Risk factors for *acanthamoeba* keratitis in contact lens users: a case-control study

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Abstract

Objective—To investigate reasons for an increase in cases of *Acanthamoeba* keratitis related to contact lenses.

Design—Case-control study. Cases were contact lens related *acanthamoeba* keratitis patients treated between 1 September 1989 and 31 August 1992. Controls were lens users without lens related disease who presented as new patients to the casualty department from 1 March 1992 to 31 August 1992. All subjects completed a questionnaire detailing lens use and hygiene practices.

Setting—Eye hospital.

Subjects—35 cases with *acanthamoeba* keratitis and 378 controls.

Main outcome measures—Relative risks comparing different contact lens types, socioeconomic classification, age, sex, lens use, lens wearing experience, hygiene compliance, and hygiene systems.

Results—The crude relative risk for developing *acanthamoeba* keratitis with the use of daily wear disposable lenses was 49.45 (95% confidence interval 6.53 to 2227; $P < 0.001$) compared with conventional soft lenses (the referent). Multivariable analysis showed that this increased risk could be largely attributed to lack of disinfection (relative risk 55.86 (10 to 302); $P < 0.001$) and use of chlorine based disinfection (14.63 (2.8 to 76); $P = 0.001$) compared with other chemical systems (the referent). None of the other outcome measures showed a significant association.

Conclusions—Both failure to disinfect daily wear soft contact lenses and the use of chlorine release lens disinfection systems, which have little protective effect against the organism, are major risk factors for *acanthamoeba* keratitis. These risks have been particularly common in disposable lens use. Over 80% of *acanthamoeba* keratitis could be avoided by the use of lens disinfection systems that are effective against the organism.

Introduction

Acanthamoeba keratitis is an uncommon but potentially devastating corneal infection. In a recent series, 34 corneal grafts were performed in 23 of 73 eyes (32%), and for 15 of the 72 patients (21%) the characteristically recalcitrant pain and protracted clinical course culminated in severe visual loss.¹

Although *acanthamoeba* keratitis occurs after contaminated corneal injuries,² 85% of cases are in contact lens users of all lens types.³ Conventional soft lens wearers account for the majority of cases, reflecting the popularity of this lens type, in whose users the use of homemade saline, swimming in lenses, and irregular disinfection are risk factors.⁴

Acanthamoebas are free living amoebas found in air, dust, and water, including bathroom tap water.⁵ Their cysts are resistant to antimicrobial agents, including current lens disinfection solutions,⁶ and may contaminate lens storage cases in asymptomatic users.⁷

At Moorfields Eye Hospital there has been an increase in the number of *acanthamoeba* cases corres-

ponding to the introduction and increasing popularity of disposable lenses.¹ We carried out a retrospective case-control study to investigate causes for the increase in *acanthamoeba* keratitis cases in London. We determined the relative risks of *acanthamoeba* keratitis associated with different lens types and the relative importance of lens type, disinfection regimens, and other risk factors.

Subjects and methods

SUBJECTS

Cases were patients presenting to Moorfields between 1 September 1989 and 31 August 1992 with *acanthamoeba* keratitis diagnosed by corneal culture or by previously described clinical criteria⁸; separate analysis of the cases with positive cultures was undertaken to validate the inclusion of the clinically diagnosed cases. Controls were lens users with disease unrelated to contact lens wear presenting as new patients to the casualty department between 1 March 1992 and 31 August 1992. Cases or controls with a medical indication for lens wear were excluded from the study.

In the first part of the study, the relative risk for *acanthamoeba* keratitis of each lens type was assessed, using the conventional daily wear soft lens as the referent. For this study cases were limited to those presenting during the last 12 months of the study period, to be as contemporaneous as possible with the controls, because the penetrance of disposable lenses had increased during the three year study period.^{8,9}

The second part of the study consisted of multivariable analysis of hygiene practices and other risk factors for the disease. All cases presenting during the three year period were included, since the availability and market share of lens care systems did not change during this time.^{8,9}

METHODS

Cases and controls completed a self administered questionnaire detailing occupation, age, sex, lens use, experience, and hygiene practices. These data were confirmed by telephone when they were insufficient or ambiguous. Socioeconomic classification was carried out using the 1991 census coding.¹⁰ Extended wear was defined as overnight use occurring at least once per week, although less frequent overnight use was included in the analysis. For each individual a hygiene score for each aspect of lens care was derived. Daily mechanical lens cleaning, disinfection with fresh solution on every lens removal, weekly case cleaning, and fortnightly enzyme treatment (or equivalent disposal frequency) scored maximally. Points were deducted for less frequent or suboptimal attention to these aspects of lens care. Use of non-sterile water for any aspect of lens care received a zero score for disinfection. For the statistical analysis each step in the hygiene regimen was classified dichotomously as optimal or suboptimal. Clinical data were derived from hospital notes and previous study data.¹

STATISTICAL ANALYSIS

The EGRET software package (Statistics and

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Epidemiology Research Corporation, Seattle) was used to carry out multivariable logistic linear regression analysis. STATXACT (CYTEL Software Corporation, Cambridge, MA) was used for estimation of exact odds ratios (relative risks), 95% confidence intervals, and P values. The population attributable risk percentage, a measure of the proportion of cases that can be attributed to a specific risk factor, was estimated where appropriate.

Results

Thirty nine patients with lens related acanthamoeba keratitis were identified. Four were excluded: one therapeutic lens user and three patients, attending before 1 September 1991, who could not be traced for verification of lens wear data. Results of tissue cultures

TABLE I—Characteristics of contact lens wearers studied for risk of *acanthamoeba* keratitis. Values are numbers (percentages) unless stated otherwise

	Different lens types		Hygiene practices and other risk factors	
	Cases (n=12)	Controls (n=378)	Cases (n=31)	Controls (n=240)
Mean (range) age	31.50 (18-55)	31.34 (14-66)	31.39 (18-56)	29.89 (14-66)
Ratio of males to females	3:9 (25:75)	134:244 (35:65)	14:17 (45:55)	90:150 (37:63)
Social class:				
1	3 (25)	63 (17)	9 (29)	39 (16)
2	7 (58)	175 (46)	11 (35)	106 (44)
3	2 (17)	103 (27)	11 (35)	68 (28)
4	0	29 (8)	0	19 (8)
5	0	6 (2)	0	6 (3)
6	0	2 (<1)	0	2 (1)
Soft contact lens:				
Conventional daily wear	1 (8)	208 (55)	12 (39)	203 (85)
Conventional extended wear	1 (8)	18 (5)		
Disposable daily wear	9 (75)	37 (10)	19 (61)	37 (15)
Disposable extended wear	1 (8)	11 (3)		
Rigid contact lens	0 (0)	104 (27)		
Disinfection of soft contact lens:				
None	5 (42)	12 (4)	9 (29)	10 (4)
Hydrogen peroxide	1 (17)	145 (53)	1 (3)	132 (55)
Chlorine based:	6 (50)	49 (18)	19 (61)	47 (20)
Softab*	5 (83)	18 (37)	17 (90)	39 (83)
Aerotab†	1 (17)	2 (4)	1 (5)	6 (13)
Either			1 (5)	2 (4)
Other chemical	0	54 (20)	1 (3)	49 (20)
Thermal	0	5 (2)	0	Excluded
Rigid contact lens solution	0	7 (1)	1 (3)	2 (1)
Disposal	0	7 (2)	0	0

*Sodium dichloroisocyanurate 0.065 mg.

†Halazone 0.16 mg.

TABLE II—Relative risks of *acanthamoeba* keratitis for different contact lens types and wear schedules

Type of lenses	No of cases (n=12)	No of controls (n=378)	Relative risks (95% confidence interval)	P value
Soft contact lenses				
Conventional daily wear	1	208	1.0	
Conventional extended wear	1	18	11.27 (0.14 to 911)	0.320
Disposable daily wear	9	37	49.45 (6.53 to 2227)	<0.001
Disposable extended wear	1	11	18.15 (0.22 to 1491)	0.106
Rigid contact lens	0	104		

TABLE III—Relative risks of significant exposure factors for *acanthamoeba* keratitis obtained by multivariable analysis

Exposure factor	Odds ratio (95% confidence interval)	P value
Type of soft contact lens		
Conventional daily wear	1.0	
Disposable daily wear	3.82 (1.01 to 14.48)	0.049
Disinfection system:		
Hydrogen peroxide or chemical other than chlorine	1.0	
Chlorine:		
Optimal use*	14.63 (2.8 to 76)	0.001
Suboptimal use	41.05 (7.3 to 232)	<0.001
None	55.86 (10 to 302)	<0.001
Cleaning with surfactant:		
At least twice a week	1.0	
Less than twice a week	3.50 (0.94 to 13.10)	0.062
Advice on aftercare:		
Given	1.0	
Not given or not recalled	3.49 (0.95 to 12.81)	0.06

*Disinfection with a new tablet and fresh, non-preserved sterile saline whenever lenses removed.

Risk factors incorporated in multivariable analysis

Age
Sex
Socioeconomic class
Contact lens type (conventional or disposable)
Refraction
Length of experience with current contact lens type
Total length of experience with contact lens wear
Contact lens age
Occasional overnight use
Duration of contact lens wear
Frequency of contact lens wear
Contact lens cleaning score
Contact lens disinfection method and hygiene score
Frequency of enzyme use or contact lens disposal
Contact lens storage case hygiene score
Practitioner's advice regarding frequency of aftercare

were positive for 14 patients (40%), and *Acanthamoeba* was isolated from the lens, lens case, or solutions from a further eight patients (23%). Table I shows the characteristics of the study population.

RISK WITH DIFFERENT LENS TYPES

Daily wear disposable soft lenses were used by 9/12 (75%) of the cases and 37/378 (9.8%) of the controls (table II). The crude relative risk associated with daily wear disposable as opposed to conventional daily wear soft lenses was estimated as 49.45 (95% confidence interval 6.53 to 2227, $P < 0.001$).

HYGIENE PRACTICES AND OTHER RISK FACTORS

As the use of daily wear soft lenses was associated with 31 of the 35 cases, analysis of further risk factors was restricted to patients using daily wear conventional or disposable soft lenses. Five controls who used heat disinfection were excluded from this analysis because no cases used this method.

The 16 variables incorporated in the analysis of risk factors for this group are listed in the box. The multivariate model was constructed with a step up procedure, in which significant variables were added one at a time to assess their effect on the fit of the model.

The use of non-sterile saline or water could not be incorporated into the model as it was too closely linked with the disinfection score. Separate analysis, however, showed a significantly increased risk of *acanthamoeba* keratitis (12.51 (1.37 to 156), $P = 0.023$) associated with its use. The risk of swimming in lenses, which occurred in three of the cases, was not evaluated as these data were not available for the controls.

The type of disposable lens used was also excluded from the main analysis, owing to insufficient numbers using types other than Acuvue (Vistakon, UK). Among patients wearing daily wear disposable soft lenses all 19 cases and 24/37 (65%) of the controls were using Acuvue. A crude minimum relative risk for Acuvue compared to other disposable lens types was estimated as 2.63 (2.63 to ∞ ; $P = 0.004$).

Table III shows the relative risk and 95% confidence intervals of the most important exposure factors. Although the crude analysis of risk with different lens types showed a 49.45 increased risk associated with daily wear disposable lenses, multivariate analysis showed that the excess risk attributable to the lenses is comparatively small (3.82, $P = 0.049$).

The factor with the greatest effect on the risk of keratitis was the type and standard of disinfection used. As expected, failure to disinfect carried a greatly increased risk of keratitis (55.86, $P < 0.001$), but chlorine based disinfection, even when used optimally, was also shown to carry a significantly increased risk

TABLE IV—Multivariable analysis of risk factors for *acanthamoeba keratitis* among users of daily wear soft contact lenses who had positive results on tissue culture

	Disinfection				Lens type	
	Hydrogen peroxide*	Chlorine		None	Conventional	Disposable
		Optimal use†	Suboptimal use			
Cases	0	7	2	4	7	6
Controls	181	35	12	12	203	37
Total	181	42	14	16	210	43
Relative risk adjusted for age and lens type	1.0	∞‡	∞	∞		
95% Lower confidence limit		6.49	7.29	15.20		
P value		<0.001	0.004	<0.001		
Relative risk adjusted for sex and lens type	1.0	∞	∞	∞		
95% Lower confidence limit		5.14	5.54	8.02		
P value		0.002	0.006	<0.001		
Relative risk adjusted for cleaning and lens type	1.0	∞	∞	∞		
95% Lower confidence limit		4.43	4.19	14.93		
P value		0.002	0.010	<0.001		
Relative risk adjusted for cleaning and disinfection					1.0	2.19
95% Confidence interval						0.25 to 14.12
P value						0.589

*Or chemical other than chlorine.

†Disinfection with a new tablet and fresh, non-preserved sterile saline at every removal.

‡Point estimate undefined due to a zero for one frequency.

compared with hydrogen peroxide or other chemical systems (14.63, $P=0.001$). The population attributable risk percentage, after lens type was controlled for, was 56.3% (27% to 86%) for chlorine based disinfection and 31.8% (8 to 55) when disinfection was omitted.

MULTIVARIATE ANALYSIS WITH CULTURE POSITIVE CASES

Because of the small number of cases with positive results of corneal culture, and because of the absence of cases among the referent group exposed to some factors, analysis was carried out by stratifying the data by a few important extraneous factors and using exact procedures for significance tests and estimations of relative risks. Table IV shows that exclusion of cases with negative results on tissue culture gives similar or slightly increased lower confidence limits for the excess risks associated with the use of chlorine disinfection and omitting disinfection although, with the smaller number of cases, the excess risk associated with disposable lens use was not statistically significant.

Discussion

We have shown that the use of daily wear disposable lenses is associated with a greatly increased risk of *acanthamoeba keratitis*. Multivariable analysis showed that this is largely attributable to a lack of disinfection, the use of non-sterile saline, and the use of chlorine based disinfection rather than alternative chemical systems. Case-control studies have also shown an increased risk for bacterial keratitis with disposable lenses.^{8,11} In one study this was attributed largely to overnight wear, rather than to the effects of lens hygiene and the lens itself¹ that we have shown for *acanthamoeba keratitis*.

DISPOSABLE LENSES AND ACANTHAMOEBA KERATITIS

A relatively small excess risk was associated with disposable lenses independent of other risk factors. The reasons for this may include confounding factors that we could not assess, such as the use of disposable lenses as a "problem solver" in patients at higher risk of keratitis. Alternatively, physical factors such as increased in vivo lens dehydration¹² and protein absorption,¹³ due to the high water content ionic material from which many of these lenses are made, or the presence of manufacturing defects affecting corneal integrity¹⁴ might account for this finding.

DISINFECTION SYSTEMS AND ACANTHAMOEBA KERATITIS

Chlorine has been compared with other disinfection solutions and shown to increase the risk for *acanthamoeba keratitis*; it accounted for 56% of cases. It is also less protective against bacterial keratitis.¹⁵ *acanthamoeba* cysts can survive 10 times the concentration of chlorine used in these systems,¹⁶ and chlorine based disinfection has been associated with contamination of storage cases by *acanthamoeba*.¹⁷ Other chemical systems are either ineffective against *acanthamoeba* cysts or effective only in the absence of organic debris or after a prolonged soaking time.⁶ However, since concomitant bacterial contamination may be important to the survival and growth of *acanthamoeba* in the lens case,¹⁸ the relative protection apparently provided by these systems may be due to their greater antibacterial efficacy.

Comparative in vitro studies on the efficacy of chlorine release systems against a panel of bacteria and fungi have shown relatively poor activity¹⁹ and equivalent activity.²⁰ These differing results may be due to interstrain variability in susceptibility to disinfectants. Furthermore, these in vitro tests, used by licensing authorities for premarket evaluation of the efficacy of contact lens disinfectants in Britain,²¹ probably do not reflect the relative efficacy of these agents in vivo, where organisms contaminating both contact lenses and cases have been shown to live in biofilms.²² Organisms in biofilms exist as a sessile phenotype and are more resistant to disinfectants than the planktonic phenotype used in the laboratory for in vitro tests.²³

Although *acanthamoebas* were isolated from the lens storage cases of half the patients with *acanthamoeba keratitis*, lens case hygiene did not affect the risk of developing keratitis. Given the misunderstandings regarding lens case hygiene,²⁴ many people may have been using inappropriate methods that increased the risk of lens case contamination.⁵ Since this study was conducted, the manufacturers of Softab (Alcon Laboratories, UK), whose product accounted for 85% of the chlorine based disinfection in this study, have repackaged their system to include a new storage case with each month's supply of tablets. This may reduce both the prevalence of contamination of storage cases and the excess risk associated with the use of chlorine based disinfection.

PREVENTING ACANTHAMOEBA KERATITIS

Over 80% of cases of *acanthamoeba keratitis* could be prevented by the adequate use of an effective disinfection system. This avoidable burden of disease seems to have two major causes: the "low care" philosophy of daily disposable lens use has resulted in "no care" practised by ill informed contact lens practitioners and users, and the easy to use chlorine release systems, commonly dispensed with disposable

Key messages

- Failure to disinfect soft contact lenses and the use of chlorine disinfection systems are major factors accounting for the increase in cases of *acanthamoeba keratitis*
- These risk factors are both more common in users of disposable daily wear soft lenses
- Over 80% of *acanthamoeba* infections could be eliminated by daily disinfection of reused lenses with systems effective against the organism
- Disinfection systems ineffective against *acanthamoeba* should not be licenced for use

lenses, seem to be particularly ineffective against *Acanthamoeba*. Although contact lens disinfection systems in Britain have to comply with stringent tests of efficacy against a panel of microbes, these are directed against planktonic organisms in vitro, rather than the more resistant sessile organisms that are found in vivo and do not include *Acanthamoeba*.²¹ Increased emphasis on the importance of maintaining good hygiene with soft conventional and reused disposable lenses, using hydrogen peroxide or other disinfection systems that are effective against *Acanthamoeba*, could almost eliminate this severe cause of keratitis. Contact lens practitioners, the contact lens industry, and the Department of Health all have roles to play in achieving this aim—not least by holding back licences from disinfection systems that are ineffective against *Acanthamoeba*.

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Macular degeneration and early menopause: a case-control study

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Age related macular degeneration is a main cause of blindness in elderly people. The disease affects the macula lutea and results in a central scotoma in the visual field. The cause of the disease is poorly understood, and treatment is only successful in a few cases. Recent findings of an association between use of postmenopausal exogenous oestrogens and a lower risk of macular degeneration suggest a role for oestrogens in the pathogenesis of the disease.¹ We hypothesised that a higher risk of macular degeneration occurs in women with an early menopause.

Subjects, methods, and results

Data were obtained from the Rotterdam study.² All women aged 55 years and over who were resident in the suburb of Ommoord in Rotterdam were invited for the study. The response rate was 78% (4616/5918). Macular degeneration was considered to be present if either atrophic or neovascular age related macular degeneration was visible on colour pictures of the fundus. Age at and type of menopause were self reported and checked by a study physician. The cause of menopause was classified as natural hysterectomy, removal of one or both ovaries with or without hysterectomy, radiotherapy, or drug treatment. Overall, 3680 women (80%) had gradable fundus photographs of at least one eye and complete data on the menopause. Macular degeneration was present in 59

women (1.6%). We matched each case with five controls born in the same year who did not have macular degeneration, resulting in 295 controls. We calculated relative risks with 95% confidence intervals using conditional logistic regression analysis.

The table shows the relative risk of macular degeneration according to age and type of menopause. No significant excess risk was found for early spontaneous menopause and early hysterectomy. Women with early menopause after removal of one or both ovaries had a significantly increased risk of macular degeneration compared with women who had their menopause at 45 years or later (relative risk 3.8;

Relative risk of macular degeneration by type of menopause. Values are numbers of women.

	Macular degeneration		Relative risk (95% confidence interval)*
	Absent	Present	
Age at menopause (years):			
≥45	253	45	1.0
<45	42	14	1.9 (1.0 to 3.8)
Cause of early menopause:			
Spontaneous	30	6	1.2 (0.5 to 3.3)
Surgical:			
Hysterectomy only	4	1	2.1 (0.2 to 24.9)
Oophorectomy†	6	5	3.8 (1.1 to 12.6)
Irradiation	1	2	4.2 (0.6 to 30.2)
Drug use	1	0	—

*Adjusted for age.

†Unilateral or bilateral oophorectomy with or without hysterectomy.