiltrates clinically due to immune-mediated causes, such as staphylococcal hypersensitivity or various rheumatologic diseases, or to viral causes, such as herpes simplex virus, neurotrophic ulceration, or ulcerations secondary to vernal or atopic keratoconjunctivitis. Patients who were not treated with topical antibiotic eye drops were also excluded.

The cause of the ulcerative keratitis was based on medical record descriptions and drawings, as well as culture findings. If the medical record was incomplete or unclear as reviewed (by 1 of us [B.H.J., D.C.G., A.B.K., or D.S.H.], the patient's medical record was excluded. All medical records coded as (by 1 of us [B.H.J., D.C.G., A.B.K., or D.S.H.]), the patient's medical record was excluded. All medical records coded as (by 1 of us [B.H.J., D.C.G., A.B.K., or D.S.H.]), the patient's medical record was excluded.

The R software package for Apple Macintosh. Multivariate relative risk regression was conducted using the Relative-risk package for R (command est.tr): interaction was tested using the Wald test for the coefficient of the interaction term at the 0.1 level. Models without evidence of interaction were refit without the interaction terms. Kaiser Foundation Research Institute’s institutional review board approved the protocol for this study.

STUDY POPULATION CHARACTERISTICS

The midperiod study population size was 1 093 210. Of these, 128 191 were contact lens wearers. In the study population, 2944 people were known to have HIV-positive status, and of these, 345 were contact lens wearers.

GENERAL EPIDEMIOLOGY AND THE INCIDENCE OF ULCERATIVE KERATITIS

Of the 468 patients coded with the diagnosis of corneal ulcer, 302 patients (173 females and 129 males) fulfilled the inclusion criteria. The reasons for exclusion of 166 patients included staphylococcal hypersensitivity marginal keratitis (95 [57.2%]), insufficient information to make a definitive diagnosis (31 [18.7%]), epithelial defects without stromal infiltration (12 [7.2%]), herpes simplex viral keratitis (10 [6.0%]), and other reasons (18 [10.8%]), including cases of eyes ultimately found to have corneal scars, rheumatoid melts, neurotrophic ulcers, dellen, phlyctenules, and vernal shield ulcers. Patient ages ranged from 4 to 100 years (mean age, 42.8 years; median age, 40.0 years). On average, females were younger than males (40.1 vs 46.5 years, P = .03). The age and sex-stratified distribution of patients with ulcerative keratitis is given in Table 1.

The number of patients with ulcerative keratitis seeking treatment each month during the study period ranged from 15 (October) to 33 (May). No seasonal variation in the number of patients with ulcerative keratitis was observed. During the rainy season (November 1998...
Of the 302 patients with ulcerative keratitis diagnosed by clinical examination, 60 had cultures taken, with 29 (48.3%) yielding positive results. *Staphylococcus aureus* was the most commonly recovered organism (8; 27.6%) (Table 2).

### Table 2. Microorganisms Recovered From 29 Positive Corneal Cultures

<table>
<thead>
<tr>
<th>Organism</th>
<th>Cultures, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcus</em></td>
<td>7 (24.1)</td>
</tr>
<tr>
<td><em>Moraxella</em></td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Diphtheroids</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td>2 (6.9)</td>
</tr>
<tr>
<td><em>Gemella morbillorum</em></td>
<td>2 (6.9)</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>1 (3.4)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td><em>Candida parapsilosis</em></td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Yeast (otherwise unidentifiable)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td><em>Phialophora</em></td>
<td>1 (3.4)</td>
</tr>
<tr>
<td><em>Pasturella multocida</em></td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Normal flora</td>
<td>1 (3.4)</td>
</tr>
</tbody>
</table>

*Total is greater than 29 (100) because of 7 cultures yielding 2 organisms each.*

### PROBABLE PREDISPOSING FACTORS

One hundred sixty-six patients (55.0%) were contact lens wearers, with 123 (74.1%) of them wearing soft lenses. The mean age of contact lens wearers was 34.5 years, with more females wearing contacts than males (107 vs 59, *P* = .005). Ocular trauma occurred in 36 patients (11.9%). The mean age of these patients was 46.9 years, with 27 males vs 9 females having ocular trauma (*P* < .001). Ocular surface disease was present in 54 patients (17.9%), with blepharitis accounting for the largest proportion (18; 33.3%) of cases of surface disease. The mean age of patients with ocular surface disease was 54.1 years, with more males than females having ocular surface disease (29 vs 21, *P* = .02). Of the patients with ocular surface disease, bullous keratopathy was present in 4 patients with ulcerative keratitis, with a mean age of 79 years. None of these 4 patients had previously been wearing bandage soft contact lenses, and all patients developed central ulcers. Seropositivity for HIV was found in 7 patients with ulcerative keratitis.

Because age and sex data were not available for those HIV patients and contact lens wearers who did not develop ulcerative keratitis, relative risk regression was conducted for ulcerative keratitis as an outcome using only HIV seropositivity and contact lens wear (and their interaction) as predictors; we found that the interaction of HIV seropositivity and contact lens wear was not significant (*P* = .39). Refitting this model without the interaction term allowed us to compute adjusted relative risks for HIV seropositivity and contact lens wear.

The estimated incidence of ulcerative keratitis in contact lens wearers was 130.4 per 100 000 person-years (95% CI, 111.3-151.7), whereas the incidence of ulcerative keratitis in non–contact lens wearers was 14.0 per 100 000 person-years (29 vs 21, *P* = .02). Of the patients with ocular surface disease, bullous keratopathy was present in 4 patients with ulcerative keratitis, with a mean age of 79 years. None of these 4 patients had previously been wearing bandage soft contact lenses, and all patients developed central ulcers. Seropositivity for HIV was found in 7 patients with ulcerative keratitis.

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Of the 7 HIV-positive patients with ulcerative keratitis, 5 were contact lens wearers. The overall incidence of ulcerative keratitis in HIV-infected individuals was...
The incidence of ulcerative keratitis in HIV-negative people was 27.1 per 100,000 person-years (95% CI, 24.1-30.3), and this difference was statistically significant (P < .001). The relative risk (adjusted for contact lens wear) for developing ulcerative keratitis in HIV-positive individuals compared with HIV-negative individuals was 8.81 (95% CI, 4.17-18.6; P < .001) (Table 3).

### COMMENT

The KP Health Care Program in northern California offers a unique opportunity to study a large, socioeconomically and racially diverse general population and is this study's source for the largest population study of ulcerative keratitis in the United States, to our knowledge. If one were to use estimates from this study to project to the US population, the number of cases of ulcerative keratitis occurring in the United States might actually be twice as many as previously reported.1,2

### INCIDENT

In this study, the high incidence rates for all patients with ulcerative keratitis and for the subgroup of women between the ages of 25 and 39 years (51.3 per 100,000 person-years) may be related in part to the popularity of cosmetic contact lens use. The overall number of people using contact lenses is increasing, and contact lens wear is common among young women.12 From 1998 to 1999, an estimated 33 million people in the United States wore contact lenses.12 The proportion of cases of ulcerative keratitis associated with contact lens wear has also increased in the general population from 0% in the 1950s and 1960s to 31% in the 1970s to 52% in the 1980s.1 The results of this study are consistent with previous observations.

The proportion of contact lens–related ulcerative keratitis in this study was higher than that in reports from several academic referral centers. At the Wills Eye Hospital, there was an upward trend of contact lens–related ulcerative keratitis from 9% in the late 1970s to 44% in the late 1980s.13-16 Subsequent reports17,18 showed a decreasing trend from 9% to 18% in the late 1990s. Other studies19,20 also showed percentages of contact lens–related ulcerative keratitis that were consistent with the Wills Eye Hospital results. The most recent report21 from the Wills Eye Hospital, however, demonstrated an increase in contact lens–related ulcerative keratitis in the early 2000s to 30%. It is unclear why the percentage of contact lens–related ulcerative keratitis has changed in this institution.

The present study may have estimated a greater incidence of contact lens–related ulcerative keratitis because it studied a general population treated by subspecialists and comprehensive ophthalmologists rather than individuals treated in an academic referral practice. The decreasing number of patients with contact lens–related ulcerative keratitis cared for in an academic referral practice may be owing to improved treatment of ulcerative keratitis in the community since the introduction of topical fluoroquinolones in the 1990s.20,22-25 The large proportion of contact lens–related ulcerative keratitis in this community-based study supports this hypothesis.

### RISK FACTORS

The risks of ulcerative keratitis related to contact lenses are well known, and several studies26-29 have reported its increased incidence among contact lens users. For discretionary contact lens use, the annual incidence of ulcerative keratitis caused by bacteria depends on the type of contact lens used: 4.4 to 15 per 100,000 persons for rigid lenses, 22 to 41 per 100,000 persons for daily-wear soft contact lenses, and 93 to 209 per 100,000 persons for extended-wear soft contact lenses. For wearers of aphakic contact lenses, the overall annual incidence of ulcerative keratitis for all lens types is estimated to be 520 per 100,000 persons.30

The type of contact lens or wearing schedule could not be reliably determined by medical record review in 27 (16.2%) contact lens–related ulcerative keratitis cases in this study. In addition, although 123 contact lens wearing patients (74.1%) in this study wore soft contact lenses, the wearing schedule of 99 contact lens wearers (59.6%) could not be determined by medical record review. Given these statistics, this study’s overall incidence rate of ulcerative keratitis of 130.4 per 100,000 person-years in contact lens wearers may be similar to those reported in earlier studies.

Another important risk factor associated with ulcerative keratitis in this study was a history of trauma to the eye unrelated to any surgery, occurring in 36 (11.9%) of all 302 patients with ulcerative keratitis. This result is lower than that in other published series3,5,10,20 in the United States citing nonsurgical trauma as accounting for between 16% and 27% of all cases of ulcerative keratitis. In this study, trauma may be lower because of the higher percentage of cases of contact lens–related ulcerative keratitis and possible referral bias in the other studies. In this...
study, the opposite phenomenon, in which trauma patients may seek care directly at an outside tertiary care center, may exist, accounting for the lower figure, but we do not believe this is the case to any significant extent because patients within the KP system almost always seek care at a KP medical center before receiving authorization for referral to another hospital system. In this setting, even if the patients were ultimately referred outside the system, their data would still be captured because of their initial visit within the KP system.

The percentage of patients with ulcerative keratitis related to bullous keratopathy (1.3%) is less than the 6% to 9% reported in other series.32-38 Luchs and associates31 reported that approximately 4.7% of patients with bullous keratopathy experienced a corneal ulcer during a 10-year period. The smaller proportion of patients with ulcerative keratitis associated with bullous keratopathy in this study may be owing to a decreased incidence of bullous keratopathy since the 1980s with improved intraocular lenses and surgical techniques. Also, greater availability of donor tissue compared with the past may decrease the number of patients at risk.

Although cases of apparently spontaneous corneal infections in HIV-infected individuals have been previously reported,32-39 it was generally believed that HIV infection alone does not predispose a person to bacterial ulcerative keratitis.38 This study suggests that HIV infection is indeed a risk factor for ulcerative keratitis. This study assumed that the percentage of contact lens wearers in the HIV-positive population was the same as that in the general population. If this assumption was correct, the risk of developing ulcerative keratitis in HIV-positive individuals is nearly 9 times that in HIV-negative individuals.

Estimates of the prevalence of known HIV infection in the United States at the end of 2000, using an estimated 850 000 to 9 500 000 persons living with HIV, with 25% of these not knowing they were infected (leaving 637 500 to 7 122 500 persons with known HIV infection), and a population size of 281 421 906, yields a prevalence range of 0.23% to 0.25%.40 This range is in close comparison to the prevalence of known HIV infection in our study of 0.27%. Because the population that we considered HIV negative may encompass individuals who are unaware that they are HIV positive, our calculations of relative risk may underestimate the true relative risk that HIV infection carries with regard to ulcerative keratitis.

The individuals with HIV-positive status may be at greater risk of developing ulcerative keratitis because of HIV-associated keratoconjunctivitis sicca, anatomical eyelid abnormalities owing to Kaposi sarcoma and molluscum contagiosum, and the underlying immunodeficiency.41 In this study, CD4 T-lymphocyte counts and HIV-related disorders could not be reliably documented by medical record review. However, given that this study may have uncovered a suggestion that HIV disease may be a significant risk factor for the development of ulcerative keratitis, this possibility should be further studied.

In this study, the incidence of ulcerative keratitis with the different potential risk factors could only be estimated in the contact lens–wearing and HIV subgroups because these were the only subgroups for which we had accurate numbers with regard to those individuals who were nonwearers and were HIV negative. Our relative risk regression analysis found that there was no evidence of an interaction between HIV seropositivity and contact lens wear (P = .39); therefore, we modeled our analyses of these subgroups without interactions.

**STUDY STRENGTHS AND LIMITATIONS**

The strength of this study is the ability to analyze a large, stable, and diverse population covering a vast geographic area. Approximately 30% of the overall population in northern California is insured by the KP Health Plan, and those insured come from a variety of socioeconomic backgrounds, including those participating in Medicare and Medicaid, as well as employer-based and self-pay programs. The large denominator size of more than 1 million provided substantial statistical power for this study, providing information on the general population and for subgroups. In addition, data from the 2003 California Health Interview Survey found that the KP membership is overall similar to the general population (Table 4 and Table 5). Generalizing a study's findings to the overall population is sometimes not appropriate; however, the size, diversity, and similarity of this study's population with the general population make extrapolation of these data a reasonable choice when performed with the methods described herein.

Misclassification bias could exist because of miscoding, resulting in a spuriously low estimate of disease in this study. The random sampling of medical records at 1 facility found that less than 5% of medical records coded as cornal disorder NOS or keratitis fit inclusion criteria. Misclassification bias in this study could have led to a lower or higher estimate compared with the true incidence of ulcerative keratitis, but the conservative and strict inclu-
Table 5. Comparison of the Kaiser Permanente Study Population With the 2000 US Census Population for Race

<table>
<thead>
<tr>
<th>Race</th>
<th>US Population, No. (%)</th>
<th>Study Population, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>211 460 626 (75.1)</td>
<td>571 749 (52.3)</td>
</tr>
<tr>
<td>Hispanica</td>
<td>35 305 818 (12.5)</td>
<td>172 727 (15.8)</td>
</tr>
<tr>
<td>African American</td>
<td>34 658 190 (12.3)</td>
<td>133 372 (12.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 242 998 (3.6)</td>
<td>144 304 (13.2)</td>
</tr>
<tr>
<td>Other</td>
<td>18 233 864 (6.5)</td>
<td>72 152 (6.6)</td>
</tr>
<tr>
<td>≥2 Races</td>
<td>6 826 228 (2.4)</td>
<td>Not delineated</td>
</tr>
</tbody>
</table>

*aTotal does not equal 100% because in the US Census data, Hispanic race and the designation of 2 or more races potentially overlap with other groups.

From a public health perspective, it is important to recognize that the incidence of ulcerative keratitis in the United States is substantially higher than previously reported. Although it is well known that contact lens wear has been and continues to be a major risk factor for ulcerative keratitis, this knowledge has not effectively reduced the occurrence of the disease in contact lens wearers. Instruction in proper contact lens use and hygiene is an important public health task in which all providers of contact lens care must participate.

In conclusion, discouraging patients from sleeping while wearing extended-wear contact lenses, despite the fact that those lenses are approved for overnight wear, may also decrease the risk of ulcerative keratitis. Although encouraging the use of daily disposable soft contact lenses may not further decrease the risk of ulcerative keratitis, vision loss is less likely to occur in users of these lenses compared with those who use reusable soft contact lenses.

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REFERENCES


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Call for Papers

Archives of Ophthalmology, along with JAMA and other Archives specialty journals, will participate in a consortium theme issue on infectious diseases/immunology in April 2011. Manuscripts on uveitis, ocular infections, and ocular involvement in systemic infectious and immunological diseases received by October 1, 2010, will have the best chance for consideration for this theme issue.