Acanthamoeba keratitis: risk factors and outcome

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Abstract

Aims/Background—This study was initiated to investigate risk factors for and outcome of Acanthamoeba keratitis.

Methods—Results of treatment were studied in 22 patients (23 eyes) presenting to Bristol Eye Hospital between 1985 and February 1995. Details related to the use and disinfection of contact lenses were also obtained. An additional two patients who were seen at Bristol but mainly treated elsewhere were surveyed for contact lens related information only.

Results—The incidence of Acanthamoeba keratitis rose substantially in the 1990s: three patients presented before 1990, while the remaining 21 presented between January 1990 and February 1995. Eleven patients have presented since January 1994. All of the patients in this series were contact lens wearers, 16 (67%) using daily wear disposable contact lenses. Contact lens disinfection data were available in 22 patients of whom 11 (50%) were using chlorine disinfectant. Other types of disinfection were much less common. Four patients (18%) had not used any disinfectant. During the course of the series the average diagnostic delay has fallen markedly, although in 77% of patients a diagnosis of a viral keratitis, most commonly herpes simplex, was made on first presentation. All but three of the series were treated with a combination of polyhexamethylene biguanide and propamidine isethionate. Penetrating keratoplasty was performed in 9/23 eyes (39%); in all of these eyes diagnosis was delayed for at least 6 weeks. All but one of the eyes in the series achieved a visual acuity of 6/9 or better after treatment, and 18 eyes (78%) saw 6/6 or better.

Conclusions—Most patients with Acanthamoeba keratitis can now expect a good visual result and cure by medical therapy alone is favoured by early diagnosis.

(Br J Ophthalmol 1995; 79: 1078–1082)

Acanthamoeba keratitis is a serious corneal infection that occurs mainly in contact lens wearers. The true incidence in the UK is difficult to establish since there is no national register of cases, but data from a number of sources suggest that the incidence is rising.1 2 Most recently reports of cases in wearers of disposable soft lenses have been prominent,1 but it can also occur in patients wearing non-disposable daily wear soft lenses and in wearers of hard and gas permeable lenses.3–5 Less commonly it may affect non-contact lens wearers.3

The clinical picture of Acanthamoeba keratitis is remarkable for its variability. Most patients complain of symptoms of photophobia, pain, and watering. It is well known that pain is a particularly marked symptom. The earliest signs may be non-specific and take the form of microcorneal erosions or epithelial irregularities and opacities. Most commonly the initial appearance is of a dendiform keratitis that is often mistaken for herpes simplex keratitis,6 7 and a pattern of radial perineural infiltrates is said to be virtually pathognomonic.8 A ring infiltrate may be seen, particularly at a later stage in the disease.9 The infection may progress to involve the sclera and, in long standing cases, cataract may occur,10 as may glaucoma.1

The most commonly used treatment in the UK is currently topical polyhexamethylene biguanide (PHMB) which is effective against both trophozoites and cysts,11 is non-toxic in vitro,12 and has been found to have a high cure rate if used early enough in the course of the disease.1 Reports from the USA13 and New Zealand14 have confirmed the efficacy of this compound. Topical propamidine isethionate (Brolene), which until the introduction of PHMB was the main anti-amoebal agent, is usually used concurrently. In advanced cases corneal transplantation may be necessary. Corneal grafting is usually successful in an uninfamed eye but failures have been reported when grafts have been performed in inflamed eyes.1 15

We have reviewed our experience of Acanthamoeba keratitis in order to examine particular risk factors, especially contact lens type and disinfectant system, to ascertain the efficacy of different treatments, and to establish prognosis in eyes that have been treated.

Methods

The patients were all seen by the corneal surgeon at Bristol Eye Hospital between 1985 and early 1995. This is a regional referral centre for corneal disorders which has a large catchment area in the southwest of England, and also sees some patients from other regions. All cases of Acanthamoeba keratitis seen in Bristol by February 1995 were reviewed. In two cases seen in Bristol but largely treated elsewhere, data relating to contact lens use were obtained and included, but treatment details were not included. Patients treated before 1993 were reviewed retrospectively from case notes, supplemented where necessary by contacting the patient to obtain additional data relating to the use of contact lenses. A database was kept of patients presenting from January 1993 onwards and these patients were followed up prospectively.
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## Diagnosis

Diagnosis was made on the basis of clinical features and laboratory investigations. Patients who had clinical features suggestive of Acanthamoeba keratitis underwent epithelial sampling by needle scrape after application of topical amethocaine drops, combined with scraping of any infiltrate present. The material obtained was inoculated onto the centre of a non-nutrient agar plate spread with *E. coli* and observed for up to 2 weeks. Cultures were considered positive if amoebal migration tracks could be seen and amoebal trophozoites with the typical appearance of *Acanthamoeba* observed with the light microscope. In all cases where there was significant stromal infiltrate additional samples were inoculated onto blood, chocolate, and Sabouraud’s agar plates for bacterial and fungal cultures. In cases where there was only mild epithelial disease these additional cultures were usually not performed.

In addition contact lenses, washings from contact lens cases, and contact lens fluids were cultured for *Acanthamoeba*, bacteria, and fungi.

In the few cases where all cultures were negative for *Acanthamoeba*, a firm diagnosis was made on clinical grounds alone provided that certain criteria were met. In our series a contact lens wearer with an atypical keratitis resistant to antiviral and antibiotic therapy which exhibited perineural or ring infiltrate (which are considered typical of *Acanthamoeba* keratitis) was included if the disease proved sensitive to anti-amoebal therapy.

## Treatment

In the majority of our cases treatment was with both PHMB and Brolene drops, initially used hourly or 2 hourly and reduced to four times daily when clinical improvement occurred. Long term treatment was considered essential and was continued for at least 4 months (more commonly 6 months) except in one case where the patient became sensitive to the drops and treatment was discontinued after 2 months.

In three cases treatment was with Brolene alone. These were early cases that were treated before PHMB and Brolene became available. No other topical anti-amoebal medications were used in this series.

Anti-amoebal treatment was supplemented with topical cycloplegics and often with topical steroids, according to clinical severity. Steroids were only used after improvement had occurred on anti-amoebal therapy, and were also used after penetrating keratoplasty. Non-steroidal anti-inflammatory drugs were used orally if pain was a prominent symptom.

Surgical treatment by penetrating keratoplasty was considered in severe disease, which was often in cases with delayed diagnosis, especially where there was a poor response to medical therapy. All corneal buttons were sent for histological analysis, and topical anti-amoebal treatment was continued for at least 4 months postoperatively.

## Results

### Demographic Details

A total of 24 patients with *Acanthamoeba* keratitis were seen between 1985 and February 1995, of which eight were male and 16 female. The average age was 31-2 years (range 17-69).

Geographical distribution of patient source can be divided into those from Bristol (13/24) and those from elsewhere (11/24). Most of the patients from elsewhere lived in the southwest region. There has been a marked increase in the annual number of cases since 1991 (Table 1).

### Use of Contact Lenses

All of the patients in this series were contact lens wearers. The most common type of lens, in 16 patients (67%), was daily wear disposable soft contact lenses, while five (21%) were wearing daily wear soft lenses, two (8%) were wearing hard lenses, and one (4%) was wearing gas permeable lenses. None of the patients in the series was wearing extended wear contact lenses although four of the disposable lens wearers reported that they had occasionally worn their lenses overnight.

Data on contact lens cleaning and disinfection were obtainable for 22 patients (92%) and among these the most commonly used disinfectant, in 11 patients (50%), was chlorine in tablet form. Two of the patients using chlorine tablets disinfected the lenses only occasionally, and of the remaining nine, one did not use a surfactant cleaner before disinfection. Nine of the patients who used chlorine disinfectant were wearing disposable lenses. Other types of disinfection were much less common. Three patients (14%) used a peroxide disinfectant, and of these, one used the disinfectant rarely and another did not use a surfactant. One patient (4-5%) used chlorhexidine and one (4-5%) used heat disinfection. The latter patient had worn an old lens that had not been disinfected 9 days before the onset of symptoms. Four (18%) patients used no disinfectant and one patient (4-5%) only rinsed the lenses in disinfectant (and could not remember the type). One patient (4-5%) had used a disinfectant only occasionally, and could not remember the type (Table 2).

### Past Ocular History

Of the 24 patients in the series, 21 had no past ocular history except the use of contact lenses for myopia. Two patients (three eyes) were wearing contact lenses for aphakia and one had had a corneal graft for keratoconus.

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**Table 1. Analysis of annual number of cases of Acanthamoeba keratitis and contact lens type**

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**Note:** Data for 1995 to end February 1996.
Table 2  Analysis of annual number of cases of Acanthamoeba keratitis and contact lens disinfectant type

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DIAGNOSTIC DELAY
The average diagnostic delay, measured as the time between initial presentation to an ophthalmology unit (either at Bristol or elsewhere) and commencement of anti-amoebal therapy, was 11-0 weeks (range 3 days to 56 weeks) in the 22 patients who were treated in Bristol. There has been a marked decrease in diagnostic delay in the latter part of the series: the average was 15-6 weeks before 1994 (13 patients) and 3-4 weeks from January 1994 onwards (nine patients). Of those presenting directly to Bristol Eye Hospital since January 1994, 5/8 have been started on anti-amoebal therapy within 1 week. The most common initial diagnosis, in 17/22 (77%), was of a viral keratitis (either herpes simplex, adenovirus, or unspecified), and in 8/22 (36%) a working diagnosis of herpes simplex keratitis was made at presentation. The initial treatment reflects this, since 10/22 (46%) were started on acyclovir at presentation. The early appearances were also occasionally attributed to epithelial abrasion.

CLINICAL FEATURES
The general pattern was for initial mild epithelial changes to progress to more marked epithelial loss and to subepithelial and stromal infiltrate in cases of late diagnosis (Table 3). An initial punctate epithelial loss was seen in 10/23 eyes (44%) and an initial dendriform appearance in 9/23 eyes (39%). Overall, 14 eyes (61%) displayed dendriform epithelial loss at some stage in the disease. Rarer epithelial signs at presentation were a ring-shaped epithelial defect in two eyes (9%) and a large central ulcer in two eyes (9%). Punctate changes progressed to a dendriform appearance in six eyes (26%) and dendriform epithelial loss progressed to a central ulcer in six eyes (26%). In eight cases that developed a central ulcer, the average diagnostic delay was 16-1 weeks (range 4-56).
A variety of infiltrate patterns could be seen.

Table 3  Clinical features and need for keratoplasty related to diagnostic delay

<table>
<thead>
<tr>
<th>Diagnostic delay</th>
<th>&lt;6 Weeks</th>
<th>6-12 Weeks</th>
<th>&gt;12 Weeks</th>
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<tr>
<td>Total number of patients</td>
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<td>4</td>
</tr>
<tr>
<td>Punctate epithelial loss</td>
<td>8</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Dendriform epithelial loss</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Central ulcer</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Subepithelial infiltrates</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Perineural infiltrate</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ring infiltrate</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dense central infiltrate</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Penetrating keratoplasty</td>
<td>0</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Multiple subepithelial infiltrates were seen in seven eyes (30%) and a dense central infiltrate occurred in seven eyes (30%). A ring infiltrate was noted in only six eyes (26%) and a perineural infiltrate in seven eyes (30%). The average diagnostic delay in eyes that developed a dense central infiltrate was 24-1 weeks (range 6-56).
Keratic precipitates were seen in 15 eyes (65%) and anterior chamber cells in 10 eyes (44%). Hypopyon occurred in one eye. Intraocular pressure remained normal in all cases and scleritis was seen in only one eye. Cataract did not occur in any eyes.

LABORATORY DIAGNOSIS
Acanthamoeba was cultured from the cornea, contact lens, or contact lens case in 17 patients (77%). In 13 patients (59%) the organism was cultured when a corneal epithelial scraping was placed on an E coli seeded non-nutrient agar plate. In an additional four patients (18%) the organism was cultured from the contact lens or contact lens case. Of the remaining five cases a scrape was not performed in two (contact lenses and cases were sent for culture but grew no Acanthamoeba) but all were contact lens wearers who had either perineural or ring infiltrate and responded to anti-amoebal therapy, and had not responded to other therapy. In the bilateral case Acanthamoeba was cultured from the corneal scrapings from one eye only, but the organism was identified histologically in the corneal buttons obtained from both eyes at the time of penetrating keratoplasty. Bacterial co-isolates from corneal scrapes were not a prominent feature of this series. One scrape grew Corynebacterium and three grew coagulase negative Staphylococcus. No corneal biopsies were performed.

MEDICAL TREATMENT
Topical PHMB was used in combination with Brolene in 20 eyes. In two of these eyes treatment with PHMB was added to treatment with Brolene alone after intervals of 13 and 17 weeks, as PHMB became available. In three eyes Brolene was used alone, since these cases occurred before PHMB was available. Initial frequency of instillation of PHMB drops was either hourly or 2 hourly depending on severity, and treatment continued at this frequency for an average of 5-9 weeks (range 0-5-9 weeks), after which it was continued four times daily and eventually tapered off and discontinued. Out of 16 PHMB treated patients who had stopped treatment by April 1995, the average length of treatment was 24-7 weeks.
All but one patient received cycloplegics, either atropine or cyclopentolate, and in 18/23 eyes (78%) topical steroids were used for at least 2 months. In seven cases, where the disease was mild, steroids were not used. No patients were treated with systemic steroids except post keratoplasty (see below) but oral non-steroidal anti-inflammatory drugs were used in eight cases. Supplementary antibiotics were not used except in eyes that underwent...
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Corneal grafting. Most patients were admitted to hospital for treatment except for five with relatively mild symptoms and signs.

Results of medical treatment have mainly been good. Of those eyes treated with medical therapy alone, 10/14 regained a corrected visual acuity of 6/6 or better after treatment and 3/14 achieved an acuity of 6/9. All of these eyes had been followed up for at least 3 months by April 1995, and all had become quiet. None has developed any subsequent reactivation of inflammation. However, one eye became blind despite lengthy treatment. In this case a severe anterior uveitis was recorded and PHMB only became available after 17 weeks of treatment with Brolene, by which time the visual acuity was already recorded at no perception of light. One patient developed intolerance to topical therapy, manifested as extreme discomfort on application of the drops, and treatment was discontinued after 2 months without any subsequent relapse. No other toxic effects were seen in the series.

SURGICAL TREATMENT
Penetrating keratoplasty was performed in nine eyes. All but one of these had dense central infiltrate with poor vision before grafting and they were all characterised by a lengthy period between first presentation and institution of anti-amoeobal therapy (average 22-4 weeks, range 6-56 weeks). The patient without dense infiltrate had been treated with Brolene for 19 weeks and with PHMB for 4 weeks before keratoplasty with little sign of improvement, and was experiencing severe pain. The average length of time between institution of anti-amoeobal therapy and keratoplasty was 45 days (range 3-120 days). None of the patients treated since January 1994 has had a keratoplasty. All of the patients who underwent keratoplasty were treated with topical anti-amoeobal agents and steroids postoperatively, and two were given systemic steroids. Only one had a rejection episode, which settled rapidly after treatment with topical steroids. One has required suture adjustment but none has required other refractive surgery. Postoperative cylinder averages 3-08 dioptres (range 0-5-6-00). All have a corrected visual acuity of 6/6 or better except one with a visual acuity of 6/7-5. The minimum follow up period was 15 months.

Discussion
These results corroborate many of the findings of other series of cases of Acanthamoeba keratitis. Especially prominent are the increase in numbers of cases, especially since 1992, the increase in numbers of patients wearing disposable contact lenses, and the decrease in diagnostic delay as the disease has become more common. This series differs from earlier ones in certain ways, particularly in the presence of contact lens wear as a predisposing factor in every case, the high proportion of patients attaining a very good visual outcome from either medical or surgical treatment, and the use of topical steroids in most cases. We have also presented results relating to contact lens cleaning and disinfection, which show a predominance of cases associated with chlorine disinfection.

The reason for the apparent increase in cases is not clear, although an obvious factor might be an increase in the number of contact lens wearers in recent years. An additional possibility is a change in the pattern of use of contact lens disinfectant systems, particularly in the case of disposable contact lenses, where the use of chlorine disinfectants has been suggested as a possible aetiological factor. Acanthamoeba cysts have been reported to be resistant to chlorine disinfection, and Acanthamoeba has been isolated from contact lens cases disinfect by this method. In this series chlorine is the most common type of disinfectant used by patients who went on to develop Acanthamoeba keratitis, and all of the cases in users of chlorine have occurred since 1992. In addition, some patients did not follow normal contact lens cleaning and disinfection procedures, either using no disinfectant or using disinfectant only seldom, or failing to use a surfactant cleaner before lens disinfection. The use of a surfactant cleaner has been shown to be an effective way of removing Acanthamoeba trophozoites and cysts. In the light of these findings further research into the types of disinfectant used by patients with Acanthamoeba keratitis is required, with a view to calculating the relative risks of different lens type and disinfectant combinations. This series also shows that it is important that contact lens practitioners should ensure at the time of prescribing lenses that patients have understood disinfectant procedures. A few patients reported occasional overnight wear of lenses, which may increase the risk of infection, since users of extended wear disposable contact lenses have been reported to have an increased risk of developing bacterial keratitis.

Another striking feature is the number of patients whose initial diagnosis was of a viral keratitis, especially herpes simplex. Increasing clinical suspicion in contact lens wearers who develop an apparent viral keratitis has led to faster diagnosis as Acanthamoeba keratitis has become more common. Our findings also confirm the therapeutic effectiveness of PHMB, since all but three eyes in our series were treated with this compound and 18/23 achieved a visual acuity of 6/6 after treatment, while only one case resulted in a post-treatment acuity of less than 6/9. Penetrating keratoplasty is likely to be necessary only where diagnosis has been delayed. The one poor visual outcome in the series occurred in a patient who was treated with PHMB only after a lengthy period of treatment with Brolene alone, by which time the eye was already severely damaged. Overall, the results show a considerable improvement on earlier experience of treating Acanthamoeba keratitis which we believe is due to the effectiveness of PHMB and to increasingly early diagnosis. We also used topical steroids in most patients, which has in the past been reported to be relatively...
contraindicated in Acanthamoeba keratitis.24 In our experience steroids have proved safe if used in moderate doses when clinical improvement has occurred after 1 to 2 weeks of antimanoebal therapy.

An encouraging feature of this series is that all nine of the eyes that have undergone penetrating keratoplasty have achieved a very good visual result, and that there has so far been only one rejection episode in one eye, which resolved quickly. A review of previous reports would not lead one to expect such a high success rate for keratoplasty in Acanthamoeba keratitis, but it should be noted that seven of these eyes were treated with PHMB (rather than other anti-amoeobal compounds) both before and after the operation, which could be expected to improve prognosis. Most of the graft failures reported in the literature were not treated with PHMB. However, the total number of patients is small and is likely to remain so, since the need for keratoplasty has diminished with earlier diagnosis, and it is therefore difficult to draw definite conclusions about the prognosis for keratoplasty.

The main recommendation that arises from this series is that an increasingly high index of suspicion is necessary in contact lens wearers who have an atypical keratitis. This is especially the case in disposable contact lens wearers and in lens wearers who have a dendriform keratitis that responds poorly to antiviral medication, as well as in other unusual forms of keratitis. We would recommend that these patients undergo epithelial sampling and culture, since this is a simple procedure, and also culture of contact lenses, lens cases, and solutions. A negative culture does not rule out Acanthamoeba keratitis, however, and in a few cases where the clinical features are suspicious a trial of PHMB for at least 2 weeks may be necessary. In patients with a definite diagnosis intensive treatment at an hourly or 2 hourly frequency should be continued until marked clinical improvement is seen, and then continued at a maintenance level for a further 4–6 months. Long term treatment is thought to be necessary to eliminate the cyst form of the amoebae which is more resistant to antiamoebal agents than the active trophozoite.11 Current treatment may be over cautious, but recurrence of infection has been noted in previous series, and therapy using topical PHMB has so far proved relatively free of toxic effects. In general, the prognosis may now be said to be very good, especially if the diagnosis is made early, when medical treatment alone is likely to be effective. It can also be concluded that penetrating keratoplasty remains a viable option in severe disease, but is now usually unnecessary except in cases of late diagnosis.

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