

Acanthamoeba keratitis: multicentre survey in England 1992-6

Cherry F Radford, Ordan J Lehmann, John K G Dart, for the National Acanthamoeba Keratitis Study Group

Abstract

Aim—To investigate the frequency, outcomes, and risk factors for acanthamoeba keratitis (AK) in England during the past 4 years.

Methods—An ophthalmologist in 12 of the 14 regional health authorities (RHAs) coordinated identification of patients in their region presenting with AK between 1 October 1992 and 30 September 1996. Clinical and postal patient questionnaire data were analysed.

Results—243 patients (259 eyes) with an AK diagnosis were identified, equating to an annualised incidence of 0.14 per 100 000 individuals. UK resident patients for each year numbered 50, 71, 73, and 32 respectively. Among patients with sufficient data 170/237 (72%) were diagnosed early (within 30 days of presentation), 197/218 (90%) were treated with polyhexamethyl biguanide and/or chlorhexidine, and 40/243 (16%) underwent surgery. Visual acuities of 6/12 or better were achieved by 222/259 (86%) eyes, including 84 eyes of patients under review or lost to follow up. Non-contact lens (CL) wearers were associated with delayed diagnosis, increased need for surgery and a poorer visual outcome (only 10/18 eyes, 56%, achieved 6/12 acuity). 225/243 (93%) patients were CL wearers, and 205/243 (84%) were soft CL (SCL) users. Among SCL user respondents, previously identified risk factors—swimming with CL (47/138, 34%), non-sterile CL rinsing (11/138, 8%), omitted disinfection (85/138, 62%), and chlorine release disinfection (65/138, 47%)—were identified for 125/138 (91%) patients.

Conclusions—Earlier diagnosis and more effective medical therapy have improved the prognosis for most AK patients. The study demonstrates the highly preventable nature of the disease: 91% of the SCL wearers could have avoided the disease by refraining from inadvisable practices, and a marked fall in frequency was seen after intensive media attention to AK, possibly in conjunction with increasing penetrance of new CL products. Since the frequency of AK appears to be largely determined by the ever changing trends in CL use, continued monitoring is indicated.

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spite recent improvements in diagnosis and treatment, the characteristically recalcitrant pain and protracted clinical course still culminates in severe visual loss for over 15% of patients.¹ Although AK can occur after corneal trauma,² particularly in a rural environment, up to 92% of cases have been associated with contact lens (CL) use.³⁻⁵

Although reliable incidence data for AK are not available, in most series the organism has been implicated in less than 5% of CL related microbial keratitis cases.⁶⁻⁸ The incidence in the USA showed a dramatic increase in parallel with the growing popularity of soft CL (SCL) during the 1980s.⁴ The association with SCL wear was attributed to use of non-sterile CL solutions, swimming while wearing CL, and inadequate disinfection of lenses after use.⁹ Subsequently in the UK a review of 72 cases presenting to Moorfields Eye Hospital between 1984 and 1992 showed a marked rise in the number of cases associated with the introduction and increasing popularity of disposable SCLs.³ Further reviews at both Moorfields¹⁰ and Bristol¹¹ confirmed that this trend had continued, at least until mid 1995. A case-control study showed that the association with disposable lenses was largely attributable to the increased frequency of omitted or chlorine based disinfection among users of these CLs at the time.¹²

The incidence of AK appears to be much influenced by changing trends in contact lens care and use. Although the disease is rare, over 7% of adults in the UK are CL wearers (Eyecare Information Service, London, personal communication, May 1997) and therefore at a greatly increased risk. This multicentre survey was conducted to provide national data on the frequency, outcomes, and associated risk factors for AK during the 4 year period to September 1996 in England.

Methods

Data were collected for patients with a diagnosis of AK presenting between 1 October 1992 and 30 September 1996.

For each of the 14 regional health authorities (RHAs) in England a senior ophthalmologist in a large eye unit was invited to act as a regional coordinator for data collection. Regional coordinators organised the completion of clinical data sheets for AK patients in their hospital and sent data sheets to consultants in all other eye departments in their RHA. Patients were usually identified prospectively from late 1995, and retrospectively for earlier presentations. Where necessary, requests for

Moorfields Eye Hospital, London
C F Radford
J K G Dart

Southampton Eye Unit, Southampton
O J Lehmann

Correspondence to:
Dr C F Radford, Moorfields Eye Hospital, City Road, London EC1V 2PD.

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Acanthamoeba keratitis (AK) is a rare but potentially devastating corneal infection; de-

Table 1 AK patients identified as presenting 1 October 1992–30 September 1996 in 12 English RHAs (17 overseas patients excluded)

RHA	1992–3	1993–4	1994–5	1995–6	Total cases	RHA population (from 1991 census)	Annualised incidence per 100 000
East Anglian	0	0	0	1	1	2 136 023	0.0117
Mersey	0	1	2	2	5	2 400 582	0.0521
Northern	1	1	1	2	5	2 986 934	0.0418
North Western	4	7	8	0	19	4 006 900	0.1185
Oxford	3	1	2	0	6	2 558 551	0.0586
*NE Thames	36	39	37	20	132	3 768 783	0.8756
SE Thames	0	0	3	0	3	3 659 866	0.0205
South Western	5	9	9	4	27	3 289 255	0.2052
Trent	0	7	2	0	9	4 629 928	0.0486
Wessex	0	1	3	3	7	2 962 329	0.0591
West Midlands	1	2	4	0	7	5 225 395	0.0335
Yorkshire	0	3	2	0	5	3 535 201	0.0354
Total	50	71	73	32	226	41 159 747	0.1373

Data were unavailable from North West Thames and South West Thames.

*Includes Moorfields Eye Hospital.

follow up data were made up to 6 months after the end of the study period.

Clinical data sheets were checked for diagnostic criteria. Confirmed cases were defined as patients with a positive culture of *Acanthamoeba* or a clinical diagnosis which included perineural infiltrates (pathognomonic for the disease³). Patients with a clinical diagnosis excluding perineural infiltrates but including an array of other typical characteristics—such as positive culture from a CL, CL case or solutions, severe or disproportionate pain, epitheliopathy, limbitis, ring ulcer, and recalcitrant keratitis responding to appropriate anti-amoebal therapy—were categorised as having presumed acanthamoeba keratitis.

A postal questionnaire, detailing CL use and care as well as contact with soil, dust, and different types of water, was sent to patients in order to detect possible associations with previously established risk factors.^{9 12} These data supplemented the risk factor information supplied by the reporting ophthalmologist on the clinical data sheet. Data were entered on to a computer database.

Results

DISEASE FREQUENCY

Data were received from 12 of the 14 English RHAs. A total of 243 patients (259 eyes) with a diagnosis of AK were identified among this population of approximately 41 million. The total annualised incidence was 0.14 per 100 000 individuals, but there was considerable variation between the 12 participating RHAs (0.01–0.88 per 100 000) (Table 1). At Moorfields Eye Hospital the increase in frequency of cases presenting in the early 1990s^{3 10} (1990, n=22; 1991, n=27) has continued, reaching a plateau of approximately 40 cases per year in 1994 and 1995. This has been followed by a dramatic 46% decrease in the number of cases during the final year of the survey. Although small numbers in the majority of the other RHAs prevent detailed analysis, this pattern appears to have occurred throughout the country (Table 1). Seasonal variations in frequency were also identified: a calculation based on Poisson probabilities showed that the observed number of cases was significantly higher than expected for August and Septem-

ber and significantly lower than expected for February and March (Table 2).

DIAGNOSIS

A positive tissue diagnosis of *Acanthamoeba* was made for 131/243 (54%) patients, and for a further 53 (22%) diagnosis was confirmed by the presence of perineural infiltrates.

There were 59 cases of presumed AK who had atypical keratitis with an array of characteristic signs and symptoms³ such as positive culture from CL paraphernalia accompanying other typical features (n=48), epitheliopathy (n=27), limbitis (n=19), severe or disproportionate pain (n=17), and ring infiltrates (n=6).

The proportion of patients diagnosed early (antiamoebal therapy commenced within 30 days of presentation) was 137/200 (69%) during the first 3 years, significantly rising to 33/37 (89%) in the final year ($\chi^2 = 6.591$, $p < 0.02$) (Table 3). For six patients insufficient data prevented accurate calculation of diagnostic delay. Among patients who had not been wearing contact lenses only 9/18 (50%) were diagnosed early.

TREATMENT AND OUTCOME

For 197/218 patients (90%) medical therapy included polyhexamethyl biguanide (PHMB) (168/218, 77%) and/or chlorhexidine (44/218, 20%); the most common treatment combination was propamidine isethionate and PHMB (108/218, 50%) (Table 4). For 25 patients medical therapy details were incomplete. The average duration of medical therapy for patients in the study was 6 months (median 135 days; range 16–886 days), although 26 patients were still on medication or lost to follow up at the time of analysis (6 months after the study period).

Table 2 Seasonal variation in frequency of disease (among UK residents)

Month of presentation	New cases	p Values (Poisson probabilities)
January	18	0.484
February	8	0.004
March	10	0.020
April	16	0.305
May	17	0.393
June	21	0.338
July	25	0.100
August	28	0.028
September	33	0.002
October	24	0.142
November	14	0.158
December	12	0.065
Total	226	

Expected/month = 18.83.

Table 3 Numbers of patients (n=237) with an early diagnosis in each year of the study (for six patients insufficient data prevented calculation of diagnostic delay)

Presentation	Diagnosis	
	Early (<31 days) No (%)	Late (31 days or more) No (%)
1 Oct 92–30 Sep 93	37 (71)	15 (29)
1 Oct 93–30 Sep 94	47 (64)	26 (36)
1 Oct 94–30 Sep 95	53 (70)	22 (30)
1 Oct 95–30 Sep 96	33 (89)	4 (11)
	170 (72%)	67 (28%)

Table 4 Antiamoebal treatments received by acanthamoeba keratitis patients in the survey

Treatments received (in combination or separately)	No (%)
Propamidine + polyhexamethyl biguanide (PHMB)	108 (50)
Propamidine + neomycin + PHMB	31 (14)
Propamidine + neomycin	16 (7)
Propamidine + chlorhexidine	15 (7)
Propamidine + neomycin + chlorhexidine	12 (6)
Propamidine + PHMB + chlorhexidine	8 (4)
Propamidine + neomycin + PHMB + chlorhexidine	7 (3)
Propamidine + PHMB + topical antifungal	6 (3)
Propamidine alone	5 (2)
Propamidine + neomycin + PHMB + topical antifungal	3 (1)
Propamidine + chlorhexidine + topical antifungal	1 (<1)
Propamidine + neomycin + chlorhexidine + topical antifungal	1 (<1)
Propamidine + PHMB + oral antifungal	1 (<1)
Propamidine + neomycin + PHMB + oral antifungal	1 (<1)
Propamidine + neomycin + PHMB + topical and oral antifungal	1 (<1)
Propamidine + neomycin + PHMB + oral antifungal + topical interferon	1 (<1)
Propamidine + neomycin + PHMB + oral metronidazole	1 (<1)
Total	218* (100)

*Data were insufficient for 25 patients.

Table 5 Surgery among 243 acanthamoeba keratitis patients (259 eyes) in the survey

	No	(% of patients in survey)
Surgery	40 (41 eyes)	(16)
Penetrating/lamellar keratoplasty	30 (1 bilateral)	(12)
Cataract extractions	16	(7)
Superficial keratectomy	7	(3)
Trabeculectomy	5	(2)
Enucleation	2	(1)
Discharged, no surgery	149	(61)
Under review, no surgery yet	54	(22)
Total	243	

Surgery was performed on 40/243 (16%) patients (41/259 eyes), 30/243 (12%) patients (31 eyes) receiving penetrating or lamellar keratoplasty (Table 5). No significant difference existed in the proportions of confirmed and presumed AK cases known to have required surgery (29/181 and 7/58 respectively, $\chi^2 = 0.537$). Of the 203 patients who had not had any surgery there were 54 who were still under review, 17 of whom still had visual acuities of less than 6/12. Among non-CL wearers (18 unilateral patients) surgery (including two enucleations) was required in 8/18 (44%) of cases.

The final acuities for eyes of patients who had been discharged (n=161, 175 eyes) were 6/6 or better for 113/175 (65%), 6/9 to 6/12 for 53/175 (30%), and 6/18 to 6/60 for 5/175 (3%). Four patients with unilateral infection were left with light perception (n=2) or anophthalmos (n=2). Among patients still under review (n=61, 61 eyes) or lost to follow up (n=21, 23 eyes) acuities had reached 6/6 or better for 25/84 (30%) eyes, 6/9 to 6/12 for 31/84 (37%), 6/18 to 6/60 for 11/84 (13%), and unknown for three eyes. Fourteen of 84 eyes had perception of light only. In all, 25/82

(31%) of these patients were known to be still on medical therapy. When confirmed and presumed AK cases were compared, there was no significant difference in the numbers of patients known to have achieved 6/12 or better (153/182 and 53/58 respectively, $\chi^2 = 1.935$). Although similar numbers in the early and late diagnosed patients achieved at least 6/12, a significantly greater proportion of the early diagnosed group achieved 6/6 or better (99/170 compared with 25/67, $\chi^2 = 8.433$, $p < 0.01$). The proportions of patients achieving 6/12 or better among those treated with propamidine and PHMB only (99/107) or propamidine and chlorhexidine only (15/15) were both significantly higher than the proportion of patients with this outcome among those initially treated with propamidine and neomycin sulphate with PHMB added later (21/30) ($\chi^2 = 10.936$, $p < 0.001$ and 5.625, $p < 0.02$ respectively). Patients who had undergone surgery were significantly less likely to achieve 6/12 or better (23/35) than patients who had received medical therapy only (23/35 compared with 180/202, $\chi^2 = 13.287$, $p < 0.001$).

The visual outcome among non-CL wearers was markedly worse: at the time of analysis (nine were still under review) only 10/18 (56%) had achieved 6/12 or better, and six (33%) had perception of light or anophthalmos following enucleation.

PATIENT CHARACTERISTICS

Patient ages ranged from 4 to 64 years, with a mean age of 31.5 years; 135 (56%) were male and 108 (44%) were female.

RISK FACTORS AMONG NON-CONTACT LENS WEARERS

Questionnaires were completed by 12/18 (67%) patients who had not been wearing contact lenses. Eleven (61%) of these non-CL wearers had a recent history of trauma (minor in all but three cases) in a garden (n=4), building site (n=3), dairy farming (n=2), fishing (n=1), or nautical (n=1) environment. Four patients had developed the disease following water/snow sporting activities. Data were insufficient for the remaining three patients.

RISK FACTORS AMONG CONTACT LENS WEARERS

A total of 225 of the 243 patients (93%) had been wearing CLs when their symptoms started, and 157/225 (70%) completed a questionnaire; 221/225 (98%) had worn CLs for more than 6 months, and only 5/225 (2%) CL patients had a medical indication for CL wear (three were aphakic, one was keratoconic, and one had a corneal graft). Data on penetrance of different CL types and modalities are not available for each year of the study period. Recent data on current prescribing habits,¹³ however (which inevitably overestimate the proportion of the population wearing newer CL modalities) suggest that SCLs were over-represented, and rigid gas permeable lenses markedly underrepresented among the study patients (Table 6).

In contrast with the non-CL users, a minority of the CL wearers had a recent history of

Table 6 Distribution of contact lens (CL) types among AK patients who had been using CL

Contact lens use	No (%)	(Estimated % of CL users, ¹⁴ sample size=832)
Soft: disposal frequency 1-4 weeks	134 (60)	(50)
Soft: disposal frequency >4 weeks or not known	71 (32)	(30)
Rigid gas permeable	14 (6)	(19)
Hard	3 (1)	(1)
Soft-rigid combination	2 (1)	None recorded
Scleral	1 (<1)	None recorded
Total	225 (100)	(100)

Table 7 Distribution of types of soft contact lens (SCL) disinfection systems used by AK patients

SCL disinfection	No (%)
Chlorine release	83 (41)
Unknown type	38 (19)
Hydrogen peroxide	33 (16)
Multipurpose	8 (4)
Thiomersal and/or chlorhexidine	5 (2)
Disposal on removal	3 (1)
None (no lens disposal)	35 (17)
Total	205 (100)

trauma (14/225, 7%), and few (5/225, 2%) had acute concurrent ocular disease (two had acute epithelial necrosis after overnight CL use, an aphakic patient with glaucoma had anterior uveitis, one had conjunctivitis unrelated to CL wear, and one had CL related dry eye).

Adequate CL storage case hygiene (weekly rinsing of the case with sterile saline, boiled water, or disinfection solution followed by drying by leaving it open or by wiping with a clean tissue) was carried out by only seven of the 135 (5%) CL wearers for whom these data were available. Eighty two of 131 storage cases (63%) tested were culture positive for *Acanthamoeba*.

Among patients with rigid lenses, 11/17 (65%) failed to perform regular disinfection, and for three of the four subjects who had been compliant with correct disinfection routines there was a history of swimming pool bathing with contact lenses in situ.

Among SCL wearers for whom disinfection data were sufficient there were 56/150 (37%) who were disinfecting irregularly and a further 40/150 (27%) who failed to carry out *any* disinfection. Chlorine release systems were over-represented among the AK patients using soft lenses (Table 7). Fourteen of 158 (9%) patients (for whom these data were available) were known to have rinsed or soaked their SCL in tap water or other non-sterile water. Forty seven of the 205 (23%) SCL users were known to have swum or engaged in water sports while wearing their lenses before infection. Among questionnaire respondents who had been wearing SCL, one or more established CL related risk factors^{9 12} were identified for 125/138 (91%) patients (Table 8).

Discussion

DISEASE FREQUENCY

Despite the wide coverage of this multicentre survey the national annualised incidence of acanthamoeba keratitis may be substantially greater than calculated from the results (0.14 per 100 000); regional coordinators could not

Table 8 Frequency of pre-established risk factors for soft contact lens (CL) related acanthamoeba keratitis among questionnaire respondents (n=138)

	No (%)
Swimming with CL in ^a :	
Chlorinated water	34 (25)
Lakes, rivers, etc	9 (7)
Sea water	17 (12)
Any of the above	47 (34)
Omitted disinfection ^{9 12} (without lens disposal)	85 (62)
Chlorine disinfection ¹²	65 (47)
Non-sterile (eg tap water, homemade saline) rinsing ⁹	11 (8)
None of the above	13 (9)

be found for two of the 14 English RHAs, and within each of the contributing RHAs there were units that declined participation or were unable to identify cases retrospectively. In addition, the likelihood of enhanced case detection by larger specialist referral centres, as strongly suggested by the considerably higher incidence rates for North East Thames, North Western, and South Western, prevents any reliable analysis of the geographical distribution of the disease. This large database of cases does, however, enable detection of changing frequency of disease during the 4 year study period, and can show that these changes appear to have occurred throughout the country.

The continued increase in frequency during the 1992–5 period is likely to be associated with the growing popularity of disposable lenses and the inadequate disinfection routines with which they were associated at the time.¹² Growing recognition of the disease may also have increased the number of cases diagnosed.

With SCL associated with 205/243 (84%) of the total number of patients, it is hypothesised that a number of factors improving SCL hygiene practices may have brought about the marked decline in the number of AK cases during the final year (October 1995–September 1996). During 1993 the first “multipurpose” soft lens disinfection systems were introduced, providing a practical alternative to the chlorine release disinfection systems previously advocated for use with disposable lenses. The latter have been shown, when compared with other systems, to be associated with a 15 times greater risk of developing AK.¹² The most widely used brands of these new, multipurpose solutions are ineffective against *Acanthamoeba*.¹⁴ It is possible, however, that they may provide greater protection from AK (compared with chlorine release systems) as a result of their surfactant content and recommended “rub and rinse” step, which may be expected to significantly reduce the microbiological load.¹⁵ These systems also eliminate the need for a separate saline rinsing solution, which, if contaminated or substituted by inappropriate rinsing solution, increases the risk of AK.⁹ The growing popularity of these new solutions, together with the introduction in early 1995 of lenses for disposal after 1 day (thereby obviating the need for lens care solutions), may have contributed to the reduced number of cases in the final year of the study (after autumn 1995). The *suddenness* of the decline in numbers, however, suggests that the predominant factor may be improved CL hygiene and increased use of more effective disinfection systems after widespread media attention in November 1995 to a CL related AK study publication emphasising the risks associated with chlorine release or omitted disinfection.¹²

As in previous reviews of cases in the USA,^{5 16} a higher frequency of new cases during the summer/early autumn months was identified. This pattern has been attributed to an increased prevalence of *Acanthamoeba* in the environment during warmer weather.^{5 16} An additional association with a summertime flooding of the Iowa River (USA) has also been

described.¹⁶ It is also likely that warmer weather greatly increases the number of individuals engaging in water sports and outdoor activities (either in the UK or in much warmer climates), thereby increasing the number of people at increased risk of developing AK after contact with dust, soil, insect vectors, or environmental water.⁵

TREATMENT AND OUTCOMES

As in a previous series,³ outcomes as measured by final acuity and need for surgery were similar among confirmed and “presumed” cases, validating the inclusion of the latter in the survey.

When comparisons are made with a review³ of 72 cases presenting to Moorfields Eye Hospital between 1984 and 1992 a marked improvement in diagnosis and outcome is apparent.

The proportion of patients with an early diagnosis, which, as previously,³ is strongly associated with a more successful outcome, increased from 49% (35/72) to 72% (170/237). Possibly mainly as a consequence of this, the percentage of eyes known to receive a corneal graft reduced from 32% (23/73) to 18% (31/175). The percentage of eyes known to have achieved at least 6/12 visual acuity rose from 79% (58/73) to 87% (222/256), even though 84 eyes were still under review (including 26 eyes on medical therapy) at the time of analysis. Increased use of chlorhexidine and (particularly) PHMB, which have been shown to be the most effective agents against *Acanthamoeba* both in vitro¹⁷ and clinically,¹⁸ appears to be another contributing factor.

Failure to show a significantly poorer outcome among patients treated with propamidine and one of the biguanides compared with propamidine and neomycin is probably due to the tendency to introduce a biguanide to failures on the latter regime; patients who received propamidine, neomycin, and subsequent PHMB had a significantly poorer visual outcome compared with those who had received propamidine and a biguanide as the first line of treatment, illustrating the effect of delayed appropriate therapy on the final outcome.

The prognosis for patients contracting the disease in the absence of contact lens wear remains poor. This is probably related to the their frequently more delayed diagnosis. Earlier consideration of AK as a diagnosis among non-CL wearing patients with atypical keratitis following a history of (usually minor) trauma in a rural, dusty, or watery environment—as described in this study and previously^{2 4 5}—is advised. It has also been suggested, however, that infection acquired in rural settings may involve a heavier inoculate and/or more virulent organisms,¹ perhaps leading to more severe disease.

RISK FACTORS AMONG CONTACT LENS WEARERS

As in previous series,³⁻⁵ a very high proportion of patients were CL wearers (93%), and more than 90% of these were experienced CL wearers without any other predisposing factors. Rigid lenses were underrepresented in the survey, and all but one case had a history of

irregular disinfection and/or swimming pool bathing while wearing contact lenses. Easier removal of *Acanthamoeba* trophozoites and cysts from the rigid CL surface¹⁹ may be contributing to the apparently reduced risk with these lenses. The most likely explanation for the apparent difference in risk, however, is that the number of cases using rigid CL has remained fairly static during the 4 year period, while the number associated with SCL rapidly increased during the first 3 years of the survey.

Among normal CL wearers, storage case hygiene is known to be inadequate among 28–86%²⁰ and storage case contamination by *Acanthamoeba* occurs in up to 7%.²¹ Perhaps as a result of these universally poor standards, case hygiene has previously failed to be identified as a significant risk factor.¹² The very high proportion of patients (95%) in this study failing to carry out the most basic level of case hygiene, together with the frequency with which lens storage cases tested were found to be positive for *Acanthamoeba* (63%), however, suggests that increased education regarding this aspect of CL care could further reduce the incidence of AK.

Among SCL wearer questionnaire respondents (n=138) there was a history of at least one previously established risk factor⁹⁻¹²—swimming in lenses (34%), omitted disinfection (62%), chlorine disinfection (47%), and non-sterile lens rinsing (8%)—in 91% of these patients. These results, together with the high proportion of inadvisable practices among rigid lens wearers, emphasise the highly preventable nature of this disease among contact lens wearers.

Conclusion

An increased likelihood of earlier diagnosis and the widespread use of more effective medical therapy have greatly improved the prognosis for patients with acanthamoeba keratitis, although a successful outcome for the small proportion of patients with no recent history of CL wear remains less assured. The study demonstrates the highly preventable nature of the disease: 91% of the soft lens wearers (and probably 94% of the rigid lens wearers) could have avoided the disease by carrying out more effective disinfection and/or refraining from swimming while wearing lenses, and a dramatic fall in the incidence was seen after intensive media attention prompted widespread discussion and increased education of CL wearers. The gaining penetration of new CL disinfectants and daily disposable CL may also be contributing factors. There is a continued need to educate CL wearers about these risks, and since the frequency of AK appears to be largely determined by the ever changing trends in contact lens use, continued monitoring is indicated.

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National Acanthamoeba Keratitis Study Group participants: Birmingham: PJ McDonnell; Bristol: SD Cook, C Illingworth, S Kilvington; Cambridge: MG Kerr-Muir, J Prydal; East Grinstead: SM Daya, N Habib; Leeds: B Noble; Liverpool: SB Kaye; London: CF Radford, JKG Dart, M Matheson;

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