EDITORIAL REVIEW

# Diagnosis and management of *Acanthamoeba* keratitis
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**Purpose of review**
This paper reviews the literature generated on
*Acanthamoeba* keratitis since 1998.
**Recent findings**
*Acanthamoeba* infections may be on the rise. Contact
lenses are the biggest risk factor for their development.
Silicone hydrogel lenses are increasingly prescribed and
may be 'more sticky' to *Acanthamoeba* organisms.
Orthokeratology for the treatment of myopia has been
associated with many new cases of *Acanthamoeba*
keratitis. Daily disposable contact lenses are the safest form
of soft contact lens. Patients continue to be misdiagnosed
as having herpetic keratitis. Impression cytology and
confocal microscopy are newer diagnostic modalities.
Topical polyhexamethylene biguanide, chlorhexidine and
propamidine are the mainstay of medical therapy. Amniotic
membrane may be used for cases of persistent epithelial
defect and to control inflammation. Penetrating keratoplasty
in a medically treated eye affords a good chance of positive
outcome.
**Summary**
*Acanthamoeba* keratitis continues to be a difficult infection
to diagnose and manage. The frequency of these infections
may be on the rise, most commonly associated with
frequent replacement soft contact lenses. The best chance
for a good outcome is based on early diagnosis, so it is
important for ophthalmologists consider it in patients,
especially in the contact lens wearer with suspected herpes
simplex keratitis.

**Keywords**
*Acanthamoeba*, contact lenses, cornea, keratitis, review,
risk factors

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## Introduction
First described in the early 1970s, a dramatic increase in
cases of *Acanthamoeba* keratitis was observed in the early
to mid-1980s. This rise was associated with the increasing
use of soft contact lens wear. In 1985, the US Centers for
Disease Control issued a report [1] to alert ophthalmo-
logists about the association between contact lens wear
and this difficult infection. The use of table salt for
homemade saline solution was determined to be the
unifying risk factor for many of the initial cases in the
epidemic [2]. Despite the abandonment of this method of
disinfection, *Acanthamoeba* infections continue to occur.
Over the last 20 years, papers have identified other risk
factors, described the clinical features and course, and a
discussed multiple medical and surgical treatments,
which underscore the difficult nature of treating this
infection. Additional information about the history of
*Acanthamoeba* keratitis are nicely detailed in a review
by Schaumberg *et al.* [3]. The purpose of the present
review is to discuss this body of literature since 1998,
when excellent reviews were published [3–5].

## Epidemiology
The incidence of *Acanthamoeba* keratitis may vary based
on region and contact lens practices. In the UK, Europe,
Hong Kong and other countries with the same contact
lens fitting and hygiene, the rate of incidence is estimated
at 0.33 per 10 000 hydrogel contact lens wearers per year
[6]. No recent, similar studies from the USA exist,
although some have estimated the rate to be as high as
1 in 10 000 contact lens wearers annually [3]. In 2004 and
2005, our group noted an increased incidence of new
cases of *Acanthamoeba*, which we presented at the annual
meeting of the American Academy of Ophthalmology in
2005 [7]. The incidence of *Acanthamoeba* in rigid contact
lenses is 9.5 times lower than for soft lens wearers [6].
Recently, however, patients using rigid contact lenses for
orthokeratology have displayed high rates of *Acantha-
moeba* keratitis [8]. This body of literature is discussed
in a separate section.

## Risk factors
Contact lenses remain the most common risk factor for
development of *Acanthamoeba* keratitis. In recent series,
contact lens wear was reported in 80–86% of cases
[9•,10,11]. While compliance with contact lens hygiene
is often noted to be poor in patients who develop *Acantha-
moeba*, patients are noted in these studies who disinfect
regularly with multipurpose and hydrogen peroxide

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systems and who still develop this infection [11]. The literature surrounding contact lens disinfection varies in methodology and subsequent results may be misleading [12]. The unfortunate fact is that most commercially available contact lens-disinfection solutions are ineffective against *Acanthamoeba* [13–15].

In the last few years, silicone hydrogel lenses have become popular and accounted for 30% of new fits in 2005 [16]. The first generation of silicone hydrogel lenses, Purevision (Bausch & Lomb, Rochester, New York, USA), composed of balafilcon A, and Focus Night and Day (Ciba Vision, Duluth, Georgia, USA), composed of lotrafilcon A, were found to be very 'sticky' to trophozoites [17]. Trophozoite attachment rates with these lenses were significantly higher than with conventional hydrogel lenses. These lenses are approved for continuous-wear regimens. In a large prospective study of patients in Purevision lenses, microbial keratitis was more likely in those wearing the lenses for less than the prescribed 3–4 weeks [18]. While this study did not have any cases of *Acanthamoeba* infection, continuous-wear regimens obviate contact lens handling, cases and solutions. Thus, if these lenses are used, it is recommended that they be used in a continuous-wear fashion [19]. More recently, the same group studied the so-called second generation of silicone hydrogel lenses, Acuvue Advance (Johnson & Johnson Vision Care, New Jacksonville, Florida, USA), composed of galyfilcon A[19]. Trophozoite attachment rates for this lens were much lower than for the first generation and not statistically different from those of conventional hydrogel lenses. As such, it may be safer to use these lenses for daily wear. Further prospective studies are necessary to see what impact the shift to increased use of silicone hydrogel lenses has on the rates of *Acanthamoeba* infection.

The safest form of contact lens wear remains daily disposable lenses. There have been very few cases reported in which patients using daily disposable lenses developed *Acanthamoeba* keratitis [11]. It is unclear in these reports if the patients adhered to a strict single-use regimen, and most of these patients had additional risk factors, such as swimming in contact lenses. It is crucial to educate patients on the importance on wearing the lenses once only, avoiding the risks of problems related to inadequate disinfection and overnight wear [20].

## Orthokeratology

The practice of orthokeratology, employing a rigid contact lens to alter corneal shape and providing temporary correction of corneal power, has increased since the late 1990s, especially in Asia. Since 2001, many case reports and series have addressed infectious keratitis, especially *Acanthamoeba*, in patients using orthokeratology [8,21–27]. In a review [8] of the first 50 cases of

microbial keratitis reported in overnight orthokeratology, a surprisingly high frequency (30%) of *Acanthamoeba* was found. It is especially concerning that this practice is usually used in teenagers, with the peak incidence in the 15–19-year age range. One study estimates that 30% of those using orthokeratology are under the age of 18 years [28]. Inappropriate lens-care procedures, patient noncompliance, and wearing lenses despite discomfort were blamed for this high rate.

A large portion of the October 2005 issue of *Cornea* was dedicated to case reports and series of infections following orthokeratology from around the world [21–27]. This edition also included an editorial from a member of the US Food and Drug Administration, who reported that the agency is currently evaluating whether a post-market surveillance study is the appropriate tool for addressing the question of safety issues raised by overnight orthokeratology [28]. Any patient who is prescribed this therapy should be counseled on the associated risks of infection, including serious infections such as *Acanthamoeba*.

## Additional risk factors

Recent studies [9[•],10,11] have noted additional risk factors in 40–91% of contact lens wearers. These factors include swimming in lenses, irregular or inadequate disinfection, cleaning the lens case with tap water, minor corneal trauma, and exposure to contaminated water.

## Noncontact lens wearers

The diagnosis of *Acanthamoeba* keratitis in the noncontact lens wearer is more difficult and often takes longer, as the suspicion for this infection is usually lower [29,30]. Due to this delay in diagnosis, these patients also have worse visual outcomes. A recent case series from India presents the characteristics and outcomes of 39 noncontact lens wearers with *Acanthamoeba* keratitis who presented to one center in a 2.5-year period [31]. A predisposing factor was elicited in 19/39 (48.7%) of the patients, the most common of which was trauma. The majority of these patients were misdiagnosed as having fungal keratitis, as there are high rates of fungal keratitis found in this region. The authors note that the main differences, in this series and others, from mostly contact lens-related keratitis were the lack of severe pain and rapid progression. They hypothesize that certain isolates are responsible for noncontact lens keratitis and unique to certain geographic areas. Additional speciation and susceptibility data are necessary to confirm this possibility.

## Diagnosis

Making the diagnosis of *Acanthamoeba* is difficult. The most important step is to suspect it. *Acanthamoeba* keratitis is often mistaken for herpes simplex keratitis. It should be considered in any patient with a history of

contact lens wear and a new diagnosis of herpes simplex keratitis, especially in those with significant pain or poor response to therapy. Numerous studies have shown that a delay in diagnosis is associated with worse visual outcome and a more severe course. Once the diagnosis is suspected, confirmation is also challenging. Corneal scrapings stained with Giemsa, periodic acid–Schiff (PAS), hematoxylin & eosin, Wright's, calcofluor white, or acridine orange stains may demonstrate the cyst and trophozoite forms. *Acanthamoeba* is best cultured on nonnutrient agar overlaid with *Escherichia coli*, on which characteristic trails form as trophozoites move across the plate. Not all microbiology laboratories are willing or equipped to provide this culture. A recent, small case series [32] demonstrated the ability to make the diagnosis using impression cytology and bright-field microscopy. This eliminates a large epithelial scraping and subsequent pain. The limitations of this technique are that it is only useful in early disease and requires a willing, skilled pathologist. The diagnosis is made much more easily when the disease is in its early stages and superficial in nature. Once deeper involvement of the stroma occurs, a corneal biopsy may be necessary.

Confocal microscopy is a noninvasive tool that may aid in the diagnosis of *Acanthamoeba* and may be useful in monitoring for improvement. The cystic form of *Acanthamoeba* is more distinct and appears as a double-walled, hexagonal, hyperreflective structure that is 10–25 μm in diameter [33]. The trophozoite form is more difficult to discern, as it appears similar to normal corneal keratocyte nuclei: an ovoid, S-shaped, structure within the corneal stroma. There are different confocal microscopes available, including the Nidek ConfoScan and the Heildelberg retina tomography II (HRT II). A recent paper [34] from Brazil presents the findings from 15 eyes with *Acanthamoeba* keratitis using the Nidek ConfoScan. Cysts were easily evident at varying stromal depths. Swollen nerves were visualized, some of which were surrounded by a highly reflective area, which authors believe represent a trophozoite migrating along a nerve. A case report [35] was recently published demonstrating the findings visualized by the Heildelberg retina tomography II. This technology, which has also been prominently displayed at many research meetings over the last few years, produces impressive, high-quality images. Limitations to confocal microscopy remain its cost and lack of standardized interpretation.

We recommend initiating treatment in the cases where the clinical picture causes a strong suspicion of *Acanthamoeba* but the diagnosis cannot be confirmed.

## Treatment

This section discusses medical and surgical treatments of *Acanthamoeba* keratitis.

## Medical treatment

The treatment of *Acanthamoeba* keratitis is challenging, as the cystic form is highly resistant and may persist for years. The first medical cure was noted in the mid-1980s through the use of propamidine 0.1% (Brolene) and neomycin 1%. Since that time, the effectiveness of the cationic antiseptic agents chlorhexidine (0.02%) and polyhexamethylene biguanide (PHMB, 0.02%) has been demonstrated [36,37]. Whereas these medications are the most effective, neither is commercially available and must be obtained through compounding pharmacies. Treatment with PHMB or chlorhexidine is often combined with a diamidine, either propamidine (Brolene) or hexamidine (Desmodine). Once again, availability of these medications is an issue, as neither is commercially available or approved for usage in the USA. Propamidine is widely available over the counter in the UK and Australia, and hexamidine is available in France. It is our practice to obtain propamidine via the Internet and provide it to patients, utilizing informed consent. Other physicians direct patients on how to obtain these medications themselves. Some feel that combination therapy is out-dated and recommend intensive topical monotherapy with either chlorhexidine or polyhexamethylene biguianide [38]. Most cysts are resistant to neomycin – a medication which also has a fairly high hypersensitivity rate. Thus the use of neomycin is no longer recommended [6].

Therapy with topical PHMB (0.02%) or chlorhexidine (0.02%) with or without propamidine 0.1% should be given every hour around the clock for the first few days of treatment. Treatment is then tapered based on clinical response, but usually lasts for 2–6 months. Topical cycloplegic therapy and oral nonsteroidal drugs are helpful in the management of pain. Some also advocate the use of topical nonsteroidal drugs, although that is not our practice [6]. Narcotic analgesics are often necessary for pain control.

Many other agents have been or are being investigated for treatment of *Acanthamoeba*. Topical imidazoles, when applied in a 1% solution, are effective against trophozoites, but not against cysts [6,39]. They should never be used as monotherapy. Oral ketoconazole and, to a lesser extent, itraconazole penetrate into the cornea and are used by some practitioners as adjunctive therapy to PHMB and chlorhexidine. The levels obtained in the cornea via this route are likely too low to be even trophozoiticidal [38]. Possible new therapies include antineoplastic and antimalarial medications [6].

The question of appropriateness and timing of topical corticosteroid use to control inflammation associated with *Acanthamoeba* remains a controversial one. *In vitro*, dexamethasone phosphate inhibits encystment of

trophozoites, which may make the infection more susceptible to antiamoebic agents [40]. It has also been demonstrated that the dead cysts which persist in the cornea cause significant inflammation [41]. One retrospective study [42] showed that topical corticosteroid use was not associated with medial treatment failure, although it was associated with a prolonged course of therapy. Corticosteroids suppress the activity of the macrophage, which is essential in scavenging and destroying the amoeba [6]. Thus, in general, it is recommended to delay and limit steroid use as much as possible, utilizing it in combination with antiamoebic agents and only in those patients with severe pain, scleritis, or severe anterior-chamber inflammation [38,42,43]. In patients with severe scleral involvement, systemic immunosuppression may be necessary and has been described using oral steroids, cyclosporine, and azathioprine [44].

### Surgical treatment

Penetrating keratoplasty in eyes with active infection usually portends a poor outcome [45]. Thus it is important to make every attempt to 'quieten' the eye before a transplant is performed. Most often this is achieved via medical therapy, but some infections may be recalcitrant to all antiamoebic agents. Lamellar keratoplasty with a conjunctival flap has been successful in some patients [46]. Amniotic membrane transplantation for progressive stromal lesions with persistent epithelial defects may also be effective in controling inflammation and delaying penetrating keratoplasty [47]. Initially reported by Bourcier *et al.* [47] in 2004, we have used this technique on some of our more difficult cases, with good success. It is sometimes necessary to repeat the amniotic membrane transplantation to ensure complete reepithelialization.

Once eyes with *Acanthamoeba* are quiet, the success rate for penetrating keratoplasty is much higher [48]. A recent cases series of patients with noninflamed eyes following successful medical treatment describes excellent visual rehabilitation, with the majority of patients obtaining better than 20/40 visual acuity. Several patients did require additional glaucoma surgery, and one patient had severe loss of vision secondary to glaucoma. The authors recommend that there should be a minimum of 3 months between the discontinuation of treatment and subsequent penetrating keratoplasty.

### Conclusion

*Acanthamoeba* keratitis continues to be a difficult infection to diagnose and manage. The frequency of these infections may be on the rise, and it is most commonly associated with frequent-replacement soft contact lens wear. Overnight orthokeratology patients have also shown high rates of *Acanthamoeba*. The best chance for a good outcome is based on early diagnosis, so it is important for ophthalmologists to consider it in patients, especially in the contact lens wearer with suspected herpes simplex keratitis.

## References and recommended reading

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