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ORIGINAL ARTICLE

Overnight orthokeratology-associated *Acanthamoeba* keratitis at a tertiary referral hospital in Taiwan: A retrospective case-control study

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ABSTRACT

Background: *Acanthamoeba* keratitis (AK) is a vision-threatening disease, usually associated with contact lens (CL) wear. As overnight orthokeratology (OOK) is increasingly used to control myopia, we have found incidence of OOK-associated AK is increasing. This study aimed to investigate the clinical presentation and visual outcomes of OOK-associated AK.

Methods: Demographic characteristics, clinical features, and treatment outcomes were collected by reviewing the medical charts of CL-associated AK patients (n = 35) diagnosed at Taipei Veterans General Hospital from 2001 to 2016. Cases were OOK-associated AK patients (n = 13), and controls were all other CL-associated AK patients (n = 22). Student *t* tests and chi-square tests were used to compare cases and controls. Linear regression analyses were used to identify factors associated with the final visual outcome in CL-associated AK.

Results: OOK-associated AK accounted for half of all CL-associated AK after 2010. OOK-associated AK patients and other CL-associated patients had similar best-corrected logarithm of the minimum angle of resolution visual acuity (BCLVA) before treatment (1.10 ± 0.75 vs 1.13 ± 0.76, $p = 0.893$), but OOK-associated AK patients were younger (17.15 ± 3.21 vs 26.36 ± 12.81 years, $p = 0.004$), had less severe disease (ring infiltration, 0% vs 31.82%, $p = 0.023$), and had better post-treatment BCLVA (0.06 ± 0.15 vs 0.51 ± 0.95, $p = 0.041$). Multiple linear regression analysis showed that better BCLVA after treatment in CL-associated AK was associated with initial presentation without ring infiltration ($p = 0.002$) but not with OOK use itself ($p = 0.793$). Twenty-six of 35 CL-associated AK patients had final BCLVA equal to or better than 0.10 (Snellen visual acuity of 6/7.5). All 13 OOK-associated AK cases were treated with chlorhexidine 0.02% ± voriconazole 1% ± oral voriconazole, and 12 of these patients had final BCLVA equal to or better than 0.10.

Conclusion: Most CL-associated AK patients had satisfactory visual outcomes. Half of AK at our hospital is OOK-associated since 2010. Early diagnosis and correct treatment may be the reason why OOK-associated AK patients had better vision prognosis.

Keywords: *Acanthamoeba* keratitis; Chlorhexidine; Prognosis; Voriconazole

1. INTRODUCTION

Acanthamoeba keratitis (AK) is a severe but unusual infectious disease of the cornea. It is commonly associated with contact lens (CL) wear, especially disposable soft CLs.[1–3] The *Acanthamoeba* pathogen is a free-living, cyst-forming protozoan that is distributed in diverse environments, including the air, soil, dust, and water. The active form of *Acanthamoeba*, the trophozoite, has an ameboid shape with pseudopodia, and it phagocytoses small particles that it encounters. In the cornea, *Acanthamoeba* feeds on keratocytes. The cystic form can survive in difficult environments, and cysticidal drugs are needed to effectively treat AK.[2] The incidence of AK is around 0.15 to 1.4 per million, and the variety found in each country is related to the popularity of CL use, the habits of CL users, the CL care systems used, and the contamination of domestic water and swimming pools by *Acanthamoeba*.[4]

In Taiwan, the prevalence and incidence of myopia in children are high, even in 7- to 8-year-old children.[5,6] Nearly one-fourth of myopic children show increases of >1 diopter in one year.[7] Overnight orthokeratology (OOK) lenses, a type of rigid gas-permeable CL, were approved for myopia control by Taiwan Food and Drug Administration (FDA) in 2008. The increase in reports of OOK-associated AK[8–13] has raised concerns that the increased use of OOK lenses to treat myopic children in Taiwan has led to the increased incidence of AK.[14] The benefits of orthokeratology in slowing myopia progression versus the risk of infectious keratitis should be evaluated carefully. Because in a more conservative manner, any risk of significant vision loss in a child is unacceptable; practitioners must discuss the potential for infection and

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vision loss with patients and their parents.[15] We thus analyzed and compared the demographic characteristics, clinical features, and outcomes of patients with OOK-associated AK with those of patients with other CL-associated AK who were treated at Taipei Veterans General Hospital between 2001 and 2016.

2. METHODS

2.1. Design and subjects

A retrospective chart review was conducted of 36 CL-associated AK patients (a total of 40 AK eyes) who were treated from 2001 to 2016 at the Medical Center at Taipei Veterans General Hospital. Of these patients, 35 patients (39 eyes) completed treatment and were included in this case-control study. A 68-year-old patient with other CL-associated AK was lost to follow-up and was not included. The more severely affected eye was analyzed in bilateral disease. Of the 35 included patients, 13 patients had OOK-associated AK, and 22 patients had other CL-associated AK. A definitive diagnosis of AK was made based on culture or histology findings or based on the presence of amebic deoxyribonucleic acid (DNA) as determined using polymerase chain reaction (PCR) analysis. In the absence of a tissue-based diagnosis, patients with perineural corneal infiltrates and a typical clinical course who responded to antiamebic treatment were presumed to have AK (Fig. 1). In our case series, OOK-associated and the other CL-associated AK cases can have similar presentations of pseudodendrite, stromal infiltration, and neuritis (Fig. 1A and 1B), but only the other CL-associated AK cases can have presentations of ring infiltrates (Fig. 1C).

We recorded the clinical features and the type of CL that was used. All patients were then treated with polyhexamethylene biguanide (PHMB) or chlorhexidine 0.02% ± propamidine ± voriconazole 1%. In two cases, oral voriconazole was also used to help control AK. The best-corrected logarithm of the minimum angle of resolution (logMAR) visual acuity (BCLVA) of the affected eyes was recorded before and after treatment. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital and adhered to the tenets of the Declaration of Helsinki.

2.2. Statistical analyses

Student *t* tests and chi-square tests were used to compare the demographics, clinical characteristics, and outcomes of patients with OOK-associated and other CL-associated AK in Table 1. In Table 2, simple and multiple linear regression analyses were used to assess which factors were associated with the final visual outcomes of patients with CL-associated AK. Statistical analyses were performed with commercially available software (SPSS ver. 19.0; SPSS Inc, Chicago, IL). p values of ≤0.05 were considered to be statistically significant.

3. RESULTS

Fig. 2 shows the distribution of annual cases of CL-associated AK from 2001 to 2016. The number of patients with OOK-associated AK began to increase since 2010; strikingly, in 2015 and 2016, more than half of all patients with CL-associated AK was OOK-associated AK. The patients with CL-associated AK

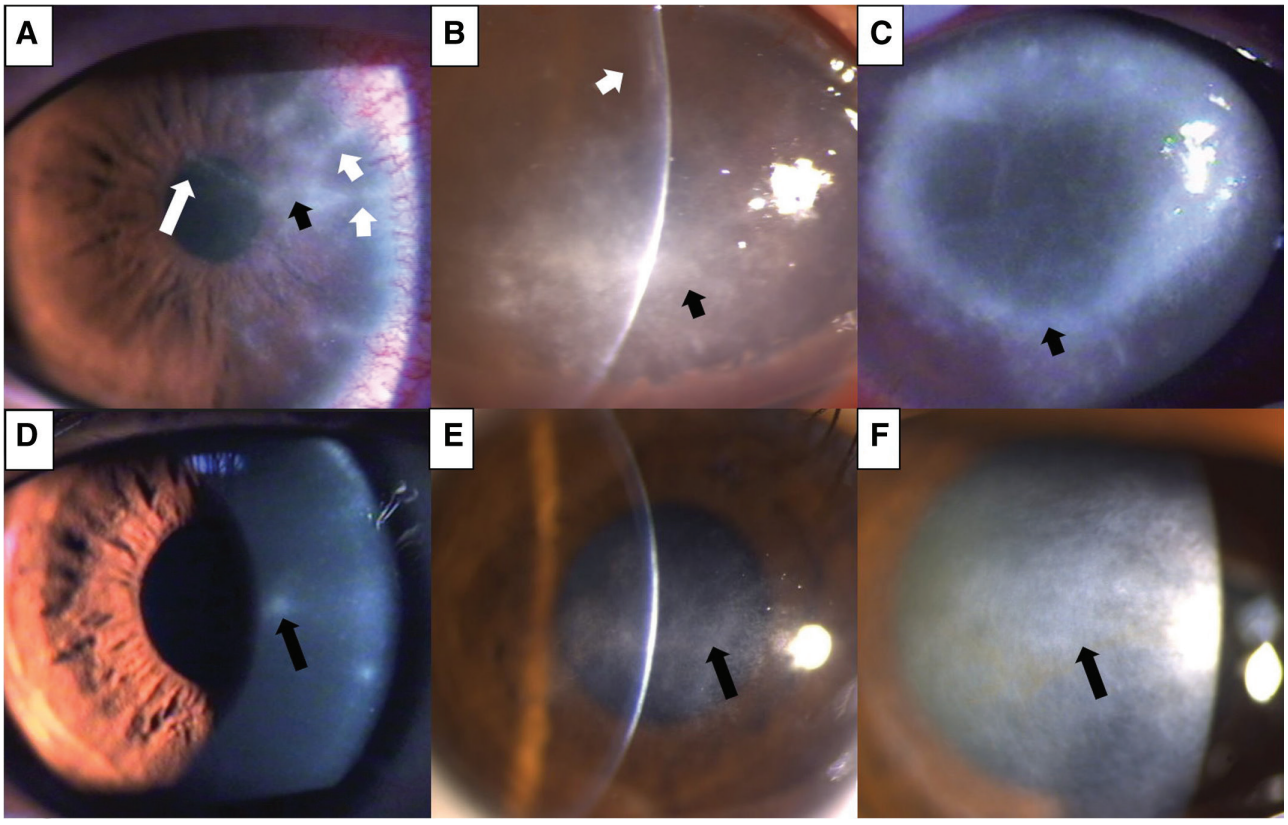

Fig. 1 The initial presentation of *Acanthamoeba* keratitis (AK). A, The long white arrow indicates pseudodendrites, and the short black arrow indicates anterior stromal infiltrates. The short white arrows in A and B indicate neuritis. The short black arrow in B indicates deep stromal infiltrates and that in C indicates ring infiltrates. In panels D, E, and F, the long black arrows point to the residual corneal scars after antiamebic treatment in A, B, and C, respectively. A and B are two overnight orthokeratology–associated AK cases and C is one other contact lens–associated AK case in our case series.

Table 1

Demographics, clinical characteristics, and outcomes of patients with OOK-associated AK and other CL-associated AK

	CL-associated AK (N = 35)				
	OOK-associated AK (*n* = 13)		Other CL-associated AK (*n* = 22)		
Characteristic	***N/mean***	***%/SD***	***N/mean***	***%/SD***	***p***
Age, y	17.15	3.21	26.36	12.81	**0.004**
Age distribution					
20 or younger	12	92.31	11	50.00	
21 or older	1	7.69	11	50.00	
Male	3	23.08	10	45.45	0.283
Affected eye					0.572
One	11	84.62	20	90.91	
Both	2	15.38	2	9.09	
Patient noncompliance or contact with contaminated water sources	6	46.15	19	86.36	**0.011**
Sign					**0.023**
No ring infiltration	13	100.00	15	68.18	
Ring infiltration	0	0	7	31.82	
BCLVA before treatment[a]	1.06	0.78	1.04	0.74	0.951
BCLVA after treatment[a]	0.06	0.15	0.51	0.95	**0.041**
Receiving penetrating keratoplasty	1	7.69	2	9.09	0.886

Bold indicates *p* value <0.05.

AK = *Acanthamoeba* keratitis; BCLVA = best-corrected logarithm of the minimum angle of resolution visual acuity; CL = contact lens; OOK = overnight orthokeratology.

[a]When both eyes were affected, only the worse eye was included in the analysis.

ranged in age from 11 to 55 years old (mean, 22.94 ± 11.20 years), and most patients were female (62.86%) and had unilateral involvement (88.57%). Fig. 1A–C show the initial representative presentation of these AK eyes at our hospital. After antiamebic treatment (Fig. 1D–F), the mean best-corrected logMAR visual acuity (BCLVA) of these AK patients improved from 1.04 ± 0.75 to 0.34 ± 0.78. Table 1 shows the demographics and clinical characteristics of patients with OOK-associated AK and other CL-associated AK. Before treatment, there were no significant differences between patients with OOK-associated AK versus other CL-associated AK in terms of sex, eye affected (single or bilateral), or BCLVA (1.10 ± 0.75 vs 1.13 ± 0.76, $p = 0.893$). However, patients with OOK-associated AK were significantly younger (17.15 ± 3.21 vs 26.36 ± 12.81, $p = 0.004$), less noncompliance rate (46.15% vs 86.36%, $p = 0.011$), had less severe diseases (ring infiltration 0% vs 31.82%, $p = 0.023$), and showed better post-treatment BCLVA (0.06 ± 0.15 vs 0.51 ± 0.95, $p = 0.041$).

Table 2 shows the associations between the visual outcomes of all 35 AK patients and the investigated potential prognostic factors. Younger age ($p = 0.001$), initial presentation without ring infiltration ($p < 0.001$), and better BCLVA ($p = 0.003$) before treatment were associated with better BCLVA after treatment in simple linear regression analysis. However, only initial presentation without ring infiltration ($p = 0.002$) was associated with better BCLVA after treatment in multiple linear regression analysis.

Table 3 shows the clinical features, visual outcomes, and treatment of the 35 patients with OOK-associated and other CL-associated AK that were treated in our hospital between 2001 and 2016. 26 patients (74.29%) had BCLVA of 0.10 (Snellen visual acuity of 6/7.5) or better. All 13 OOK-associated AK patients received topical chlorhexidine 0.02% ± voriconazole 1% ± oral voriconazole to control AK, and 12 (92.31%) of them had a final BCLVA that was equal to or better than 0.10. One OOK-associated AK patient had a final BCLVA of 0.52 (Snellen visual acuity of 6/20). This patient was diagnosed and treated for AK for 3 weeks before she presented at our hospital on the advice of her doctor, who suggested therapeutic corneal transplantation due to progression of the keratitis. Perineuritis and more extensive corneal stromal infiltrates were noted in this patient (Fig. 1B). After treatment with topical chlorhexidine and voriconazole, the keratitis resolved with a central scar (Fig. 1E). Future optical corneal transplantation is considered to improve her vision.

Table 2

Associations between the visual outcomes[a] of all patients with CL-associated AK and the investigated potential prognostic factors

	Linear regression[b]								
	Simple linear regression				Multiple linear regression				
Characteristics	***p***	**β**	**SE**	**95%**	***p***	**β**	**SE**	**95% CI**	**VIF**
Sex (male/female[ref.])	0.769	-0.051	0.283	-0.659–0.492	0.727	-0.047	0.219	-0.525–0.371	1.081
Age, y	**0.001**	0.537	0.010	0.017–0.058	0.139	0.248	0.011	-0.006–0.041	1.595
CL used (OOK CL/other CLs[ref.]	0.103	-0.281	0.267	-0.992–0.095	0.793	0.039	0.244	-0.435–0.563	1.340
Initial presentation (R/N[ref.])	**0.000**	0.703	0.239	0.872–1.844	**0.002**	0.571	0.325	0.436–1.768	1.708
BCLVA before treatment	**0.003**	0.495	0.163	0.194–0.859	0.866	-0.025	0.425	-0.943–0.798	1.350

Bold indicates *p* value <0.05.

AK = *Acanthamoeba* keratitis; BCLVA = best-corrected logarithm of the minimum angle of resolution visual acuity; CL = contact lens; OOK = overnight orthokeratology; R/N = ring infiltration/no ring infiltration; VIF = variance inflation factor.

[a]Visual outcome was defined as the BCLVA after treatment.

[b]For statistical analysis, simple and multiple linear regression models were used to examine the associations between visual outcomes and the investigated potential prognostic factors.

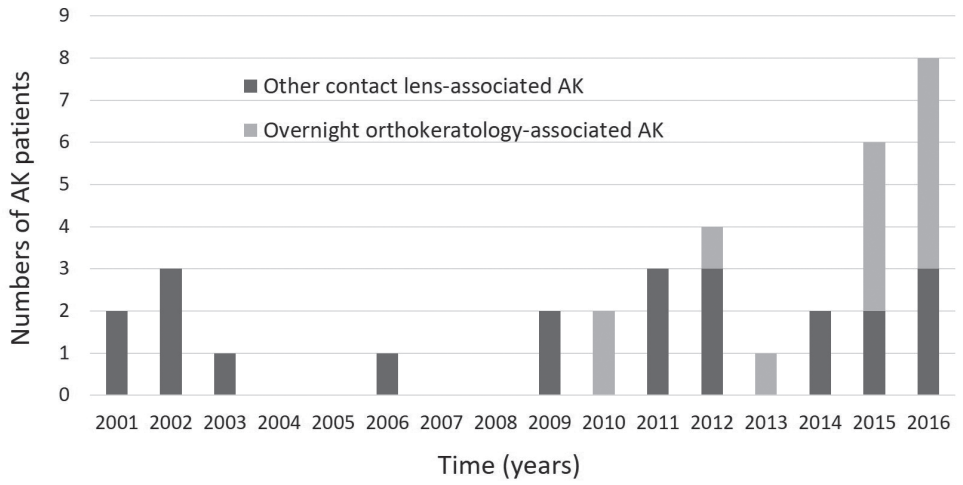

Fig. 2 The number of patients per year with *Acanthamoeba* keratitis (AK) from 2001 to 2016.

Table 3

Clinical characteristics, visual outcomes, and treatment of patients with OOK-associated and other CL-associated AK

Time, y	Age, y	Sex	Affected eye	Clinical features	Final BCLVA	Types of CL and patient noncompliance	Treatment	DOIS, wk
OOK-associated AK								
2010	19	F	Both	Neuritis, deep stromal infiltrates	0.10/0	OOK CL. No patient noncompliance.	Chlorhexidine 0.02%	1
2010	19	F	Single	Neuritis, anterior stromal infiltrates	0	OOK CL. No patient noncompliance.	Chlorhexidine 0.02%, voriconazole 1%	3
2012	21	F	Single	Neuritis, deep stromal infiltrates	0.10	OOK CL. No patient noncompliance.	Chlorhexidine 0.02%, voriconazole 1%	2
2013	14	F	Single	Neuritis, anterior stromal infiltrates	0.10	OOK CL. Using tap water to clean CL.	Chlorhexidine 0.02%, voriconazole 1%	1
2015	15	F	Both	Neuritis, anterior stromal infiltrates	0/0.05	OOK CL. No patient noncompliance.	Chlorhexidine 0.02%	3
2015	15	F	Single	Pseudodedrite, neuritis	0	OOK CL. No patient noncompliance.	Chlorhexidine 0.02%	
2015	19	F	Single	Neuritis	–0.08	OOK CL. Using tap water to clean CL.	Chlorhexidine 0.02%, voriconazole 1%	2
2015	20	M	Single	Neuritis, deep stromal infiltrates	0	OOK CL. Using tap water to clean CL.	Chlorhexidine 0.02%, voriconazole 1%	2
2016	13	M	Single	Neuritis, anterior stromal infiltrates	0	OOK CL. Using Normal Saline that was not properly stored to clean CL.	Chlorhexidine 0.02%	3
2016	20	F	Single	Deep stromal infiltrates	0	OOK CL. Using OOK CL for 30 hours continuously.	Chlorhexidine 0.02%, voriconazole 1%, oral voriconazole	2
2016	20	M	Single	Neuritis, anterior stromal infiltrates	0	OOK CL. Using water from drinking fountain to clean CL.	Chlorhexidine 0.02%	1
2016	17	F	Single	Neuritis, deep stromal infiltrates	0.52	OOK CL. No patient noncompliance.	Chlorhexidine 0.02%, voriconazole 1%	1
2016	11	F	Single	Pseudodendrite, neuritis	0	OOK CL. No patient noncompliance.	Chlorhexidine 0.02%, voriconazole 1%, oral voriconazole	1
Other CL-associated AK								
2001	50	F	Single	**Ring infiltrates**	1.30	Conventional soft CL. Using normal saline to clean and store CL.	PHMB, propamidine 0.1%	3
2001	17	M	Single	Anterior stromal infiltrates, pseudodendrite	0	Conventional soft CL. Using normal saline to clean and store CL.	PHMB, propamidine 0.1%, chlorhexidine 0.02%	4
2002	23	F	Single	Neuritis, anterior stromal infiltrates, pseudodendrite	0	Conventional CL. Using CL when swimming.	PHMB, propamidine 0.1%, chlorhexidine 0.02%	3
2002	19	F	Single	Deep stromal infiltrates, **ring infiltrates**	0	Conventional soft CL. Irregularly using multi-purpose solutions to clean and store CL.	PHMB, propamidine 0.1%, chlorhexidine 0.02%	4
2002	20	F	Both	**Ring infiltrates** in both eyes	0.22/3	Conventional soft CL. Using normal saline, mineral water to clean and store CL.	PHMB, propamidine 0.1%	4
2003	20	M	Single	Neuritis, deep stromal infiltrates	0	RGP. No patient noncompliance.	PHMB, propamidine 0.1%, chlorhexidine 0.02%	2
2006	55	F	Single	**Ring infiltrates**	3	Biweekly disposable soft CL. Using CL more than two weeks.	Propamidine 0.1%, chlorhexidine 0.02%	2
2009	18	F	Single	Neuritis, anterior stromal infiltrates, pseudodendrite	0	Biweekly disposable soft CL. Not changing the storage solution in the case.	Chlorhexidine 0.02%	1
2009	26	F	Single	Neuritis, anterior stromal infiltrates, pseudodendrite	0	Daily disposable soft CL. Using CL when swimming.	Chlorhexidine 0.02%	3

(*Continued next page*)

Table 3 (Continued)

Time, y	Age, y	Sex	Affected eye	Clinical features	Final BCLVA	Types of CL and patient noncompliance	Treatment	DOIS, wk
2011	23	F	Single	Neuritis, anterior stromal infiltrates	0	Daily disposable cosmetic soft CL. No patient noncompliance.	Propamidine 0.1%, chlorhexidine 0.02%	1
2011	19	F	Single	**Ring infiltrates**	0	Biweekly disposable soft CL. Using CL when swimming.	Propamidine 0.1%, chlorhexidine 0.02%, voriconazole 1%	8
2011	18	M	Single	Anterior stromal infiltrates	0	Daily disposable soft CL. Using CL when swimming.	Chlorhexidine 0.02%	2
2012	43	M	Single	Neuritis, anterior stromal infiltrates, pseudodendrite	0.52	Weekly disposable soft CL. Not changing the storage solution in the case.	Chlorhexidine 0.02%, voriconazole 1%	2
2012	20	F	Single	Neuritis, anterior stromal infiltrates	0.05	Daily disposable cosmetic soft CL. Using for more than 8 hours each day.	Chlorhexidine 0.02%	6
2012	14	F	Both	Neuritis, ant stromal infiltrates in both eyes	0/0	Biweekly disposable cosmetic soft CL. Using normal saline to clean and store CL.	Chlorhexidine 0.02%	7
2014	19	M	Single	Neuritis, anterior stromal infiltrates, pseudodendrite	0	Biweekly disposable soft CL. Using normal saline to clean and store CL.	Chlorhexidine 0.02%	1
2014	25	M	Single	**Ring infiltrates**	2	Biweekly disposable soft CL. Using normal saline to clean and store CL.	Chlorhexidine 0.02%, voriconazole 1%	2
2015	34	M	Single	Neuritis, anterior stromal keratitis, pseudodendrite	0.22	Daily disposable soft CL. No patient noncompliance.	Chlorhexidine 0.02%	1
2015	32	F	Single	Neuritis, deep stromal keratitis	0.40	Daily disposable soft CL. Changing every 3 days. Using normal saline to clean and store CL.	Chlorhexidine 0.02%, voriconazole 1%	1
2016	54	M	Single	**Ring infiltrates**	0.70	Daily disposable soft CL. His job is to sell raw pork.	Chlorhexidine 0.02%, voriconazole 1%	3
2016	13	F	Single	Neuritis, pseudodedrite	0	Biweekly disposable soft CL. Using CL when being in the hot spring.	Chlorhexidine 0.02%	5
2016	18	M	Single	Neuritis, anterior stromal keratitis	0	Biweekly disposable soft CL. Using normal saline to clean and store CL.	Chlorhexidine 0.02%, voriconazole 1%	2

Ring infiltrates are in bold as it implies more severe AK.

AK = *Acanthamoeba* keratitis; BCLVA = best-corrected logarithm of the minimum angle of resolution visual acuity; CL = contact lenses; DOIS = duration of initial symptoms before diagnosis of AK; F = female; M = male; OOK = overnight orthokeratology; PHMB = polyhexamethylene biguanide.

4. DISCUSSION

OOK was approved by Taiwan FDA in 2008, and some children began to be treated with OOK instead of atropine to control myopia progression. The five brands of OOK lenses available in Taiwan are DreimLens VST rigid gas-permeable contact lens, Hiline overnight orthokeratology contact lens, Euclid Systems orthokeratology contact lenses for overnight wear, Smartlens Euclid Systems orthokeratology contact lenses for overnight wear, and progressive Boston diamond orthokeratology shaping lenses for overnight wear. These OOK lenses are all made of Oprifocon A with Dk 85 (ISO/Fatt) which were proved to be suitable for overnight wear. No patients with OOK-associated AK were treated at our hospital before 2008, but there were 13 in our hospital from 2010 to 2016 (50% of all patients with CL-associated AK). Strikingly, in 2015 and 2016, more than half of the patients with CL-associated AK used OOK lenses. Thus, OOK lenses replaced soft CL as the most commonly used CL types in AK patients at our hospital in recent years, although many more people use soft CL than use OOK lenses in Taiwan. Our small number of cases may make people question whether our cases are sufficiently representative or not. However, Taipei Veterans General Hospital, located in the capital of Taiwan, is one of the largest tertiary referral hospitals in Taiwan. It has >2.5 million outpatient visits per year and includes 2947 patient beds, 1249 doctors, and 6375 employees. Although it mainly serves the population (around ten million people) living in the north part of Taiwan, it indeed accepts patients from other parts of Taiwan and even neighboring countries. It is one of the few hospitals that provide antiamebic drugs for the treatment of AK before 2017.

Bullimore et al[16] believed orthokeratology as a risk factor for microbial keratitis and found that the risk of microbial keratitis in OOK lens wearers was similar to that of other overnight methods.[16] There is decreased oxygen transmission through the OOK lens when the eye is closed; the epithelial surface is compromised, secondary to the compressive effect on the cornea; and there is an absence of eye blinking to sever the microbial glycocalyx and spread lysozyme over the corneal surface. Notably, all of these may induce keratitis in nocturnal CL wearers.[15,17–20] However, in Taiwan, almost no one sleeps with soft CL at night. Perhaps this is why OOK was more likely to cause AK than soft CL in Taiwan. Another reason why OOK CL wearers are more susceptible to infection is that they are relatively young and, according to a previous report, the microbial contamination rate of OOK CL care system in this age group is high.[21] Although compared to nocturnal soft CL wearers, the use of OOK, a kind of rigid gas-permeable lenses, should minimize the risk of AK because it is easy to remove the attached *Acanthamoeba* trophozoites and cysts from the smooth and more homogeneous surface of these CL.[22,23]

In addition to patient noncompliance such as use of homemade saline, suboptimal disinfection of lens, and adding new solution to an existing volume of used solution in the lens case, CL-associated AK was associated with contact with contaminated water sources, such as swimming in contaminated water or the use of tap water for lens rinsing and storage.[15,24,25] In our AK patients, more OOK-associated cases (53.85%) were not related to patient noncompliance about cleaning and storage or contact with contaminated water sources when compared with other CL-associated AK (13.64%). This implies OOK lens wear

itself may possibly increase the risk of AK. Van Meter et al[26]. and Kam et al[27]. reviewed literature and found most OOK-associated microbial keratitis were central and severe, mainly caused by gram-negative rods or *Acanthamoeba* that can cause significant vision loss from corneal scar. Almost 10% of eyes needed surgical intervention.[27] Ladage et al[28] also found *Pseudomonas* bound to rabbit cornea more easily when fitted as OOK lenses when compared with normal rigid gas-permeable CL.[26] It is thus important for medical practitioners to fully explain the signs and potential risks of infectious keratitis to patients and parents and to regularly monitor and provide advice and treatment when children have problems with their OOK lenses. A systemic review related to the safety of OOK concluded OOK is a safe option for myopia retardation if they can follow the above rules.[29] What needs more attention is that 53.85% of OOK-associated AK patients were between the age of 19 and 21 years, and myopia progression is much slower in these teenagers. In Taiwan, after teenagers enter the university at the age of 19 years, their OOK wearing schedule may become more irregular due to staying up or other activities. The compressive effect of OOK in these teenagers may be more pronounced because the reshaped cornea does not always maintain its intended shape. In addition, patients at this age seldom come back to the clinics and change OOK lenses regularly. It may be a good time point to stop wearing OOK at the age of 18 years. In our daily practice, low-dose atropine remains the first line of treatment to slow the progression of myopia. We only use OOK for myopic children who cannot tolerate the side effects of atropine or have poor response to atropine. We believe the use of OOK to prevent the future complication of high myopia is beneficial if it is used in a more cautious manner. In our study, only one (7.69%) OOK-associated AK patient had BCLVA worse than 0.10 and her vision may improve after undergoing corneal transplantation.

The literature reports that the worst prognostic factors in AK include Snellen visual acuity less than< 20/50 and more severe disease, such as stromal involvement, at presentation.[30] Table 1 shows that patients with OOK-associated AK were younger, were less noncompliant, had less severe disease, and had a better prognosis for good visual outcome compared to patients with other CL-associated AK. We thus analyzed whether OOK CL use itself was a better prognostic factor than other CL use (Table 2). Although younger age, initial presentation without ring infiltration, and better BCLVA before treatment were associated with better BCLVA after treatment in simple linear regression analysis, only initial presentation without ring infiltration was associated with better post-treatment BCLVA in multiple linear regression. Compared with soft CLs users, OOK users in Taiwan often have regular follow-up care and are well educated about the signs and potential risks of infectious keratitis by doctors, and this may account for the better vision outcomes in OOK lens users. These patients were probably treated earlier than patients with other CL-associated AK because no patients with OOK-associated AK showed progression to ring infiltration before their consultation at our hospital. In our cases series, the duration of initial symptoms to first diagnosis of AK was shorter in OOK-associated AK patients (1.91 ± 0.90 weeks vs 3.04 ± 1.99 weeks in other CL-associated AK patients, $p = 0.03$).

Biguanides, such as PHMB and chlorhexidine, and diamidines, such as propamidine and hexamidine, are the most common antiamebic agents and have both trophozoicidal and cysticidal effects. In the past, biguanide and diamidine combination therapy was suggested for treatment.[31] However, Lim et al[32] demonstrated that the use of PHMB and chlorhexidine as monotherapy was successful in treating 78% and 85% of patients, respectively. Sunada et al[33] found isolated *Acanthamoeba* cysts were not susceptible to voriconazole in an in vitro study. But voriconazole shows good cysticidal activity against *Acanthamoeba* in vitro,[34] and successful treatment of chlorhexidine- and PHMB-resistant AK with voriconazole 1% as an adjuvant has also been reported.[35] The differences in cysticidal activity of voriconazole may be related to the maturity of the cysts being tested and variations in testing techniques. In 2010, we began using chlorhexidine 0.02% ± voriconazole 1% ± oral voriconazole to treat all AK patients, and 12 of 13 patients (92.3%) with OOK-associated AK had final BCLVA of 0.10 (Snellen visual acuity of 6/7.5) or better after this treatment. When we included all CL-associated AK treated in various regimens, 26 of 35 patients (74.29%) had BCLVA of 0.10 or better. This prognosis for visual outcome in only OOK-associated AK or that in all CL-associated AK are both comparable to results reported by Chin et al[36] and Tu et al,[37] who used propamidine and either PHMB or chlorhexidine to treat their patients, who had more severe disease. In these two studies, 80% and 65.6% of AK patients, respectively, achieved BCLVA of 0.10 or better.[36,37]

The limitations of our study are that it is a retrospective study and the time of CL worn per day, days CL worn per week, the CL care systems used by patients, and the material of CL were not recorded in detail. However, we have tried our best to explore the possible risk factors that are listed in Table 3 and recorded in our medical charts.

In conclusion, most CL-associated AK patients had satisfactory visual outcomes. Since 2010, OOK lenses have replaced soft CL as the most commonly used CL types associated with AK at our hospital. The OOK-associated AK patients were younger, had less severe disease, and had a better prognosis for visual outcome compared to the patients with other CL-associated AK in our study. All patients with OOK-associated AK were treated successfully using chlorhexidine 0.02% ± voriconazole 1% ± oral voriconazole. We found that initial presentation without ring infiltration was associated with a better prognosis for good visual outcome. We conclude that early recognition of AK and prompt and effective treatment can provide good outcomes for patients with OOK-associated AK.

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REFERENCES

1. Tanhehco T, Colby K. The clinical experience of Acanthamoeba keratitis at a tertiary care eye hospital. *Cornea* 2010;**29**:1005–10.
2. Illingworth CD, Cook SD. Acanthamoeba keratitis. *Surv Ophthalmol* 1998;**42**:493–508.
3. Naginton J, Watson PG, Playfair TJ, McGill J, Jones BR, Steele AD. Amoebic infection of the eye. *Lancet* 1974;**2**:1537–40.
4. Dart JK, Saw VP, Kilvington S. Acanthamoeba keratitis: diagnosis and treatment update 2009. *Am J Ophthalmol* 2009;**148**:487–99.e2.
5. Hsu CC, Huang N, Lin PY, Tsai DC, Tsai CY, Woung LC, et al. Prevalence and risk factors for myopia in second-grade primary school children in Taipei: a population-based study. *J Chin Med Assoc* 2016;**79**:625–32.
6. Tsai DC, Fang SY, Huang N, Hsu CC, Chen SY, Chiu AW, et al. Myopia development among young schoolchildren: the myopia investigation study in Taipei. *Invest Ophthalmol Vis Sci* 2016;**57**:6852–60.
7. Hsu CC, Huang N, Lin PY, Fang SY, Tsai DC, Chen SY, et al. Risk factors for myopia progression in second-grade primary school children in Taipei: a population-based cohort study. *Br J Ophthalmol* 2017;**101**:1611–7.
8. Kim EC, Kim MS. Bilateral acanthamoeba keratitis after orthokeratology. *Cornea* 2010;**29**:680–2.
9. Lee JE, Hahn TW, Oum BS, Choi HY, Yu HS, Lee JS. Acanthamoeba keratitis related to orthokeratology. *Int Ophthalmol* 2007;**27**:45–9.

10. Robertson DM, McCulley JP, Cavanagh HD. Severe acanthamoeba keratitis after overnight orthokeratology. *Eye Contact Lens* 2007;**33**:121–3.
11. Wilhelmus KR. Acanthamoeba keratitis during orthokeratology. *Cornea* 2005;**24**:864–6.
12. Wong VW, Chi SC, Lam DS. Good visual outcome after prompt treatment of acanthamoeba keratitis associated with overnight orthokeratology lens wear. *Eye Contact Lens* 2007;**33**(6 Pt 1):329–31.
13. Xuguang S, Lin C, Yan Z, Zhiqun W, Ran L, Shiyun L, et al. Acanthamoeba keratitis as a complication of orthokeratology. *Am J Ophthalmol* 2003;**136**:1159–61.
14. Chan TCY, Li EYM, Wong VWY, Jhanji V. Orthokeratology-associated infectious keratitis in a tertiary care eye hospital in Hong Kong. *Am J Ophthalmol* 2014;158:1130–5.
15. Kwok LS, Pierscionek BK, Bullimore M, Swarbrick HA, Mountford J, Sutton G. Orthokeratology for myopic children: wolf in sheep's clothing? *Clin Exp Ophthalmol* 2005;**33**:343–7.
16. Bullimore MA, Sinnott LT, Jones-Jordan LA. The risk of microbial keratitis with overnight corneal reshaping lenses. *Optom Vis Sci* 2013;**90**:937–44.
17. Miller MJ, Wilson LA, Ahearn DG. Adherence of Pseudomonas aeruginosa to rigid gas-permeable contact lenses. *Arch Ophthalmol* 1991;**109**:1447–8.
18. Ren DH, Petroll WM, Jester JV, Ho-Fan J, Cavanagh HD. The relationship between contact lens oxygen permeability and binding of Pseudomonas aeruginosa to human corneal epithelial cells after overnight and extended wear. *CLAO J* 1999;**25**:80–100.
19. Lin MC, Graham AD, Fusaro RE, Polse KA. Impact of rigid gas-permeable contact lens extended wear on corneal epithelial barrier function. *Invest Ophthalmol Vis Sci* 2002;**43**:1019–24.
20. Watt K, Swarbrick HA. Microbial keratitis in overnight orthokeratology: review of the first 50 cases. *Eye Contact Lens* 2005;**31**:201–8.
21. Lo J, Kuo MT, Chien CC, Tseng SL, Lai YH, Fang PC. Microbial bioburden of orthokeratology contact lens care system. *Eye Contact Lens* 2016;**42**:61–7.
22. Hay J, Seal DV. Contact lens wear by hospital health care staff: is there cause for concern? *J Hosp Infect* 1995;**30**(Suppl):275–81.
23. Beattie TK, Tomlinson A. The effect of surface treatment of silicone hydrogel contact lenses on the attachment of Acanthamoeba castellanii trophozoites. *Eye Contact Lens* 2009;**35**:316–9.
24. Arance-Gil A, Gutierrez-Ortega AR, Villa-Collar C, Nieto-Bona A, Lopes-Ferreira D, Gonzalez-Meijome JM. Corneal cross-linking for Acanthamoeba keratitis in an orthokeratology patient after swimming in contaminated water. *Cont Lens Anterior Eye* 2014;37:224–7.
25. Cope JR, Collier SA, Schein OD, Brown AC, Verani JR, Gallen R, et al. Acanthamoeba keratitis among rigid gas permeable contact lens wearers in the United States, 2005 through 2011. *Ophthalmology* 2016;**123**:1435–41.
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.
27. Kam KW, Yung W, Li GKH, Chen LJ, Young AL. Infectious keratitis and orthokeratology lens use: a systematic review. *Infection* 2017;**45**:727–35.
28. Ladage PM, Yamamoto N, Robertson DM, Jester JV, Petroll WM, Cavanagh HD. Pseudomonas aeruginosa corneal binding after 24-hour orthokeratology lens wear. *Eye Contact Lens* 2004;**30**:173–8.
29. Liu YM, Xie P. The safety of orthokeratology–a systematic review. *Eye Contact Lens* 2016;**42**:35–42.
30. Chew HF, Yildiz EH, Hammersmith KM, Eagle RC Jr, Rapuano CJ, Laibson PR, et al. Clinical outcomes and prognostic factors associated with acanthamoeba keratitis. *Cornea* 2011;**30**:435–41.
31. Duguid IG, Dart JK, Morlet N, Allan BD, Matheson M, Ficker L, et al. Outcome of acanthamoeba keratitis treated with polyhexamethyl biguanide and propamidine. *Ophthalmology* 1997;**104**:1587–92.
32. Lim N, Goh D, Bunce C, Xing W, Fraenkel G, Poole TR, et al. Comparison of polyhexamethylene biguanide and chlorhexidine as monotherapy agents in the treatment of Acanthamoeba keratitis. *Am J Ophthalmol* 2008;**145**:130–5.
33. Sunada A, Kimura K, Nishi I, Toyokawa M, Ueda A, Sakata T, et al. In vitro evaluations of topical agents to treat Acanthamoeba keratitis. *Ophthalmology* 2014;**121**:2059–65.
34. Iovieno A, Miller D, Ledee DR, Alfonso EC. Cysticidal activity of antifungals against different genotypes of Acanthamoeba. *Antimicrob Agents Chemother* 2014;**58**:5626–8.
35. Bang S, Edell E, Eghrari AO, Gottsch JD. Treatment with voriconazole in 3 eyes with resistant *Acanthamoeba keratitis*. *Am J Ophthalmol* 2010;**149**:66–9.
36. Chin J, Young AL, Hui M, Jhanji V. Acanthamoeba keratitis: 10-year study at a tertiary eye care center in Hong Kong. *Cont Lens Anterior Eye* 2015;**38**:99–103.
37. Tu EY, Joslin CE, Sugar J, Shoff ME, Booton GC. Prognostic factors affecting visual outcome in Acanthamoeba keratitis. *Ophthalmology* 2008;**115**:1998–2003.