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Update on the Management of Infectious Keratitis

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Infectious keratitis is a major global cause of visual impairment and blindness, often affecting marginalized populations. Proper diagnosis of the causative organism is critical, and although culture remains the prevailing diagnostic tool, newer techniques such as in vivo confocal microscopy are helpful for diagnosing fungus and *Acanthamoeba*. Next-generation sequencing holds the potential for early and accurate diagnosis even for organisms that are difficult to culture by conventional methods. Topical antibiotics remain the best treatment for bacterial keratitis, and a recent review found all commonly prescribed topical antibiotics to be equally effective. However, outcomes remain poor secondary to corneal melting, scarring, and perforation. Adjuvant therapies aimed at reducing the immune response associated with keratitis include topical corticosteroids. The large, randomized, controlled Steroids for Corneal Ulcers Trial found that although steroids provided no significant improvement overall, they did seem beneficial for ulcers that were central, deep or large, non-*Nocardia,* or classically invasive *Pseudomonas aeruginosa*; for patients with low baseline vision; and when started early after the initiation of antibiotics. Fungal ulcers often have worse clinical outcomes than bacterial ulcers, with no new treatments since the 1960s when topical natamycin was introduced. The randomized controlled Mycotic Ulcer Treatment Trial (MUTT) I showed a benefit of topical natamycin over topical voriconazole for fungal ulcers, particularly among those caused by *Fusarium*. MUTT II showed that oral voriconazole did not improve outcomes overall, although there may have been some effect among *Fusarium* ulcers. Given an increase in nonserious adverse events, the authors concluded that they could not recommend oral voriconazole. Viral keratitis differs from bacterial and fungal cases in that it is often recurrent and is common in developed countries. The Herpetic Eye Disease Study (HEDS) I showed a significant benefit of topical corticosteroids and oral acyclovir for stromal keratitis. HEDS II showed that oral acyclovir decreased the recurrence of any type of herpes simplex virus keratitis by approximately half. Future strategies to reduce the morbidity associated with infectious keratitis are likely to be multidimensional, with adjuvant therapies aimed at modifying the immune response to infection holding the greatest potential to improve clinical outcomes. *Ophthalmology 2017;■:1–12 © 2017 by the American Academy of Ophthalmology*

Corneal disease remains the leading cause of monocular blindness worldwide, especially affecting marginalized populations.[1] Corneal opacities, which are largely caused by infectious keratitis, are the fourth leading cause of blindness globally and are responsible for 10% of avoidable visual impairment in the world's least developed countries.[2,3] Approximately 2 million people develop a corneal ulcer every year in India alone.[4,5] In the United States, infectious keratitis often is associated with contact lens wear,[6–8] but in developing countries it is more commonly caused by ocular trauma sustained during agricultural work.[9–12] In this review, we explore the current literature and future directions of the diagnosis and treatment of infectious keratitis.

Diagnostics

Proper diagnosis of keratitis is essential to determining treatment and achieving resolution of infection. The mainstay in diagnosis is still Gram stain and culture of corneal samples despite imperfect sensitivity.[13–15] Gram and Giemsa stains are advantageous because they provide instant results, with Gram stain accurately detecting the causative organism 60% to 75% of the time in bacterial cases and 35% to 90% in fungal cases. Giemsa has a sensitivity of 40% to 85% for diagnosing fungal cases.[16–18] Blood and chocolate agar are most commonly used to culture bacteria, whereas Sabouraud's agar or potato dextrose are best for isolating fungus, and non-nutrient agar with *Escherichia coli* overlay can be used to culture *Acanthamoeba*. Thioglycollate broth is another option to identify aerobic or facultatively anaerobic bacteria, but contamination is a problem, and often it is difficult to determine whether isolated organisms are the cause of infection.[19] Viral keratitis is diagnosed largely on clinical examination because of its characteristic dendritic appearance,[20] but polymerase chain reaction is sometimes used to confirm diagnosis with high sensitivity.[21]

There is still substantial room for exploration of novel methods of diagnosing infectious keratitis. In vivo confocal microscopy has grown in popularity in recent years because of its rapidity and high sensitivity in detecting larger organisms, such as filamentous fungus, acanthamoeba, and

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Nocardia bacteria (Fig 1).[22–26] Anterior segment optical coherence tomography has been used more recently to provide an objective measure of corneal infiltrate or scar size or to monitor corneal thinning during treatment.[27,28]

Bacterial Keratitis

In the United States, bacterial keratitis is most associated with contact lens use.[19] Severe cases can progress rapidly and cause permanent vision loss requiring corneal transplantation.

Antibiotics

Topical antibiotics remain the first-line treatment for bacterial keratitis. Clinicians weigh many factors when choosing an antibiotic regimen, including broad-spectrum coverage, toxicity, availability and cost, and region-specific epidemiology of pathogens and resistance patterns. Indeed, a recent international survey of cornea specialists found that concerns over several of these factors were predictive of antibiotic choice.[29]

A recent Cochrane-style review of high-quality, randomized, controlled, clinical trials on the management of bacterial keratitis with topical antibiotics identified 16 trials comparing 2 or more topical antibiotics over at least 7 days. McDonald et al[30] found no significant difference in the relative risk of treatment success defined as complete re-epithelialization of the cornea or on time to cure. Although there was an increase in the relative risk of minor adverse events, such as ocular discomfort or chemical conjunctivitis with aminoglycoside-cephalosporin compared with fluoroquinolones, there was no difference in serious complications.[30–34]

Bacterial ulcers are usually responsive to treatment with available topical antibiotic drops, an increase in the rates of antibiotic-resistant infections such as methicillin-resistant *Staphylococcus aureus* in North America has caused concern. The US Centers for Disease Control and Prevention estimates that 2 million people are infected with drug-resistant microbes each year.[35] Approximately 80% of ocular isolates of methicillin-resistant *Staphylococcus aureus* in the United States have been reported to be resistant to the most commonly prescribed antibiotic class, the fluoroquinolones.[36–38] In the Steroids for Corneal Ulcer Trial (SCUT), in vitro susceptibility was correlated with clinical outcomes.[39–41] Therefore, corneal culture and sensitivity testing are recommended for all corneal ulcers. Assessing response to treatment is critical, and if the patient appears to be worsening on treatment, one can consider switching to fortified broad-spectrum antibiotics if the initial therapy was fluoroquinolone monotherapy. However, if initial therapy was with a broad-spectrum fortified antibiotic, toxicity from the drops can become the most important factor affecting healing, and reducing therapy is often advised.

Even when bacterial ulcer pathogens are susceptible to available topical antibiotics, clinical outcomes can be poor secondary to irregular astigmatism and corneal opacity. Therefore, investigating factors that mitigate the inflammatory response to infection, which results in corneal melting and subsequent scarring, may be the way to have the greatest impact on clinical outcomes in bacterial keratitis.

Anticollagenases

During acute infection fibroblasts, keratocytes and other inflammatory cells secrete enzymes, such as collagenases and matrix metalloproteinases, that are involved in protein degradation and keratolysis. Directing therapy toward stabilization of corneal melting may reduce the incidence of severe complications of infectious keratitis, such as corneal perforation and the need for therapeutic penetrating keratoplasty. Tetracyclines have been shown to inhibit collagenase and have demonstrated antimetalloproteinase activity in vitro.[42–44] In one laboratory study, alkali-induced corneal ulceration in rabbits was dramatically reduced from 85% to 9% in those randomized to high-dose systemic tetracycline administration.[45] In another rabbit study, systemic doxycycline reduced the rate of corneal perforation in pseudomonas ulcers by approximately 50%.[46] Unfortunately, there are no high-quality randomized controlled trials in humans to guide clinicians in the use of adjuvant doxycycline for the treatment of corneal ulceration despite its widespread use among corneal specialists.

Steroids

The use of adjuvant corticosteroids has long been debated in the treatment of bacterial keratitis.[47–49] Proponents of the use of corticosteroids argue that they improve outcomes by decreasing inflammation, thereby reducing scarring, neovascularization, and stromal melt.[49–52] However, others argue that corticosteroids delay epithelial healing and may even worsen infection.[53–56]

A recent Cochrane review of adjuvant topical steroids for bacterial keratitis identified 4 randomized controlled trials comparing adjuvant steroids with topical antibiotics alone.[57] Three small randomized controlled trials examining the benefit of adjuvant topical steroids for the treatment of corneal ulcers found no difference in visual acuity outcomes or healing times between those randomized to topical antibiotic alone and those randomized to topical antibiotic plus topical steroid.[58–60] The fourth and largest randomized controlled trial to investigate the role of steroids in the treatment of bacterial ulcers to date was SCUT. SCUT was a randomized, double-masked, placebo-controlled clinical trial that compared adjunctive topical corticosteroids with placebo in the treatment of bacterial corneal ulcers.[61] A total of 500 study participants with culture-positive bacterial ulcers were enrolled at Aravind Eye Hospitals in Madurai, Coimbatore, and Tirunelveli, India, the University of California, San Francisco, and the Dartmouth-Hitchcock Medical Center in New Hampshire. Patients were randomized to receive topical prednisolone sodium phosphate 1.0% or topical placebo starting after a 48-hour course of topical moxifloxacin 0.5%.

Despite the overall data showing no difference in outcomes such as 3-month visual acuity, 3-month scar size, or rate of perforation between the corticosteroid and placebo groups, subgroup analyses suggested that corticosteroids are beneficial in certain subgroups. Patients with low vision