What is the best therapeutic scheme for *Acanthamoeba* keratitis?

**Abstract**

*Acanthamoeba* keratitis is a sight-threatening disease that carries a favorable prognosis when diagnosed and treated early in the disease course. In some countries, the disease is more common than fungal keratitis, thus showing the importance of knowing and understanding this intriguing infection.

**Key words:** keratitis; *Acanthamoeba*; therapy.

**Relevant evidence-based information**

Amoebae of the genus *Acanthamoeba* are free-living protozoa and well known facultative human parasites that may cause granulomatous amebic encephalitis, cutaneous acanthamoebiasis, disseminated granulomatous amebic disease, and amebic keratitis, with amebic keratitis being the most common *Acanthamoeba* infection. Individuals who develop encephalitis or disseminated disease are usually immunocompromised; whereas, those with amebic keratitis are usually immunocompetent.1 *Acanthamoeba* keratitis is a sight-threatening disease that carries a favorable prognosis when diagnosed and treated early in the disease course. Keratitis is usually associated with a history of improper wearing and cleaning of contact lenses, use of contaminated lens care solutions, and swimming in fresh or swimming pool water while wearing contact lenses.2 In non–lens users *Acanthamoeba* keratitis is usually associated with trauma and exposure to contaminated water or soil, often in agricultural workers.

*Acanthamoeba* spp, one of the most common free-living amoebae, are ubiquitous eukaryotic organisms in the environment and have been isolated from soil, water (including natural and treated water), air, and dust. Most people have evidence of prior exposure to the protozoa during their lifetime as 50-100% of healthy people have serum antibodies directed against *Acanthamoeba*.1 *Acanthamoeba* genotyping is a useful tool for specific characterization at specie level and investigation of molecular clonality of the protozoan for epidemiological studies of the disease. Up to 18 genotypes designated as T1, T2, T3, etc., have been identified based on 18S rDNA gene sequencing by molecular techniques and the majority of the keratitis-causing *Acanthamoeba* isolates are genotype T4.4

*Acanthamoeba* keratitis was first described in 19755,6 but cases substantially increased in the 1980s with the introduction of disposable soft contact lenses and homemade saline solution. The estimated rates of *Acanthamoeba* keratitis vary among studies depending on the prevalence of contact lens use, the use of contact lens care systems, and exposure to contaminated water and solutions. In the United States
the rate is about 0.15 per million where as in the United Kingdom is 1.4 per million. In some countries, the incidence of *Acanthamoeba* keratitis has exceeded the incidence of fungal keratitis. *Acanthamoeba* has two forms: trophozoite and cyst (Figure 1). The trophozoite is the motile form, which is characterized by locomotion, proliferation, and feeding and has an asexual reproduction by binary fission. The cyst is the dormant form highly resistant to adverse environment, nutrient deficiency, and chemicals, and is the form responsible for persistent corneal infection.

Common symptoms of *Acanthamoeba* keratitis include foreign-body sensation, pain, redness, tearing, photophobia, blepharospasm, and blurred vision. Patients may have periods of symptom remission with a waxing and waning course. Severe pain disproportionate to the clinical signs is a hallmark of the disease, although some patients are pain free. Clinical findings of *Acanthamoeba* keratitis include epitheliochoroiditis, such as punctate keratopathy and pseudodendrites (Figure 2), epithelial or subepithelial infiltrates, epithelial ulceration, perineuritis infiltrates/perineuritis (Figure 3), ring stromal infiltrate (Figure 4), focal, multifocal and diffuse stromal infiltration, corneal abscess, corneal melt, and corneal perforation. A slit-lamp grading of corneal disease stage or depth of involvement at presentation provides a practical method to identify high-risk patients in whom clinicians should consider a more aggressive therapy. Although primarily a corneal disease, *Acanthamoeba* keratitis can present with extracorneal manifestations such as cataract, iris atrophy, glaucoma, anterior uveitis with hypopyon, scleritis, and posterior segment inflammation. *Acanthamoeba* keratitis often presents as a unilateral infection but bilateral involvement is found in 2% to 15% of cases, frequently contact lens users.

*Acanthamoeba* keratitis has been linked to a number of coinfections, including bacterial, fungal, and viral pathogens. Infectious crystalline keratopathy is one of these coinfections reported in the literature. As a primary factor in the development of infectious crystalline keratopathy in *Acanthamoeba* keratitis is the chronic corticosteroid use in the setting of a compromised ocular surface. The patients generally require surgical intervention but successful medical management is possible with early recognition of the polymicrobial disease and aggressive treatment. Anti-*Acanthamoeba* drugs have a broad spectrum of antimicrobial activity, but alone are not sufficiently prophylactic against the rise of infectious crystalline keratopathy, suggesting that the use of more effective, specific antibacterial drugs may be required in certain patients. It seems that patients with coinfection have worse outcomes in comparison to patients having only the amoebic infection.

*Acanthamoeba* trophozoites or cysts can be demonstrated with corneal scrapings or a biopsy sample by culturing method, fluorescent and histological staining techniques. Motile trophozoites may be seen in a wet-mount preparation or culture onto the non-nutrient agar seeded with avirulent and inactivated *Escherichia coli* strain. Corneal scrapings can be stained with Giemsa. The earlier detection of young and mature cystic forms of *Acanthamoeba* spp in corneal scrapings can be provided by the application of fluorescent microscopy technique using the Calcofluor White staining (Figure 5). Histological analysis of the tissue sections for detection of cysts and trophozoites include several staining techniques, for example, hematoxylin and eosin, periodic acid-Schiff and Gomori’s methenamine-silver. Polymerase chain reaction can be conducted on corneal scrapings and biopsy specimens.

In addition, tandem scanning confocal corneal microscopy is a noninvasive method also for diagnosis of *Acanthamoeba* keratitis.

**Results**

Medical therapy for *Acanthamoeba* infection is not well established but in recent years there has been great improvement in the treatment outcome with the use of some antiamebic agents. Early diagnosis and treatment are mandatory for improving outcome. Diagnostic delay usually occurs when the diagnosis is presumed to be a herpetic infection. Eradication of *Acanthamoeba* from the infection site is difficult because under adverse conditions, the amoebas encyst and medical therapy is less effective against cysts than trophozoites due to their rigid double wall. Because the cysts are the responsible for persistent infection, cidal drugs are required in the treatment. *Acanthamoeba* trophozoites are sensitive to most available chemotherapeutic agents.

The aromatic diamidines, which inhibit DNA synthesis, and the cationic antiseptics biguanides, which inhibit cell membranes, are currently the most effective cidal drugs in *vivo* and their use is supported by substantial case series.

Polyhexamethylene biguanide, PHMB (0.02% to 0.06%) and chlorhexidine (0.02% to 0.2%), for the class of biguanide, and propamidine isethionate (0.1%) and hexamidine (0.1%), for the class of diamidines, are the four drugs most used in the topical treatment of *Acanthamoeba* keratitis. Biguanides are the first-line treatment either alone as monotherapy or in combination with diamidines. Diamidines should not be used as monotherapy because they usually have high values of minimal cysticidal concentrations. Use of multiple agents has been advocated because they may have a synergic activity and greater cysticidal effect than individual drug application. However, combination therapy has the potential disadvantage of epithelial toxicity. Although *in vitro* studies have shown an additive and or synergistic effect between biguanides and diamidines, there is no clinical evidence to suggest that combined therapy is more effective than monotherapy with biguanides.

The mainstay of treatment for *Acanthamoeba* keratitis is topical therapy with biguanides (PHMB 0.02% or chlorhexidine 0.02%) and diamidines (propamidine 0.1% or hexamidine 0.1%) at a frequency of hourly day and night for the first two or three days, depending on toxicity, then reduced in frequency to hourly by day for an additional week, and then tapered as the symptoms and signs improve with the goal of maintaining topical therapy four times daily for several weeks, in an average four weeks (time that we keep the medication q.i.d, completing a total of 4 to 6 months of treatment. About 2 weeks high frequency, about 2 months tapering, and than about 4 weeks qid – total of 4 months). Some cases may not respond to the usual protocol and may present persistently positive cultures. In this situation, as a first step, we should increase the drug concentration (PHMB up to 0.06% and chlorhexidine up to 0.2%). If still no response, we should switch drugs, first the biguanides (switch between PHMB and chlorhexidine) and then the diamidines (switch between propamidine and hexamidine). Topical neomycin, frequently prescribed in the past, often encounters resistance from cysts and is no longer used. Sensitivity assays against the new antifungal voriconazole are controversial with some studies showing the drug to be active against tested strains and in resistant *Acanthamoeba* keratitis cases while some show significant *in vitro* resistance. Systemic use of antifungal drugs is then
indicated for persistently culture-positive keratitis highly resistant to usual medical therapy protocol.

The role of steroids is controversial. Animal models have shown that in the absence of antiamebic drugs, corticosteroids promote excystment of Acanthamoeba cysts and proliferation of trophozoites. Steroids may be useful for control of inflammation when administered in combination with antiamebic drugs. Corticosteroid use before diagnosis of Acanthamoeba keratitis is highly predictive of a poorer visual outcome. It has been a common practice to withhold corticosteroids until a minimum of two weeks treatment has been completed and the patient presents improvement of symptoms and signs. Mild corticosteroids (0.1% prednisolone acetate or 0.05% dexamethasone) are the first choice of corticosteroids but some cases may require stronger steroids, such as 0.1% dexamethasone or 1% prednisolone acetate to control severe inflammation. It should be kept in mind that the goal of therapy in Acanthamoeba keratitis is the eradication of viable organisms but also suppression of the inflammatory response elicited by the amoeba antigens.

It is important to discuss the dilemma of persistent inflammation against persistent infection, mainly by the fact that a negative culture result does exclude active infection and false-negative cultures are not uncommon. Several studies suggest that, in some subjects, persistent inflammation may be the result of an immune response to nonviable cysts, whereas in others it is due to viable organisms remaining in the corneal tissue. Only corneal scrapes or biopsies culture can discriminate between these two situations as clinical signs are the same, and neither polymerase chain reaction nor confocal microscopy can distinguish between viable and nonviable organisms. It is prudent to assume that the active keratitis is due to viable organisms, unless repeated microbiology is culture negative and, in these cases, the judicious and balanced use of antiamebic drugs and corticosteroids offers clue for the treatment.

The most challenging cases are those presenting persistently positive cultures after treatment with diamidines and or biguanides. It has been suggested that late diagnosis is the principal risk factor for persistently culture positive Acanthamoeba keratitis. These cases may require a susceptibility test, although a standardized method has not been established, though various methods have been reported. As an example, a recent publication on the susceptibility test of seven agents that are clinically used topically against Acanthamoeba isolates revealed that Acanthamoeba cysts were most susceptible to 5% natamycin, followed by 1% povidone-iodine, 0.05% benzalkonium chloride, 0.02% polyhexamethylene biguanide, 0.1% propamidine isethionate, and 0.02% chlorhexidine gluconate. None of the strains was susceptible to 1% voriconazole. The susceptibilities to 0.02% polyhexamethylene biguanide and 0.02% chlorhexidine gluconate may be time dependent and to 0.1% propamidine isethionate may be concentration-dependent.

Cases of scleritis associated with Acanthamoeba keratitis produce significant pain and tissue destruction, making this extracorneal manifestation one of the most challenging ocular inflammations to control. It is unknown whether the scleral inflammation has an infective or immune-mediated origin. Scleritis associated with Acanthamoeba keratitis can be treated, depending on the clinical severity, with oral nonsteroidal or steroidal anti-inflammatory drugs but some cases may require systemic immunosuppression to control the disease.

The mean duration of treatment for Acanthamoeba keratitis has been between 4 and 6 months, but there are reports in the literature with
be one of the mechanisms putting patients at risk for atypical infections such as *Acanthamoeba* keratitis. Also, patients frequently top off rather than replace their contact lens solutions; also lens cases are not replaced regularly. Patients should be counseled that overnight wear of contact lenses increases the risk of infection and that lenses should be promptly removed if there are any symptoms of ocular irritation.  

### Conclusion and Recommendations

*Acanthamoeba* keratitis usually responds to medical therapy depending on the interval between the onset of symptoms and the start of effective therapy. An interval more than four weeks of diagnosis delay compromises the disease prognosis. The mean duration of treatment for *Acanthamoeba* keratitis has been between 4 and 6 months. The role of steroids is controversial, but they should be withheld until a minimum of two weeks of antiamebic drugs has been completed and the patient presents improvements of symptoms and signs. Therapeutic keratoplasty should be indicated for cases of unresponsive medical treatment or for severe corneal complications.

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**REFERENCES**


15. Nakano E, Ohtsuki M, Portellinha W, de Freitas D, Nakano K. Therapeutic keratoplasty should be indicated for cases of unresponsive medical treatment or for severe corneal complications.