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ORIGINAL ARTICLE

The Risk of Microbial Keratitis With Overnight Corneal Reshaping Lenses

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ABSTRACT

Purpose. To estimate the incidence of microbial keratitis (MK) associated with overnight corneal reshaping contact lenses and to compare rates in children and adults.

Methods. A retrospective study of randomly selected practitioners, stratified by order volume and lens company, was conducted. Practitioners were invited to participate and those agreeing were asked to provide deidentified patient information for up to 50 lens orders and to complete a comprehensive event form for any of these patients who have attended an unscheduled visit for a painful red eye. Duration of contact lens wear was calculated from the original fitting date or January 2005 (whichever was later) to when the patient was last seen by the practitioner wearing the lenses on a regular basis. Cases of MK were classified by majority decision of a 5-member expert panel.

Results. For the 191 practitioners who could be contacted, 119 (62%) agreed to participate. Subsequently, 11 withdrew, 22 did not respond, and 86 (43%) returned completed forms corresponding to 2202 lens orders and 1494 patients. Limiting the sample to those patients with at least 3 months of documented contact lens wear since 2005 resulted in a sample of 1317 patients; 640 adults (49%) and 677 children (51%) representing 2599 patient-years of wear (adults = 1164; children = 1435). Eight events of corneal infiltrates associated with a painful red eye were reported (six in children and two in adults). Two were classified as MK. Both occurred in children but neither resulted in a loss of visual acuity. The overall estimated incidence of MK is 7.7 per 10,000 years of wear (95% confidence interval [CI] = 0.9 to 27.8). For children, the estimated incidence of MK is 13.9 per 10,000 patient-years (95% CI = 1.7 to 50.4). For adults, the estimated incidence of MK is 0 per 10,000 patient-years (95% CI = 0 to 31.7).

Conclusions. The risk of MK with overnight corneal reshaping contact lenses is similar to that with other overnight modalities. The fact that the CIs for the rates estimated overlap should not be interpreted as evidence of no difference. True differences fewer than 50 cases per 10,000 patient-years were beyond the study's power of detection.
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Key Words: microbial keratitis, overnight orthokeratology, contact lenses, extended wear, adverse effects

Corneal reshaping, also known as corneal refractive therapy or orthokeratology (OK), was initially reported in the early 1960s.[1] The original goal of corneal reshaping was to permanently change the shape of the cornea while wearing contact lenses for several hours early in the day. Early studies reported an incomplete treatment effect and transient, unpredictable refractive error reduction.[2]

In the mid-1990s, innovative materials and reverse-geometry designs coupled with videokeratography allowed for quicker, more predictable treatment effects and nighttime contact lens wear.[3] Corneal reshaping contact lenses are now typically worn during sleep to temporarily reduce myopia by flattening of the cornea. A summary of the history, safety, and effectiveness of corneal reshaping is provided in Swarbrick's[4] comprehensive review.

Reports of microbial keratitis (MK) associated with corneal reshaping contact lens wear, particularly in children, have caused concern about the safety of this modality. While these reports, summarized by Watt and Swarbrick,[5] highlight the importance of continued monitoring of complications associated with corneal reshaping contact lens wear, they do not allow comparison of the risk of severe complications associated with corneal reshaping contact lenses to other contact lens modalities. Because a low proportion of the population wears overnight corneal reshaping contact lenses, large-scale studies usually identify no cases of MK in this group.[6,7]

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Many of the cases of corneal ulcers that have been published have reported data from children; however, it should not be assumed that children have a greater risk of complications with corneal reshaping contact lens wear. Complications in children may be reported more often than in adults because of the greater potential for adverse effects due to a larger number of cumulative years that a young person may be exposed to risk. There may also be more children wearing corneal reshaping contact lenses than adults owing to the potential for myopia control with the contact lenses.[8–10] The risks of corneal reshaping contact lens wear in children cannot be compared to the risks in adults using only the data currently published in the literature. Large-scale, retrospective or prospective studies of overnight corneal reshaping contact lens wear in general, specifically in children, have not as yet been reported.

There are insufficient data on the absolute frequency of MK in overnight OK or on the relative risks compared with other contact lens modalities.[6] Nonetheless, editorials and opinion pieces have questioned the safety of corneal shaping lenses, particularly in children.[11–13]

In 2002, Paragon Corneal Refractive Therapy lenses, manufactured and distributed exclusively by Paragon Vision Sciences, were granted Food and Drug Administration (FDA) approval, although other lens designs and materials are covered by the original approval. In 2004, Bausch + Lomb received approval for the Boston Vision Shaping Treatment lens. These contact lenses are marketed as the Contex E series, the Euclid Emerald Lens, the DreamLens, and the BE Lens. In 2006, the FDA issued Section 522 orders to both companies mandating that they conduct Postmarket Surveillance of their respective corneal reshaping lenses to address concerns about the use of these lenses in children. Specifically, the orders required the companies to address ''in patients undergoing overnight OK treatment, what is the relative risk of developing MK in persons under the age of 18 as compared to adults?'' Using a retrospective cohort of patients fitted with overnight corneal reshaping lenses, this study compared the incidence of MK in children and in adult patients.

METHODS

In 2005, the FDA Office of Surveillance on Biometrics contacted Bausch + Lomb and Paragon requesting information on the incidence of MK, with particular reference to children compared to adult patients, and indicated their intention to require the conduct of a postmarket surveillance study. All parties agreed that a well-designed retrospective study would be able to address the core area of concern to the FDA—the risk of MK in patients younger than 18 years, relative to adults. There was identification of a number of areas of importance, including

- The need to determine the exposure time (duration of wear) of each patient
- The need to ascertain lost to follow-up patient data
- Consideration of incentives for practitioners to contact patients who have not returned to the practice and the collection of meaningful data from these patients
- The selection of participating practices including randomization and stratification by number of corneal reshaping patients
- The need for specific criteria for the diagnosis of MK

The protocol for the present study was developed by the authors and approved by the FDA and by the Ohio State University (OSU) Office of Research Risks and Protection. Informed consent was obtained as described below. The study was conducted in 2007.

The goal of the study was to compare the incidence of MK in children and in adult patients wearing corneal reshaping lenses using a retrospective cohort of patients fitted with these lenses in 2005 and 2006. The incidence in each age group was estimated based on the number of cases (numerator) and the years of lens wear (denominator). Years of lens wear were the total years of wear accumulated in the group. The difference in risk was estimated by comparing the incidence in the two age groups.

The sample-size goals of the study were to identify, through 200 practitioners, 1000 randomly selected patients in each age group, with sufficient follow-up to provide a total of 2000 patient-years of exposure across the two groups. With 2000 patient-years, if the true adult rate of incidence was 10 cases in 10,000 years and the true rate in children was 60 cases in 10,000 years, a difference could be detected with at least 80% power. These rates are similar in magnitude to those for other overnight wear modalities.[6]

Selection and Recruitment of Practitioners

Paragon provided OSU investigators with a comprehensive database containing names of practitioner accounts. For each account, they provided a history of all lens orders from 2005 and 2006. The information included order date and lens parameters. Similar information was provided by five authorized lens finishing laboratories licensed to sell corneal reshaping lenses under Bausch + Lomb's FDA Premarket Approval.

It is possible that the incidence of MK varies with practice volume, in terms of number of corneal reshaping lenses fitted. Therefore, for each company, a sampling strategy was developed, which targeted both practitioners fitting a large number of patients with corneal reshaping lenses and those fitting relatively few patients. The random sampling strategy recruited equal numbers of low- and high-volume practitioners, but limited the number of patients contributed by any one practitioner to 50, to minimize the respondent burden and to avoid any single practice contributing a substantial proportion of the sample.

The Optometry Coordinating Center at OSU coordinated all stratification with safeguards to mask both companies. The following protocol applied to each company. First, a complete list of practitioners along with their contact information and the number of orders in 2005 and 2006 was obtained. The practitioners were stratified into high- ($\geq$25 orders) and low- ($<$25 orders) volume groups. Within each stratum from each volume group and each company, a systematic sample was chosen, selecting every kth name, where k was determined by the desired sample size and the available population (k = population size/sample size). Second, for all practitioners, complete lens order data from 2005 and 2006 were obtained from the company. If 25 or fewer lens orders were available, all lens orders were sampled. For those practitioners with at least 25 lens orders, up to 50 orders were selected using simple random sampling methods. Lens order data for all practitioners were obtained from both companies (and affiliate lens finishing laboratories).

Paragon Vision Science mailed letters to a large group of practitioners—equal numbers of high and low volume—selected at

random from their customer database. Of these, 100 were later randomly selected for participation by the OSU investigators. The letter contained a description of the study, an indication that they *may* be approached by the OSU investigators, encouragement to participate, and assurances about confidentiality of participation and patient data. A similar letter was sent to practitioners by the following participating Bausch + Lomb laboratories—Art Optical, Essilor, Euclid, Precision Technology Services, and Truform—of whom 100 were later randomly selected for participation.

The 200 randomly selected practitioners were contacted by telephone by the principal investigator (MAB). When the practitioner was not available, a comprehensive message was left. At least three attempts were made to contact the practitioners by telephone. In addition, an e-mail was also sent to the practitioner when an address was available.

Data Forms

Participating practitioners were sent a customized Practitioner Lens Summary Form and asked to complete and return it to OSU. The form listed up to 50 pairs of corneal reshaping lenses ordered in 2005 and 2006. Practitioners were requested to provide the fitting date (quarter and year) and patient age at fitting for each of the pairs of lenses listed. In addition, they were asked whether the patient continued to wear the lenses and when the patient was last seen in the practice. Finally, the practitioner was asked to state whether each patient had experienced an episode of possible MK, defined as a painful red eye that required a visit to a doctor's office. For each case of possible MK, the practitioner completed an Event Form and returned it to OSU. This was intended to result in over-reporting so that no potential cases were missed. The practitioner may have been aware of cases in patients before the study period or in patients fitted during the study period, but not included on the list of lens orders. Such cases were ineligible for data analysis.

If the patient was treated by another practitioner, the patient was mailed a prepared packet by the practitioner containing Health Insurance Portability and Accountability Act and consent forms and a questionnaire regarding months of lens wear and any experienced adverse events. The form requested the name and address of the treating doctor. Patients were asked to return these three forms to OSU investigators. If the practitioner already knew the name of the treating doctor, the patient was not asked for the information. Only the deidentified summary information requested on the event form should have been provided, and individual patients were not contacted by OSU. The only identifiers on the form were fitting date and patient age.

Patients with less than 12 months of documented follow-up were mailed packets by the practitioner containing Health Insurance Portability and Accountability Act and study consent forms and a questionnaire regarding months of lens wear and any experienced adverse events. Patients were asked to return these three forms to OSU investigators in an accompanying prepaid envelope. This strategy was used in an attempt to capture any cases of discontinued wear because of MK.

Adjudication and Classification of Cases

An Outcomes Assessment Panel reviewed each case of possible MK independently and determined by majority vote whether the case was definite MK, probable MK, probably not MK, definitely not MK, or MK unrelated to contact lens wear (see below for details on classification of cases). The Outcomes Assessment Panel members were chosen based on their expertise in the assessment, evaluation, and management of contact lens-related complications. During classification of possible cases of MK, the panel was masked to the age of the patient to remove the potential for bias. The criteria for classification were similar to those used in a previous study of the incidence of MK.[14] The definition of definite MK was one or more corneal stromal infiltrates greater than 1 mm in size with pain more than mild and one or more of the following:

- anterior chamber reaction more than minimal,
- mucopurulent discharge,
- positive corneal culture,

and treatment consistent with standard of care for MK in terms of choice of medication, frequency, and duration.

The presence of a subsequent corneal scar was a requirement in cases in which adequate follow-up records were available. In the absence of positive or negative data concerning some of the first three criteria, the level of treatment was heavily weighted in the Outcomes Assessment Panel's determination of the presence of MK.

The definition of probable MK was the same as that of definite MK but failing to meet *all* of the specified criteria, for example, the size of the lesion was less than 1 mm, the pain was minimal, or there was no anterior chamber reaction, mucopurulent discharge, or positive corneal culture.

The definitions of probably not MK and definitely not MK were based on the extent that the above criteria were met. The category of MK unrelated to contact lens wear was reserved for cases, such as herpes simplex keratitis or staphylococcal marginal keratitis, where, in the judgment of the Panel, the etiology was unrelated to the wearing of contact lenses.

Data Analysis

The sample was described in terms of patient age, fitting date, and duration of corneal reshaping contact lens wear. A patient who was identified by multiple lens orders was only counted once in the analyses.

The primary endpoints were as follows:

- the incidence of MK in children and adults and
- the difference in risk between the two age groups.

The incidence of MK in each age group was estimated as the number of definite or probable MK cases divided by patient-years of lens wear. The difference in risk was estimated by comparing the incidence in the two patient age groups.

Only patients who had completed at least 3 months of wear were included in the data analyses. Exposure was calculated based on last patient contact with the practitioner. If less than 12 months of follow-up were available, exposure was based on the last date that the patient reported wearing the lenses. The incidence was also estimated for all infiltrative events, regardless of severity.

Statistical analyses were performed using Statistical Analysis Software (SAS, version 9.1.3) and StatXact (version 8). The parameter of central concern was the incidence rate, which is estimated as the ratio of the number of incidents in a sample divided by the total person-time accumulated by the sample. Estimates of this parameter, as well as descriptive summaries (means and

standard deviations) of practitioner and patient characteristics, were computed in SAS. Exact confidence intervals (CIs) for the absolute value of incidence rates were also computed in SAS using the method of Garwood.[15] Exact CIs for the difference in the incidence rates between children and adults were computed in StatXact using the method of Chan and Zhang.[16]

RESULTS

Of the 200 randomly selected practitioners, 9 could not be contacted because of illness, practice closure, or because the practitioner had left the practice. For the 191 practitioners who could be located and contacted, 119 agreed to participate (62%). For the 119 practitioners who agreed to participate, 66 were high volume (55%) and 53 were low volume (45%). Subsequent to agreeing to participate, 86 practitioners returned completed forms, 11 withdrew, and 22 failed to complete the study forms despite multiple and frequent reminders. There was no significant difference (χ^2 test, p = 0.085) between the proportion of high-volume practitioners (51 of the 99 contacted) and the low-volume practitioners submitting data (35 of the 92 contacted). The completed forms corresponded to 2202 lens orders and represented 1494 unique patients.

Practitioners sent 48 packets to patients who had not been followed for at least 12 months. Of these, 22 patients returned the completed forms to investigators, and 14 of these provided new information regarding duration of lens wear.

Duration of Lens Wear

Patients were identified based on lens orders in 2005 and 2006 without differentiating among patients fitted for the first time in an approved corneal reshaping lens, patients refit in a new design, or lenses ordered for other reasons. Some patients had documented lens wear before 2005, but only data on lens wear from 2005 onward and cases of possible MK from 2005 onward were analyzed to minimize bias.

For most patients, duration of lens wear was based on the date the patient was last seen in the practitioner's office wearing their lenses on a regular basis. For patients submitting forms containing follow-up information, the duration of lens wear reported by the patient was used. In patients for whom the practitioner reported an original fitting date in 2005 or after, the duration of lens wear was based on this date. In patients for whom the practitioner reported an original fitting date before 2005, the duration of lens wear was calculated conservatively from January 2005.

The above criteria resulted in a sample of 1317 patients: 640 adults (49%) and 677 children (51%). These patients are distributed relatively evenly between the two companies (697 vs. 620), and represent a total of 2599 patient-years of wear: 1164 in adults and 1435 in children. The patient-years are distributed relatively evenly between the two companies (1374 vs. 1224).

Table 1 summarizes the number of participating practitioners stratified by practice volume and company. The number of patients and contributed patient-years are also shown, stratified by age group, practice volume, and company. At the original fitting date, the mean (SD) age of the adults was 38.0 (11.1) years and the mean (SD) age of the children was 12.2 (2.5) years. The age distribution of the children and adults is shown in Fig. 1. The mean (SD) follow-up for the adults was 1.8 (1.0) years, with 497 (78%) having at least 12 months of follow-up. The mean (SD) follow-up for the children was 2.1 (0.8) years, with 620 (92%) having at least 12 months of follow-up.

Incidence of MK

A total of 50 event forms were submitted. These were from 27 practitioners, representing almost one third of those providing patient data. All forms were transcribed and sent to the five members of the Outcome Assessment Panel for adjudication. Eleven forms reported a corneal infiltrate of which seven were in children, but as described previously, panel members were masked to the age of the patient. Three of the cases of infiltrates occurred before 2005 and thus not within the years of lens wear used to determine risk. Of the eight qualifying infiltrative events, six occurred in children.

The results of the Panel's assessment are summarized in Table 2. Two cases were classified as definite MK by the Panel and used for the primary analyses. Thus two cases of MK occurred within 2599 patient-years of overnight corneal reshaping lens wear. Neither of the MK cases resulted in any documented long-term loss of best-corrected visual acuity. One adult was not examined again after an event but was classified by the Panel as definitely not MK.

Table 3 summarizes the incidence estimates for MK based on the 2599 patient-years. The overall estimated incidence of MK is 7.7 per 10,000 patient-years (95% CI = 0.9 to 27.8). For children, the estimated incidence of MK is 13.9 per 10,000 patient-years (95% CI = 1.7 to 50.4). For adults, the estimated incidence of MK is 0 per 10,000 patient-years (95% CI = 0 to 31.7).

The difference in rates (children − adults) was also calculated along with the CI. The 95% CI includes zero, so there is no statistically significant difference in the rates between children and adults (difference = 13.9 per 10,000 patient-years, 95% CI = −17.9 to +50.9).

A conservative analysis limited to the 685 patients (representing 1415 patient-years) who began wear of overnight corneal reshaping lenses after January 2005 *and* had at least 12 months of documented lens wear is presented in Table 4. The overall estimated incidence of MK is 14.1 per 10,000 patient-years (95% CI = 1.7 to 51.1). For children, the estimated incidence of MK is 25.2 per 10,000 patient-years (95% CI = 3.1 to 91.0). For adults, the

TABLE 1.
Summary of participating practitioners and eligible patients

	High volume	Low volume	Company A	Company B	Total
Number of practitioners	51	35	47	39	86
Patients contributed	1166	151	697	620	1317
Adults	554	86	383	257	640
Children	612	65	314	363	677
Patient-years contributed	2329	270	1374	1224	2599
Adults	1017	147	711	452	1164
Children	1312	123	663	772	1435

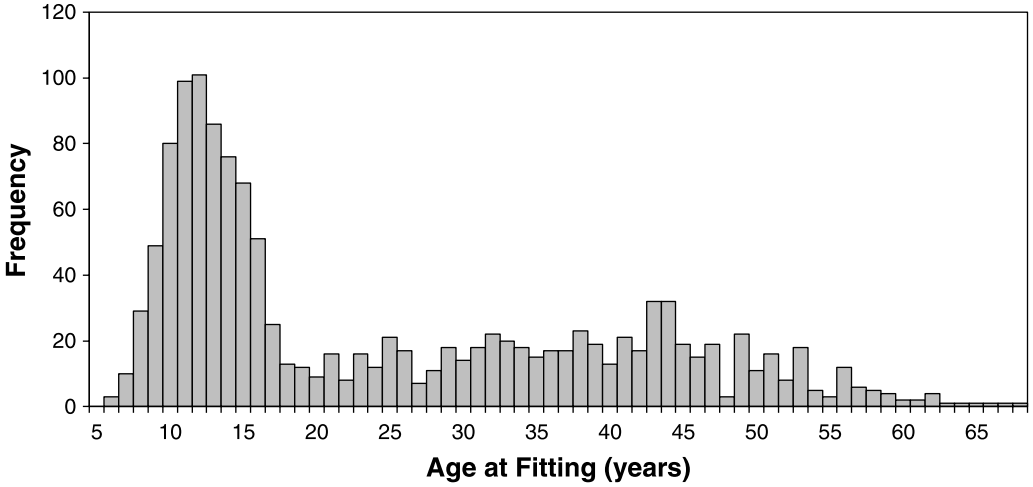

FIGURE 1.
Age distribution of patients at fitting.

estimated incidence of MK is 0 per 10,000 patient-years (95% CI = 0 to 59.4). For this more conservative criterion, there is again no statistically significant difference in the rates between children and adults (difference = 25.2 per 10,000 patient-years, 95% CI = −34.1 to +92.7).

Incidence of Corneal Infiltrates Associated With a Painful Red Eye

Table 5 summarizes the incidence estimates for all infiltrative events based on the 2599 patient-years. The overall estimated incidence of corneal infiltrates is 30.8 per 10,000 patient-years (95% CI = 13.3 to 60.7). For children, the estimated incidence of corneal infiltrates is 41.8 per 10,000 patient-years (95% CI = 15.3 to 91.0). For adults, the estimated incidence of corneal infiltrates is 17.3 per 10,000 patient-years (95% CI = 2.1 to 62.1). The rate difference is not statistically significant (difference = 24.5 per 10,000 patient-years, 95% CI = −23.9 to +76.8).

DISCUSSION

Eight events of corneal infiltrates in patients presenting for an unscheduled visit with a painful red eye were documented in 1,317 patients wearing overnight corneal reshaping lenses for a total of 2599 patient-years. Two events were judged to be MK by independent masked experts. Both cases were in children and neither resulted in a long-term loss of best-corrected visual acuity. The estimated overall incidence of MK is 7.7 per 10,000 patient-years (95% CI = 0.9 to 27.8). The estimated incidence is 13.9 per 10,000 patient-years in children (95% CI = 1.7 to 50.4) and 0.0 per 10,000 patient-years in adults (95% CI = 0 to 31.7). The difference in rates is 13.9 per 10,000 patient-years (95% CI = −17.9 to +50.9). In other words, the rate in children may be lower than the rate in adults by up to 17.9 per 10,000 patient-years or the rate in children may be higher than the rate in adults by up to 50.9 per 10,000 patient-years. The major findings of the study will be summarized in the package inserts and patient information booklets for FDA-approved overnight corneal reshaping contact lenses.

The fact that the CIs for the rates estimated overlap should not be interpreted as evidence of no difference. True differences under 50 cases per 10,000 patient-years were beyond the study's power of detection. Nonetheless, there is some evidence that the rate may be higher in children. Six of the eight cases of corneal infiltrates accompanied by a painful red eye occurred in children, and both of the cases classified as MK were in children. The estimated incidence of MK in children wearing overnight corneal reshaping contact lenses is similar in magnitude to that previously associated

TABLE 2.
Summary of classification of cases by the outcomes assessment panel

Original fit (quarter/year)	Time from original fit to event, mo	Age at fitting, y	Age at event, y	BCVA at event	BCVA at resolution	Classification
3/2006	15	11	12	20/200	20/20	Definite MK
3/2005	15	15	17	20/20	20/20	Definitely not MK
3/2005	15	15	16	20/20	20/20	Definite MK
3/2005	5	9	9	20/20	20/20	Definitely not MK
1/2005	5	12	12	20/20	20/20	Probably not MK
3/2004	6	8	8	20/30	20/20	Definitely not MK
4/2005	10	27	28	20/30	20/20	Definitely not MK
4/2004	5	28	29	20/40	Lost to follow-up	Definitely not MK

Note that although two patients were originally fit before 2005, the cases of corneal infiltrates occurred in 2005.

TABLE 3.

Incidence of MK based on at least 3 months' wear

	Children	Adults	Overall
n	677	640	1317
Cases	2	0	2
Years at risk	1435	1164	2599
Incidence rate (95% CI)	0.00139 (0.00017 to 0.00504)	0 (0 to 0.00317)	0.00077 (0.00009 to 0.00278)
Rescaled incidence rate (95% CI)	13.9 (1.7 to 50.4)	0 (0 to 31.7)	7.7 (0.9 to 27.8)

Rate is per year of wear. Rescaled rate is per 10,000 patient-years.
CI, confidence interval.

with the overnight wear of soft contact lenses. Practitioners and particularly parents should be aware of this risk because it is an important part of the risk-benefit ratio.

Most previously published articles on MK associated with overnight corneal reshaping lenses are case reports and small case series.[5,17] In the largest previous study, Lipson[18] retrospectively evaluated outcomes of overnight corneal reshaping in children and adults. Data on 296 patients were reported, of whom 52% were 12 years or younger, representing 507 patient-years. He reported three adverse events during the study. Although the definition of adverse event included "microbial keratitis, a corneal abrasion requiring medical treatment, loss of best-corrected visual acuity, or a corneal scar," none were MK (Lipson, personal communication, 2012). All three were presentations of superficial punctate keratitis or epithelial defects greater than grade 2, which did not result in a loss of best-corrected visual acuity, and all three patients were still wearing their lenses at the conclusion of the study. The two FDA premarket approval applications submitted by Paragon and Bausch + Lomb for approval of overnight corneal reshaping lenses reported no cases of MK, although each study reported one eye developing corneal infiltrates.[19,20] Collectively, these studies enrolled 396 patients followed for up to 9 months, with around 70% completing 9 months of wear.

The present study is the largest attempt by far to quantify the risk of MK associated with overnight corneal reshaping lenses with 2599 patient-years of wear. The above studies are smaller by around a factor of 10. Given the relatively low incidence of MK, it is not surprising that no cases were reported in these earlier studies. Assuming an incidence of 7.7 per 10,000, it would require a study of around 1000 patient-years for the probability of observing at least 1 case to exceed 50% ($1 - (1 - 0.00077)^{1000} = 0.54$) and more than 2000 patient-years for the probability of observing at least 1 case to exceed 80% ($1 - (1 - 0.00077)^{2000} = 0.80$). In other words, the two FDA premarket approval studies and that of Lipson were unlikely to identify cases of MK based on the incidence estimated in the present study.

Comparison With MK Rates in Other Contact Lens Modalities

The incidence of MK associated with overnight corneal reshaping lenses estimated in the present study is higher than that for daily rigid contact lens wear but similar to that for overnight wear of soft contact lenses, although corneal reshaping lenses are not worn for most of the waking hours.[6,14,21–24] A recent large-scale prospective, 12-month, population-based study estimated the risk of contact lens-related MK.[6] The authors identified 285 eligible cases of contact lens-related MK and 1798 controls. For daily wear of rigid gas-permeable contact lenses, the annualized incidence was 1.2 per 10,000 wearers (95% CI = 1.1 to 1.5). Consistent with earlier reports, the incidence for overnight wear of soft contact lenses was higher: 19.5 per 10,000 wearers (95% CI = 14.6 to 29.5) for conventional hydrogels and 25.4 per 10,000 wearers (95% CI = 21.2 to 31.5) for silicone hydrogels. Risk factors included overnight use, poor storage case hygiene, smoking, Internet purchase of contact lenses, less than 6 months of wear experience, and higher socioeconomic status. The authors conclude that overnight use of any contact lens is associated with a higher risk than daily use. The authors of this large prospective population-based surveillance study of contact lens-related corneal infection did not identify any cases of MK associated with overnight corneal reshaping lenses (Stapelton, personal communication, 2009).

Study Limitations and Strengths

A number of factors should be considered when interpreting the results of the present study. This was a retrospective study rather than a prospective trial and thus prone to a number of limitations

TABLE 4.

Incidence of MK based on patients fitted after January 2005 and with at least 12 months' wear

	Children	Adults	Overall
n	378	307	685
Cases	2	0	2
Years at risk	794	621	1415
Incidence rate (95% CI)	0.00252 (0.00031 to 0.00910)	0 (0 to 0.00594)	0.00141 (0.00017 to 0.00511)
Rescaled incidence rate (95% CI)	25.2 (3.1 to 91.0)	0 (0 to 59.4)	14.1 (1.7 to 51.1)

Rate is per year of wear. Rescaled rate is per 10,000 patient-years.
CI, confidence interval.

TABLE 5.
Incidence of corneal infiltrates associated with a painful red eye based on at least 3 months' wear

	Children	Adults	Overall
n	677	640	1317
Cases	6	2	8
Years at risk	1435	1164	2599
Incidence rate (95% CI)	0.00418 (0.00153 to 0.0091)	0.00173 (0.00021 to 0.00621)	0.00308 (0.00133 to 0.00607)
Rescaled incidence rate (95% CI)	41.8 (15.3 to 91.0)	17.3 (2.1 to 62.1)	30.8 (13.3 to 60.7)

Rate is per year of wear. Rescaled rate is per 10,000 patient-years.
CI, confidence interval.

including, but not limited to, site and patient selection and participation bias, and assumptions that disease incidence is constant over time among wearers. Study sites were selected at random, but participation was voluntary and practitioners who had observed cases of MK may have been less willing to participate. The goal of the study was to sample patients from 200 practitioners, but only 86 (43% of the goal) returned at least one completed form. In retrospect, the protocol could have planned on replacing nonparticipating practitioners using a predefined scheme based on volume. The classification of MK was determined by an Outcome Assessment Panel without direct contact with the patient or photographs. Finally, the derived CIs are broad. The study's failure to find a statistically significant difference in the rate of MK between adults and children may be due to a sample size too small to detect a true underlying difference. As indicated earlier, a study with 2000 patients and patient-years has an 80% chance to detect a rate difference of 50 cases in 10,000 patient-years, a rate difference considerably larger than the 13.9 cases in 10,000 patient-years observed in this study.

Any difference in the estimated rate of MK between children and adults could have been biased by differential loss to follow-up between the two age groups. Among the 1494 total patients, 677 of the 725 children (93%) had at least 3 months of follow-up compared with 640 of 756 (85%) adults ($\chi^2 = 28.6$, $p < 0.001$). Among the 1317 patients with at least 3 months of documented lens wear, 620 of the 677 children (92%) had at least 12 months of follow-up compared with 487 of 640 (76%) of adults ($\chi^2 = 58.9$, $p < 0.001$). Thus, for both comparisons, follow-up was better in children than in adults.

While previous published studies have reported individual or a small series of overnight corneal shaping patients presenting with MK, none have estimated its incidence. Despite the above limitations, this was a large study (2599 patient-years) of randomly selected patients fitted by randomly selected practitioners. Cases were classified by an independent group of experts using clear and established criteria and without knowledge of whether the patient was a child or an adult.

Finally, it is important to emphasize that this study was conducted in the United States, where clinical standards are high, professional competencies are well maintained, and identification and early treatment of adverse events may limit the impact of any corneal infection.

Participation Rate and Sampling Strategy

The original sampling strategy of the study protocol was to identify 100 randomly selected practitioners per company, and 1000 randomly selected patients in each age group with sufficient follow-up to provide 2000 patient-years of exposure. Only around 60% of practitioners agreed to participate, with most of the remaining practitioners not responding rather than declining to participate. This could be a source of bias, although those practitioners who did not participate did not differ from those who did based on patient volume. The study relied almost entirely on practitioners reporting corneal infiltrative events and a practitioner may have been motivated not to report. Furthermore, he/she may have been unaware of a patient who suffered an infection, was treated elsewhere and never returned to his practice. In other studies of contact lens wear, extensive efforts have gone into establishing a reliable numerator, that is, identifying all cases, for example, by contacting the exposed subjects directly to ascertain if they had experienced a painful, red eye. In this retrospective study, this was not possible because patients had not given their informed consent at the time of fitting to be contacted by a third party.

The goal of the sampling strategy was to obtain 2000 patient-years of follow-up on 2,000 patients. The response of practitioners resulted in 2599 patient-years but only 1317 patients. We considered sampling more practitioners or requesting data on more patients from participating practitioners to reach 2000 patients. However, either strategy could introduce more bias, without providing substantially more statistical power. For example, the majority of the practitioners (including all low volume practitioners) reported data for all of their lens orders. Only 20% of respondents (the highest volume practitioners) could provide additional data from patients fitted during these years. Thus, soliciting more patient data from respondents would have biased the sample toward high-volume practitioners.

In planning this study, no data were available regarding the age distribution of the patients fitted with overnight corneal reshaping lenses, but the resulting sample demonstrates that children account for around half of the patients fitted with overnight corneal reshaping lenses in the United States. Efron et al[25] reported a survey of 105,734 contact lens fits in 38 countries from 2005 to 2009 including 13,926 in minors (<18 years of age). Overall, corneal reshaping lenses accounted for 28% of the rigid lens fits in minors, attesting to the popularity of this mode of correction for younger age groups around the world. For 212,000 total contact lens fits tracked by these authors since 1996, 1025 were described as "rigid orthokeratology," of whom 51% of patients are 17 years and younger (Morgan, personal communication, 2012). In other words, the distribution of overnight corneal reshaping lenses between adults and children in the present study seems consistent with practice worldwide. The viability of these lenses for the

control of myopia progression may have increased this proportion in recent years.[8–10]

The American Academy of Ophthalmology published an Ophthalmic Technology Assessment on overnight OK in 2008.[26] The authors conducted a thorough review of the literature and identified 38 articles describing case reports or case series of MK associated with overnight corneal reshaping contact lenses. The authors acknowledge that the ''value of the data is limited, because no denominator exists for the treatment population and the total number of patients undergoing overnight orthokeratology is unknown.'' The authors state that ''the prevalence and incidence of complications associated with overnight orthokeratology have not been determined'' but that ''the large number of children and adolescents in these series and the risk of sight-threatening complications in children and adolescents necessitates the highest level of vigilance.'' They conclude, ''future research should be directed at assessing the rate of infectious keratitis among overnight orthokeratology users and whether the rate varies by age.'' This study is a first step in addressing this goal.

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REFERENCES

1. Jessen GN. Orthofocus techniques. Contacto 1962;6:200–4.
2. Polse KA, Brand RJ, Schwalbe JS, Vastine DW, Keener RJ. The Berkeley Orthokeratology Study, Part II: efficacy and duration. Am J Optom Physiol Opt 1983;60:187–98.
3. Nichols JJ, Marsich MM, Nguyen M, Barr JT, Bullimore MA. Overnight orthokeratology. Optom Vis Sci 2000;77:252–9.
4. Swarbrick HA. Orthokeratology review and update. Clin Exp Optom 2006;89:124–43.
5. Watt KG, Swarbrick HA. Trends in microbial keratitis associated with orthokeratology. Eye Contact Lens 2007;33:373–7.
6. Stapleton F, Keay L, Edwards K, Naduvilath T, Dart JK, Brian G, Holden BA. The incidence of contact lens-related microbial keratitis in Australia. Ophthalmology 2008;115:1655–62.
7. Dart JK, Radford CF, Minassian D, Verma S, Stapleton F. Risk factors for microbial keratitis with contemporary contact lenses: a case-control study. Ophthalmology 2008;115:1647–54.
8. Cho P, Cheung SW, Edwards M. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. Curr Eye Res 2005; 30:71–80.
9. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. Br J Ophthalmol 2009;93:1181–5.
10. Cho P, Cheung SW. Retardation of Myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. Invest Ophthalmol Vis Sci 2012;53:7077–85.
11. Kwok LS, Pierscionek BK, Bullimore M, Swarbrick HA, Mountford J, Sutton G. Orthokeratology for myopic children: wolf in sheep's clothing? Clin Experiment Ophthalmol 2005;33:343–7.
12. Saviola JF. The current FDA view on overnight orthokeratology: how we got here and where we are going. Cornea 2005;24:770–1.
13. Schein OD. Microbial keratitis associated with overnight orthokeratology: what we need to know. Cornea 2005;24:767–9.
14. Schein OD, McNally JJ, Katz J, Chalmers RL, Tielsch JM, Alfonso E, Bullimore M, O'Day D, Shovlin J. The incidence of microbial keratitis among wearers of a 30-day silicone hydrogel extended-wear contact lens. Ophthalmology 2005;112:2172–9.
15. Garwood F. Fiducial limits for the poisson distribution. Biometrika 1936;46:441–53.
16. Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55:1202–9.
17. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutierrez-Ortega R. Orthokeratology vs. spectacles: adverse events and discontinuations. Optom Vis Sci 2012;89:1133–9.
18. Lipson MJ. Long-term clinical outcomes for overnight corneal reshaping in children and adults. Eye Contact Lens 2008;34:94–9.
19. U. S. Food and Drug Administration Center for Devices and Radiological Health. Paragon Vision Sciences. Summary of safety and effectiveness data from Premarket Approval Application (PMA) supplement number P870024/S43; 2002. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/P870024S043b.pdf. Accessed April 29, 2013.
20. U. S. Food and Drug Administration Center for Devices and Radiological Health. Euclid Systems Corporation. Summary of safety and effectiveness data from Premarket Approval Application (PMA) supplement number P010062: 2004. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/P010062b.pdf. Accessed April 29, 2013.
21. Poggio EC, Glynn RJ, Schein OD, Seddon JM, Shannon MJ, Scardino VA, Kenyon KR. The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. N Engl J Med 1989;321:779–83.
22. Morgan PB, Efron N, Hill EA, Raynor MK, Whiting MA, Tullo AB. Incidence of keratitis of varying severity among contact lens wearers. Br J Ophthalmol 2005;89:430–6.
23. Cheng KH, Leung SL, Hoekman HW, Beekhuis WH, Mulder PG, Geerards AJ, Kijlstra A. Incidence of contact-lens-associated microbial keratitis and its related morbidity. Lancet 1999;354:181–5.
24. Nilsson SE, Montan PG. The annualized incidence of contact lens induced keratitis in Sweden and its relation to lens type and wear schedule: results of a 3-month prospective study. CLAO J 1994;20: 225–30.
25. Efron N, Morgan PB, Woods CA. International survey of contact lens prescribing for extended wear. Optom Vis Sci 2012;89:122–9.
26. Van Meter WS, Musch DC, Jacobs DS, Kaufman SC, Reinhart WJ, Udell IJ. Safety of overnight orthokeratology for myopia: a report by the American Academy of Ophthalmology. Ophthalmology 2008; 115:2301–13.

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