

## Orthokeratology lens related infections

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### Abstract

Orthokeratology is a reversible technique that temporarily changes the curvature of the cornea with the aim of addressing refractive errors. The United States Food and Drug Administration (FDA) granted approval for using reverse geometry contact lenses to correct myopia without any age restriction. Information from the pre-market applications to the FDA was rated as level II evidence. Another unapproved use of overnight orthokeratology is for the prevention of myopic progression. Although orthokeratology is advocated to reduce myopic progression, there are limited long-term studies with substantial evidence of its benefits. Much of this evidence comes from non-robust experimental studies using historical or self-selected controls with relative high dropout rates. Although some positive results have been published in temporarily reducing the myopic refractive error and its progression, the use of these lenses can be associated with serious complications such as microbial keratitis. Microbial keratitis is a potentially vision-threatening adverse response associated with contact lens wear. In fact, contact lens wear

has been shown to be the predominant risk factor of microbial keratitis in some developed countries. Most of the published cases on overnight orthokeratology related microbial keratitis occurred in children or adolescents. Parents considering orthokeratology must make an informed decision about its temporary benefit and its potential for permanent loss of vision. The ophthalmic community should be reminded of the potential complications of orthokeratology.

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**Key words:** Orthokeratology; Infections; Microbial keratitis; Cornea; Corneal ulcer; Contact lens; Myopia

**Core tip:** Orthokeratology uses specially designed rigid contact lenses to temporarily reshape the cornea to ameliorate refractive errors and it has also been suggested to slow the progression of myopia. None of the published studies to date in assessing its efficacy are rated as level I evidence. Orthokeratology carries the risk of microbial keratitis, which is potentially sight threatening and the safety of orthokeratology remains difficult to assess. Practitioners prescribing orthokeratology must receive appropriate training with respect to the local standards, inform patients and/or their parents of the potential risks, and ensure their patients' compliance in proper handling of the day to day care of their lenses to minimize the infective risks.

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### INTRODUCTION

Orthokeratology is defined as the reduction, modification, or elimination of refractive anomalies by the pro-

grammed application of contact lenses<sup>[1]</sup>. Modern day orthokeratology was first advocated during the Second World Contact Lens Congress in Chicago in 1962, where George Jessen, the father of orthokeratology, introduced fitted polymethyl methacrylate (PMMA) contact lenses which had a curve flatter than the cornea to alter the curvature of the cornea and reduce myopia<sup>[1]</sup>. These lenses were worn during daytime and provided clear uncorrected vision for a few hours after they were removed in the afternoon. Over the next few decades, few other studies comparing daily wear of orthokeratology lenses reported similar modest but not significantly different myopic reduction as compared with conventional alignment fitted lens. Disappointment began to set in as inducible corneal astigmatism was reported due to lens instability. Variable and temporary refractive outcomes were observed, requiring continuous use of retainer lens to maintain its refractive effectiveness and/stabilisation.

Re-emergence of interest in this technique came in the late 1980's with the development of rigid gas permeable (RGP) lens that has a significantly higher oxygen transmission (Dk). Such material allows for a relatively safer closed-eye contact lens usage<sup>[2]</sup>. This led to the concept of overnight orthokeratology (OOK) where lenses are worn during the night time and removed during the daytime, allowing unaided vision during waking hours. Computer-assisted corneal topographic mapping also provided more detailed assessment of the elevation and curvature of the cornea, allowing more accurate lens design and fitting. Conventional rigid lens surfaces are designed to have a central base surrounded with progressively flattening concentric curves. With the development of reverse geometry lenses, designed to have a flat-back central optical zone with steeper intermediate zone, more accelerated flattening of the central corneal zone is possible compared to the previous lens designs<sup>[3]</sup>.

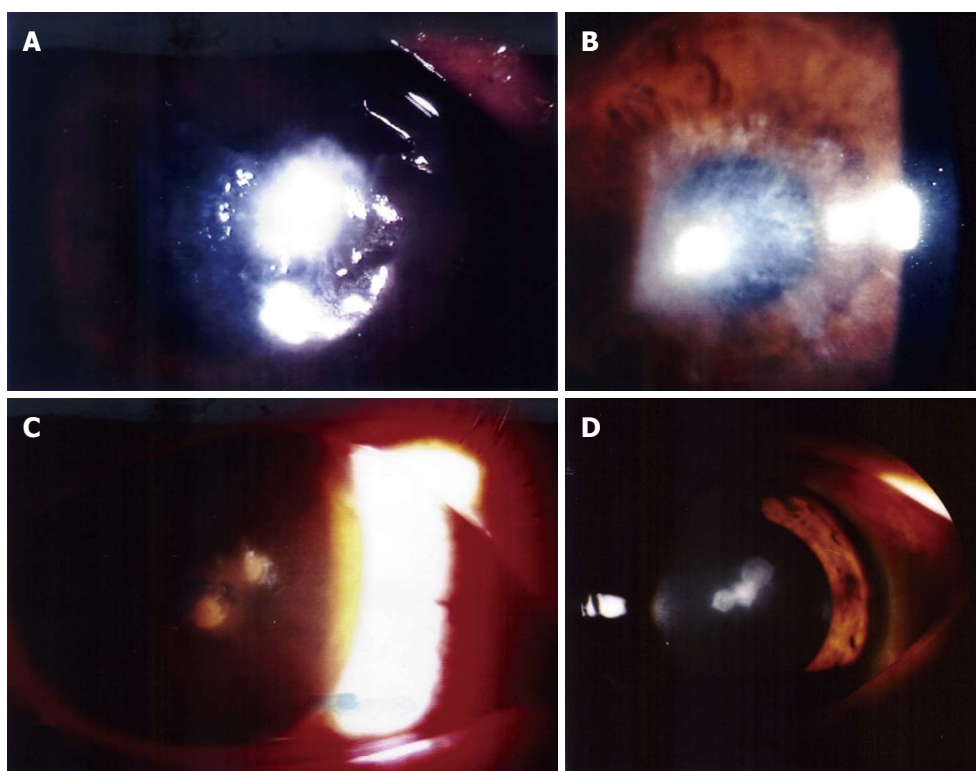
This review will highlight the published literature on the efficacy of orthokeratology and the evidence of potential limitations, and outline the complications related to the use of these lenses.

## PRINCIPLE AND EVIDENCE OF EFFICACY

Orthokeratology temporarily reduces the overall refractive power by flattening the central cornea to reduce the corneal sagittal height in order to reduce myopia<sup>[4]</sup>. The corneal periphery becomes relatively thicker, enhancing the peripheral corneal curvature. There is conflicting evidence about the time sequences of these events, but the combined effect is proposed to be the mechanism behind the refractive changes<sup>[5]</sup>. Thinning of central epithelium has been observed with optical coherence tomography<sup>[6]</sup>. Correlating with the morphological changes, unaided vision usually improves on an average by 1 wk, and stabilizes by 1 mo<sup>[7]</sup>. However, such visual improvement is transient, unless retainer lenses are continuously used at night time to maintain the flattened central cornea, where the frequency of use would depend on the degree of

myopia, and ranges from every 1-2 nights to maintain the flattening effect<sup>[7]</sup>. The US Food and Drug Administration (FDA) approved the Paragon Corneal Refractive Therapy (CRT) for myopia reduction in 2002 based on their premarket study consisting of 205 subjects, only 24 of whom were between the age of 12 and 18 years<sup>[8]</sup>. During the evaluation, the FDA advisory panel commented that they would only recommend the approval of Paragon CRT be limited to patients 18 years and older, but FDA granted the approval of OOK without any age restriction. Later in 2004, Euclid Systems also received FDA approval for their orthokeratology to control myopia.

An unapproved use of OOK is for prevention of myopic progression. It is proposed that OOK prevents myopia progression *via* "peripheral hyperopic defocus"<sup>[9]</sup>. This theory suggests that the peripherally flatter cornea reduces peripheral hyperopia by aligning the image shell onto the mid peripheral retina, signalling the peripheral retina to control axial elongation. This controversial theory was tested in studies and it was found that relative peripheral hyperopia exerts little consistent influence on the rate of myopia progression or axial elongation<sup>[10]</sup>. The reported reduction in axial length also may be attributed to the gradual slowing of myopic progression in the control group with age, which may be expected. The published studies so far were neither randomized nor prospective, leading to observer bias. Five studies using historical or self-selected controls reported relative slower myopic progression (by 32%-55%) in low-to-moderately myopic children wearing OK lenses compared with those wearing conventional eyeglasses<sup>[11-14]</sup> or single-vision soft contact lenses<sup>[15]</sup>. The dropout rate reported in these studies with orthokeratology varies from 6%<sup>[14]</sup> to 30%<sup>[15]</sup>. The Longitudinal Orthokeratology Research in Children trial studied 35 children in Hong Kong who wore OK lenses for 2 years<sup>[11]</sup>. The authors found that the axial length in the orthokeratology group increased by 0.29 mm *vs* 0.54 mm for the control group. However, a major drawback in this study was that a historical control group of children wearing single vision lenses was used as the control. The Corneal Reshaping and Yearly Observation of Near-sightedness Pilot Study<sup>[15]</sup> compared 28 participants using corneal reshaping contact lenses to a historical control subject who were randomly assigned to wear soft contact lenses during the Contact Lens and Myopia Progression study<sup>[16]</sup>. Although the authors reported the annual rate of change in axial length was 0.16 mm per year less for corneal reshaping lens wearers than soft contact lens wearers ( $P = 0.00004$ ), the low number of participants, the choice of control, as well as a 30% dropout rate limit the strength of the conclusions drawn from this study. Another study followed the OOK participants over 5 years and reported that changes in axial length over each year were significantly different; however, by the end of year 5, the changes in axial length were no longer significantly different ( $P = 0.8633$ )<sup>[13]</sup>. A recently published randomized controlled trial attempted to determine whether OK was effective in



**Figure 1** Microbial keratitis raises significant concerns in using overnight orthokeratology lenses. A: Presentation of a 13-year old girl who wore OKL for 36 mo with nocturnal wear at 10 h. Culture grew *Pseudomonas aeruginosa*; B: The 13-year-old girl with scar after treatment. Best corrected vision was 20/200 (plano/-5.00 × 165°); C: Presentation of a 12-year-old boy who wore OKL for 7 mo with nocturnal wear at 10 h. Culture grew *Pseudomonas aeruginosa*; D: The 12-year-old boy with scar after treatment.

slowing myopia progression<sup>[17]</sup>. They found that subjects wearing OOK lenses had a slower axial elongation by 43% compared with those wearing single-vision glasses. Younger children less than 7 years of age had faster axial elongation and may have additional benefit from early OK treatment. However, the examiners measuring the axial length were not masked and a dropout rate of 27% was reported in the orthokeratology group. In addition, although the OK group had a reduction in axial length over the study 2-year period, corresponding changes in refraction were not reported and the clinical significance of an isolated reduction in axial elongation without refractive changes is not known.

## SAFETY

A review by Watt and Swabrick analysed all cases of microbial keratitis (MK) associated with OOK since 2001 to 2007<sup>[18]</sup>. Not surprisingly, most of the findings remain unchanged from the initial analysis of the first 50 cases<sup>[19]</sup>. Microbial keratitis raised significant concerns in using OOK lenses. The majority of these infections were central and severe. Two of our own examples can be seen in Figure 1. The final best-corrected visual acuity (BCVA) after resolution of infection was reported in 93 cases, 18% of which had BCVA less than 20/200. Most cases occurred in children or adolescents: 55% of the cases were between 8-15 years old, 41% were between 16-25

years old, and the remaining 4% were above 25 years of age. There is particular concern with OOK in children and young adults since this is the age group with the highest number of users<sup>[20]</sup>. It would be ideal to stratify the OOK users by age cohorts and analyse the outcomes in terms of initial and final BCVA in order to identify risk factors associated within each cohort, and subsequently with strategies to reduce risk of MK. However, based on the information available related to lens design, material or fitting, lens care and compliance, it was difficult to draw conclusions about risk factors with regards to the specific cohorts by age group. In this review, *Pseudomonas aeruginosa* infection accounted for 37% of the cases while *Acanthamoeba* infection was responsible for 33%. *Acanthamoeba* infection is capable of causing corneal scarring, ultimately leading to a significant vision loss. *Acanthamoeba* infections are known to be associated with contaminated water sources, which further raise the worry regarding the care of OK lenses. Thus it is crucial not to use any tap water during the cleansing of lenses. The prevalence of *Acanthamoeba* related MK is only reported to be 3%-5% in case series for other contact lens wearing modalities. The much higher prevalence of *Acanthamoeba* infection in OOK remains a cause of concern<sup>[21,22]</sup>. Tear film immunoglobulin A level is found to be reduced in children and may contribute to increased risk of *Acanthamoeba* keratitis in this age group<sup>[23]</sup>. No significant differences were reported in the ocular flora profile over time in patients

with multiple conjunctival cultures before and during OOK use<sup>[24]</sup>. It is likely the OOK related MK is related to opportunistic pathogens already present on the corneal surface infecting the underlying compromised corneal epithelial, which resulted from the physical reshaping of the cornea and hypoxic stress from nocturnal wear. Apart from thinning of the cornea, OOK also changes the structural integrity of the epithelium, where the central epithelium significantly differs in cell shape and size. The deeper layers of the cornea may also lose their normal plicae<sup>[25,26]</sup>. Even with the most oxygen permeable lenses, animal studies found significant *Pseudomonas* adhesions to the cornea with the use of reverse geometry contact lens compared with alignment fit lenses. The enhanced binding is accompanied by thinning and reduced turnover of the epithelium. All these factors may attribute to the increased susceptibility of microbial invasion to the cornea<sup>[27]</sup>. Clinical trials in human subjects with alignment fit RGP lenses using the highest Dk material did not report an increase in *Pseudomonas* binding after 30 nights of usage<sup>[28]</sup>. This suggests that the reverse-geometry lens architecture may produce risk of *Pseudomonas* induced MK. The compressive forces of the reverse geometry lenses may lead to disrupted epithelial surfaces, and the reverse geometry lenses may provide a reservoir for bacteria deposition, which is further aggravated by a compromised ocular surface from overnight wear<sup>[29,30]</sup>. *Pseudomonas* infection is also associated with OOK related corneal ulcer in children. In an observational case series with children, 83% of cases were culture positive for *P. aeruginosa*. Although these ulcers were neither central nor paracentral, all patients suffered a loss in their BCVA with respect to the location of the corneal scar<sup>[31]</sup>. East Asian ethnicity comprised roughly 95% of the disease population in a review on microbial keratitis associated with OOK<sup>[18]</sup>. The reported demographic profile could either reflect ethnic susceptibility (as a high proportion of East Asian children are myopic) or could just reflect the demographic profile of the worldwide OK lens wearing population since the usage in more affluent economies<sup>[32]</sup>. The estimated myopia in urban Chinese children at the age of 18 years would be up to 2.0 dioptres higher than their parents, and their refractive errors at the age of 11 would already be similar to their parents. This suggests a strong environmental effect on myopia development as evident by this remarkable single-generation myopic shift. In addition, the genetic risk factors, and the environmental and lifestyle factors present in the Chinese population may lead to a lower threshold for the Chinese parents to allow their children to wear OK lens<sup>[33]</sup>. Lin *et al.*<sup>[34]</sup> reported that there is a greater increase in epithelial permeability following overnight contact lens wear in Asian as compared to Caucasian subjects, which could lead to a more easily compromised epithelial barrier, however the rates of MK were not reported to be significantly different from the rest of the world<sup>[21]</sup>. Further research is warranted to answer whether there is ethnic difference in MK susceptibility.

## DISCUSSION

The cases of microbial keratitis associated with orthokeratology were largely documented by the review published in 2007<sup>[18]</sup>. Since then, we identified another 12 cases *via* our literature search in PubMed<sup>[35-39]</sup>. Table 1 summarizes the features from the 34 published reports on orthokeratology related microbial keratitis cases up to March 2014<sup>[29,31,35-66]</sup>. Despite reported case series on MK with OOK, these do not help to determine the true incidence or the relative risks compared with other contact lens modalities. The number of cases reported in the literature likely represents an underestimation, as the values of publications on the same topic become relatively less once a few cases have already been reported in the literature, thus further publication on the same topic is less likely to be accepted by the respective journals, and the incentive for authors to prepare a manuscript also lessens. Without a good estimation of the denominator and numerator, it would be difficult to comment on the absolute risk of microbial keratitis associated with orthokeratology.

Assessment of the risks and adverse effects is limited, as none of the published articles on OOK are level I evidence. Furthermore, the issue on safety could not truly be concluded from the small number of subjects in studies. Adverse effects are often under-reported or inconsistently documented, due to poor indexing, making it more difficult to look up published literature on safety of treatment<sup>[67]</sup>. The details of reported cases vary in lens type, lens wearing regime, type of lens and compliance to cleansing regime. Despite the credentialing and training programs offered for OOK practices, a learning curve would exist. The interpretation of fluorescein patterns requires skill and experience; the central flat zone of a reverse-geometry contact lens is more discernible to experienced practitioners. Safety about usage and prescription of OOK raises scrutiny. The FDA requires OOK practitioners to be certified to a minimal standard of orthokeratology education and granted the OOK approval without age restriction on the basis that no additional safety concerns are specific to adolescents as long as OOK is fitted by trained personnel and used accordingly<sup>[68]</sup>. Manufacturers of OOK lenses launched online training program, which consists of certificate course and tests that can be completed in a short period of time. Whether such training program is adequate in providing proper knowledge and skills in the practice of orthokeratology warrants further investigations.

Contact lens use remains the commonest risk factor for microbial keratitis in the paediatric population and orthokeratology is one of the leading causes of contact lens related infection in East Asia<sup>[69]</sup>. Although many of the cases published have reported data from children, it does not necessary mean that children are at a greater risk of developing MK. Given the potential theoretical benefit in reducing myopia progression, there may be more children using OOK than adults<sup>[11]</sup>. Due to the larger number of



**Table 1** Features of microbial keratitis published in the literature

Ref.	Year of publication	Country of origin	Number of cases	Microbiology
Chen <i>et al</i> <sup>[40]</sup>	2001	Taiwan	1	<i>Serratia marcescens</i>
Lü <i>et al</i> <sup>[41]</sup>	2001	China	16	7 = <i>P. aeruginosa</i> ; 8 = <i>Acanthamoeba</i> ; 1 = fungus
Chen <i>et al</i> <sup>[42]</sup>	2002	Taiwan	1	<i>Pseudomonas putida</i>
Hutchinson <i>et al</i> <sup>[43]</sup>	2002	Australia	2	1 = <i>P. aeruginosa</i> ; 1 = <i>Acanthamoeba</i> , <i>P. aeruginosa</i> and <i>Burkholderia cepacia</i>
Keddie <i>et al</i> <sup>[44]</sup>	2002	Canada	2	<i>Acanthamoeba</i>
Lin <i>et al</i> <sup>[45]</sup>	2002	China	1	<i>Nocardia</i> sp.
Lau <i>et al</i> <sup>[46]</sup>	2003	Taiwan	2	<i>P. aeruginosa</i>
Poole <i>et al</i> <sup>[47]</sup>	2003	United Kingdom	1	Not identified
Wang <i>et al</i> <sup>[48]</sup>	2003	Singapore	1	<i>P. aeruginosa</i>
Xugang <i>et al</i> <sup>[49]</sup>	2003	China	4	<i>Acanthamoeba</i>
Young <i>et al</i> <sup>[29]</sup>	2003	Hong Kong	1	<i>P. aeruginosa</i>
Hsiao <i>et al</i> <sup>[50]</sup>	2004	Taiwan	7	6 = <i>P. aeruginosa</i> ; 1 = Not identified
Lang <i>et al</i> <sup>[51]</sup>	2004	United States	2	1 = <i>P. aeruginosa</i> ; 1 = Not identified
Van Der Worp <i>et al</i> <sup>[52]</sup>	2004	Netherlands	1	<i>P. aeruginosa</i>
Young <i>et al</i> <sup>[31]</sup>	2004	Hong Kong	6	5 = <i>P. aeruginosa</i> ; 1 = Not identified
Araki-Sasaki <i>et al</i> <sup>[53]</sup>	2005	Japan	1	<i>P. aeruginosa</i>
Macsai <i>et al</i> <sup>[54]</sup>	2005	United States	2	1 = <i>P. aeruginosa</i> ; 1 = <i>H. influenza</i>
Hsiao <i>et al</i> <sup>[55]</sup>	2005	Taiwan	21	9 = <i>P. aeruginosa</i> ; 2 = coagulase-negative <i>Staphylococcus</i> sp.; 1 = <i>Serratia marcescens</i> ; 1 = <i>Acanthamoeba</i>
Tseng <i>et al</i> <sup>[56]</sup>	2005	Taiwan	10	2 = <i>Acanthamoeba</i> ; 1 = <i>P. aeruginosa</i> ; 1 = non fermentative Gram negative bacilli; 6 = Not identified
Wilhelmus <i>et al</i> <sup>[57]</sup>	2005	United States	1	<i>Acanthamoeba</i>
Yepes <i>et al</i> <sup>[58]</sup>	2005	Canada	3	1 = <i>P. aeruginosa</i> ; 1 = <i>Serratia marcescens</i> ; 1 = <i>Acanthamoeba</i>
Lee <i>et al</i> <sup>[59]</sup>	2006	South Korea	1	<i>Acanthamoeba</i>
Priel <i>et al</i> <sup>[60]</sup>	2006	Israel	1	<i>P. aeruginosa</i>
Sun <i>et al</i> <sup>[61]</sup>	2006	China	28	8 = <i>P. aeruginosa</i> ; 13 = <i>Acanthamoeba</i> ; 1 = <i>Nocardia</i> sp.; 1 = <i>Providencia stuartii</i> ; 2 = fungus; 1 = Gram negative rods; 2 = Not identified
Voyatzis <i>et al</i> <sup>[62]</sup>	2006	United Kingdom	1	<i>P. aeruginosa</i>
Ying-Cheng <i>et al</i> <sup>[63]</sup>	2006	Taiwan	1	<i>Burkholderia cepacia</i> , <i>Pseudomonas putida</i> , and <i>P. aeruginosa</i>
Lee <i>et al</i> <sup>[64]</sup>	2007	South Korea	4	1 = <i>Acanthamoeba</i> ; 1 = <i>Acanthamoeba</i> and trophozoites; 2 = Not identified
Robertson <i>et al</i> <sup>[65]</sup>	2007	United States	1	<i>Acanthamoeba</i>
Watt <i>et al</i> <sup>[66]</sup>	2007	Australia	9	4 = <i>P. aeruginosa</i> ; 2 = <i>Acanthamoeba</i> ; 3 = Not identified
Kim <i>et al</i> <sup>[37]</sup>	2009	South Korea	1	<i>Acanthamoeba</i> (bilateral)
Shehadeh-Masha'ou <i>et al</i> <sup>[38]</sup>	2009	Israel	4	<i>P. aeruginosa</i>
Arance-Gil <i>et al</i> <sup>[35]</sup>	2013	Spain	1	<i>Acanthamoeba</i>
Greenwell <i>et al</i> <sup>[36]</sup>	2013	Australia	2	<i>Acanthamoeba</i>
Tran <i>et al</i> <sup>[39]</sup>	2014	Australia	4	1 = <i>Acanthamoeba</i> ; 1 = <i>P. aeruginosa</i> ; 2 = Not identified

*P. aeruginosa*: *Pseudomonas aeruginosa*; *H. influenza*: *Haemophilus influenza*; sp: Species.

cumulative years that a child may be exposed to potential risks, complications in children may be reported more frequently than adults. The FDA approval for overnight orthokeratology was based on the premarket study cohort where adolescents aged 12-17 years old comprised 11% of the study sample. In fact, orthokeratology fits represent 28% of all contact lenses prescribed to minors<sup>[70]</sup>. The FDA issued Section 522 in 2006, requiring manufacturers to conduct post-market surveillance to address “the relative risk of developing MK in persons under the age of 18 as compared to adults in patients undergoing overnight OK treatment”. This question was addressed in a retrospective study using a practitioner survey of 1317 OOK patients (51% children)<sup>[20]</sup>. They found 8 cases of corneal infiltrates associated with a painful red eye (six in children and two in adults). Two were classified as MK and occurred in children, but neither resulted in a loss of visual acuity. The overall estimated incidence of MK is 7.7 per 10000 years of wear (95%CI: 0.9-27.8). For children,

the estimated incidence of MK is 13.9 per 10000 patient-years (95%CI: 1.7-50.4). While for adults, the estimated incidence of MK is 0 per 10000 patient-years (95%CI: 0-31.7). This is the largest study to quantify the risk of MK associated with OOK with 2599 patient-years of wears and worthy to note the difference between children and adult rates. Based on the incidence estimated in this study, the two FDA pre-market approval studies<sup>[8,71]</sup> and another retrospective study of 296 patients by Lipson *et al*<sup>[72]</sup> did not report any cases of MK. Although the confidence intervals between the adult and children groups overlap, it should not be interpreted as no difference in incidence among the 2 groups as true differences less than 50 cases per 10000 patient-years were beyond the power of that study<sup>[20]</sup>.

## CONCLUSION

Although exact incidence of MK associated with OK

lenses is not known, it has the potential to compromise vision. Degree of damage (*i.e.*, reduction in visual acuity) is only one aspect of risk evaluation. In order to maintain the control in myopia, patients have to continue indefinite application of OK lenses overnight. Despite using high oxygen permeable lenses, this will still put the patient at risk of MK, as the reduction of myopia is only temporary without regular overnight application. Comparing OOK with other myopia corrective devices, such as daytime contact lens wear, the risk of infectious keratitis is higher in overnight contact lens wear<sup>[73]</sup>, and there is minimal risk in using spectacle wear. Comparing OOK with LASIK is inappropriate as the latter is an invasive procedure which is not FDA approved for children.

The therapeutic value of overnight orthokeratology remains unclear and many questions remain unanswered, such as the optimal treatment age and duration. Practitioners and end-users of OOK should work together to minimize the risk of MK by reinforcing compliance to proper cleansing techniques and minimizing exposure to contaminated water. OOK users should discontinue lens wear if they feel any pain and seek medical attention immediately. Practitioners must be competent in the prescription of OK lenses through accredited certification courses from appropriate statutory bodies. Better-designed prospective randomized clinical studies are needed to demonstrate the benefit of orthokeratology in reducing myopic progression and to adequately assess their safety, along with the contemporaneous reporting of adverse events. The reported dropout rates of more than 20% in the previous trials also raise concerns regarding tolerability and satisfaction in using OOK. Long-term follow-ups are needed as visual loss related to MK were only encountered in many patients who wore hard contact lens for more than 2 years. The genuine risk of severe MK associated with poor long-term visual outcomes in children needs to be highlighted to parents considering orthokeratology in an effort to avoid preventable visual loss.

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