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Update on the Management of Infectious Keratitis

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Abstract

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 while culture remains the prevailing diagnostic tool, newer techniques such as *in vivo* confocal microscopy are helpful for diagnosing fungal keratitis and *Acanthameoba*. 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 responsible for much of the morbidity associated with keratitis include topical corticosteroids. The large, randomized controlled Steroids for Corneal Ulcers trial found that while steroids provided no significant improvement overall, they did appear beneficial for ulcers that were central, deep or large, non-*Nocardia* or classically invasive *P. aeruginosa*, 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 1960's when topical natamycin was introduced. The randomized controlled Mycotic Ulcer Treatment Trial showed a benefit of topical natamycin over topical voriconazole for fungal keratitis, particularly among those caused by *Fusarium*. The second Mycotic Ulcer Treatment Trial showed that oral voriconazole did not improve outcomes overall although there may have been some effect among *Fusarium* ulcers. Given an increase in non-serious adverse events the authors concluded that they could not recommend oral voriconazole at this time.

Viral keratitis differs from bacterial and fungal cases in that is often recurrent and is common in developed countries. The first Herpetic Eye Disease Study (HEDS) 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 HSV keratitis by approximately half.

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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.

INTRODUCTION

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 is often 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 causative organism 60–75% of the time for bacterial cases and 35–90% in fungal cases. Giemsa has a sensitivity of 40–85% for diagnosing fungal cases.[16–18] Blood and chocolate agar are most commonly used to culture bacteria, while Sabouraud's agar or potato dextrose are best for isolating fungus, and non-nutrient agar with *Escherichia Coli* overlay can be used to culture *Acanthameoba*. Thioglycollate broth is another option to identify aerobic or facultatively anaerobic bacteria, but contaminant is a problem and often it is difficult to determine if isolated organisms are the etiology of infection.[19] Viral keratitis is diagnosed largely on clinical exam because of its characteristic dendritic appearance,[20] but PCR is sometimes used to confirm diagnosis because of its high sensitivity.[21]

There is still substantial room for exploration of novel methods of diagnosing infectious keratitis. *In vivo* confocal microscopy (IVCM) has grown in popularity in recent years due to its rapidity and high sensitivity in detecting larger organisms such as filamentous fungus, acanthamoeba, and *Nocardia* bacteria [Image 1].[22–26] Anterior segment optical coherence tomography (AS-OCT) has been used more recently to provide an objective measure of corneal infiltrate and/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 can 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. The authors found no significant difference in the relative risk of treatment success defined as complete re-epithelialization of the cornea or on time to cure.[30] While 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.[30–33,34]

Although 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* (MRSA) in North America has caused concern. The United States Center for Disease Control (CDC) estimates that 2 million people are infected with drug resistant microbes each year.[35] Approximately 80% of ocular isolates of MRSA in the US 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.[39,40,41] Therefore, corneal culture and sensitivity testing is 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. On the other hand, if initial therapy was with a broad-spectrum fortified antibiotic, toxicity from the drops can become the most important factor impacting 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.

Anti-collagenases

During acute infection fibroblasts, keratocytes and other inflammatory cells secrete enzymes such as collagenases and matrix metalloproteinases (MMPs) 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 reducing 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 four randomized controlled trials comparing adjuvant steroids to 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 versus 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 the Steroids for Corneal Ulcers Trial (SCUT). SCUT was a randomized, double-masked, placebo-controlled clinical trial that compared adjunctive topical corticosteroids to placebo in the treatment of bacterial corneal ulcers.[61] Five hundred 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 at the Dartmouth-Hitchcock Medical Center in New Hampshire. Patients were randomized to receive either 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, sub-group analyses suggested that corticosteroids are beneficial in certain subgroups. Patients with low vision (counting fingers or worse) at baseline had 1.7 lines better vision at 3 months in the corticosteroid group compared to the placebo group (P=0.03). Central ulcers, covering the central 4-mm pupil, that were treated with corticosteroids also had better 3-month BSCVA compared with placebo (approximately 2 lines better; P=0.02). Similarly patients with deep ulcers at baseline fared better with topical steroids (1.5 lines better; P=0.07). Timing of steroid administration also proved to be a significant factor, with patients randomized to corticosteroids after only 2–3 days of antibiotics having better BSCVA at 3 months than those randomized to placebo (approximately 1 line better BSCVA; P=0.01).[62]

Evidence from SCUT subgroup analyses also revealed organism subtype to be an important factor to consider when initiating adjuvant topical steroids in bacterial ulcers. *Nocardia,* a partially acid-fast atypical bacteria, represented 10% of all ulcers in SCUT. *Nocardia* ulcers randomized to corticosteroids had 0.40 mm larger infiltrate or scar size at 3 months compared with placebo (P=0.03), although this did not result in worse 3-month BSCVA

(*P*=0.21) [Figure 1].[63] This trend continued at 12 months, with non-*Nocardia* ulcers faring better with corticosteroids (1 line improvement of BSCVA; *P*=0.02) and *Nocardia* ulcers faring worse (average scar size increased by 0.47mm; *P*=0.02; no difference in BSCVA).[64] Overall, *Pseudomonas aeruginosa* ulcers did not benefit from the addition of corticosteroids, however the classically invasive subtype of *P. aeruginosa* demonstrated 2.5 lines of visual acuity improvement at 3-month BSCVA when randomized to steroids versus placebo [Figure 2].[65]

The authors of the Cochrane review concluded that there was not enough evidence to support the use of adjuvant steroids, given that of the four trials reviewed only SCUT was sufficiently powered.[57] Given the findings of these subgroup analyses it is our practice to administer adjuvant topical steroids in culture positive non-*Nocardia* bacterial keratitis starting 48 hours after the administration of appropriate topical antibiotics. Confirmation of the findings of the SCUT subgroup analysis is required with a well-designed randomized controlled clinical trial.

FUNGAL KERATITIS

Fungal ulcers often have worse outcomes than bacterial ulcers, and there is little evidence to guide treatment.[66] Fungal keratitis represents a relatively small percentage of infectious keratitis cases in regions with temperate climates, however in tropical climates it can cause up to 50% of infectious ulcers.[66–68] Contact lens wear has been identified as a risk factor for fungal keratitis in the United States and an outbreak of *Fusarium* keratitis among contact lens wearers was related to the ReNu Moisturelоc contact lens solution.[69–72] There have been no new FDA approved treatments since natamycin, a topical polyene, was introduced in the 1960's.

Topical Treatments

Effective treatment with topical natamycin 5% is limited by its poor penetration into the corneal stroma.[73] Topical amphotericin B 0.3% to 0.5% is an alternative, but its use requires access to a compounding pharmacy and is limited by toxicity. Voriconazole, a newer generation triazole, has gained popularity in the treatment of fungal keratitis due to its excellent ocular penetration.[74] In addition, in one *in vitro* study, voriconazole was the only drug tested in which 100% of fungal isolates commonly implicated in keratitis were susceptible.[75]

The first Mycotic Ulcer Treatment Trial (MUTT I) was a double-masked, randomized controlled clinical trial that compared topical natamycin and topical voriconazole in the treatment of filamentous fungal ulcers.[76] Smear-positive moderate fungal ulcers were enrolled and randomized to receive either 1% topical voriconazole or 5% topical natamycin. After enrollment of 323 patients, the Data Safety and Monitoring Committee (DSMC) recommended stopping the trial because those randomized to topical voriconazole had a statistically significant increase in the rate of corneal perforation and/or therapeutic penetrating keratoplasty (TPK) than those randomized to natamycin (*P*=0.009).[76] Those randomized to topical natamycin also had on average 1.8 lines better BSCVA at 3 months compared to the voriconazole group (*P*=0.006).[76] This difference was particularly notable

among *Fusarium* ulcers which had 4-lines better BSCVA if randomized to natamycin instead of voriconazole ($P<0.001$)[Figure 3].[76] Three-month scar size was smaller for *Fusarium* ulcers treated with natamycin than those treated with voriconazole (coef = −1.02 mm; $P<0.001$), but not for non-*Fusarium* ulcers (coef = −0.17 mm; $P=0.42$).[76] However, a higher percentage of patients were culture positive for fungus on day 6 of treatment in the voriconazole group than in the natamycin group regardless of the organism suggesting that voriconazole is inferior to natamycin in the treatment of all fungi ($P<0.001$).[76]

The results of MUTT I show a benefit of natamycin over voriconazole for topical treatment of fungal keratitis, and in particular for *Fusarium* keratitis. These results have been confirmed by a second randomized clinical trial[77] and a recent Cochrane review.[78]

Oral Voriconazole

Although topical voriconazole failed to show improved outcomes compared with natamycin, there are several reasons that oral voriconazole may have efficacy in the treatment of fungal keratitis. First, intermittent dosing of topical medications may result in intervals of sub-therapeutic drug levels and oral medications may provide more steady-state drug levels at the site of infection. One study comparing aqueous samples after topical and oral voriconazole found that topical administration of voriconazole resulted in highly variable aqueous concentrations with troughs well below the MIC90 for most fungi while oral voriconazole provided therapeutic drug level that remained relatively constant.[79] Of note, in many case reports of successful treatment with topical voriconazole, oral and/or intravenous voriconazole was used in conjunction with the topical medication.[80,81]

The Mycotic Ulcer Treatment Trial II (MUTT II) was a double-masked, randomized, placebo-controlled clinical trial investigating the effect of adjuvant oral voriconazole versus oral placebo for smear positive filamentous fungal keratitis.[82] There was no difference in the primary outcome, rate of perforation and/or need for TPK, between the two arms at 3 months (HR 0.82; $P=0.29$).[82] There was also no difference in secondary outcomes such as visual acuity ($P=0.77$), scar size ($P=0.35$), rate of re-epithelialization ($P=0.65$). There were significantly more adverse events in the oral voriconazole group including elevations in aspartate aminotransferase or alanine aminotransferase ($P=0.003$) and visual disturbances ($P=0.03$) than patients in the placebo group.[82]

A subsequent subgroup analysis did find a possible benefit to oral voriconazole in *Fusiarum* ulcers.[82] Other potential adjuvant treatments for fungal keratitis include intracameral injection of amphotericin with or without hypopyon drainage [83–86,87] or intrastromal injection of voriconazole.[88–90] However, more study of these techniques with well-designed randomized controlled trials is necessary to determine their benefit. Therefore, at this time, topical natamycin remains the most evidence-based treatment for filamentous fungal keratitis and oral voriconazole should be considered if the organism is *Fusarium*.

VIRAL KERATITIS

Herpes simplex virus (HSV) keratitis affects an estimated 500,000 people in the United States and an estimated 1.5 million globally.[91] It is the most common cause of unilateral

infectious corneal blindness in much of the developed world.[92] Viral keratitis differs from bacterial and fungal keratitis in that it can become chronic and recurrent. Besides being a painful, sight-threatening infection, HSV keratitis has been shown to significantly impact quality of life even when patients are not experiencing an active infection.[93] Less common forms of viral keratitis include varicella-zoster virus (VZV) keratitis, and cytomegalovirus (CMV) keratitis.

Topical Treatments

Topical treatments for viral keratitis include antiviral medications and adjuvant topical corticosteroids. The topical antiviral trifluridine is the most commonly prescribed topical antiviral medication for HSV keratitis in the United States.[94] While it is effective in treating HSV keratitis, it has low bioavailability and causes ocular surface toxicity, so its use has become more limited as newer topical antivirals are developed.[95] Topical acyclovir is the first line treatment for HSV keratitis in Europe as it has been shown to be just as effective as trifluridine with less ocular surface toxicity. Unfortunately, it is unavailable in the United States. Ganciclovir is a newer synthetic medication with more broad-spectrum antiviral coverage. In addition to treating HSV and VZV keratitis, topical ganciclovir is also effective in treating keratitis caused by CMV.[96] Ganciclovir has been shown to be just as effective as acyclovir, while causing less ocular toxicity. It may also be less likely to promote drug resistance.[96,97] Northwestern University is currently conducting a large randomized controlled trial investigating ganciclovir for the treatment of VZV keratitis (NCT02382588).

Topical corticosteroids are also sometimes used as adjuvant therapy to topical antivirals. The Herpetic Eye Disease Study I (HEDS I) evaluated the effectiveness of corticosteroids in treating HSV stromal keratitis. In this randomized controlled trial 106 patients with active HSV stromal keratitis were randomized to receive either topical prednisolone phosphate or placebo, tapered over a 10 week period. All patients received topical trifluridine. HEDS I found that the median time to treatment failure was drastically shorter in the placebo group: 17 days in the placebo group and 98 days in the topical steroids group ($P<0.001$).[98] Time to resolution of infection was significantly shorter in the group receiving topical corticosteroids, with a median of 26 days for those taking corticosteroids and 72 days for those taking placebo ($P<0.001$). Visual acuity at 6 months was similar across groups.

Oral Treatments

The HEDS I trial also investigated adjuvant oral acyclovir as a treatment for HSV stromal keratitis. One hundred and four patients receiving both topical trifluridine and corticosteroids were randomized to receive 200mg oral acyclovir or placebo, to be taken 5 times daily for 10 weeks.[99] Although the investigators found that oral acyclovir delayed treatment failure (from 62 days in the placebo group to 84 days in the acyclovir group), this result was not statistically significant ($P=0.46$). Oral acyclovir did result in a statistically significant improvement in BSCVA at 6 months ($P=0.04$) but the importance of this result is hard to determine given that there was a relatively large difference in baseline BSCVA between groups. Oral acyclovir has also been shown to be efficacious against VZV keratitis and the results of HEDS I are often applied similarly to its treatment.

Valacyclovir, a newer antiviral, is well tolerated and there is some evidence that it may have better ocular penetration.[100,101] Additionally, the treatment dose for valacyclovir is 1g three times daily, as opposed to acyclovir which is 400mg five times daily (800mg five times daily for VZV), which aids in patient compliance. Oral valganciclovir is the preferred treatment for CMV stromal keratitis, but it has significant side effects, including aplastic anemia, which must be closely monitored.[102]

In our practice we generally use oral antivirals to avoid ocular toxicity that can complicate topical therapy and obscure the clinical picture. We reserve topical medications for adjuvant treatment when oral medications are not adequate or in patients who are not good candidates for systemic therapy.

Prophylaxis

HEDS II examined the prolonged use of oral acyclovir for recurrent ocular HSV. This large, multi-center, randomized, placebo-controlled trial, found that ocular HSV recurrence was 45% lower in the acyclovir group, with 19% in the acyclovir group experiencing recurrence and 32% in the placebo group experiencing recurrence by 12 months ($P<0.001$).[103]

Herpes zoster ophthalmicus (HZO) is caused by reactivation of VZV after a primary infection. Since the introduction of routine varicella vaccination in children there has been an increased incidence of HZO which has been attributed to a lack of passive natural immune boost against the virus.[104] At this time the recommendation is to vaccinate all older adults with the zoster vaccine to prevent HZO and other zoster infections. The Zoster Eye Disease Study will investigate the extended use of oral valacyclovir for the prophylaxis of VZV keratitis.

FUTURE DIRECTIONS

Next Generation Sequencing

Culture negative keratitis remains a significant problem for clinicians. At Aravind Eye Hospital in India, for example, 38% of corneal scrapings from eyes with presumed infectious keratitis tested negative on both culture and smear between 2002 and 2012.[105] Next Generation Sequencing (NGS) may improve on the diagnostic accuracy of infectious keratitis, particularly for organisms that are difficult to culture by conventional methods such as atypical or anaerobic bacteria.[106] NGS can detect more organisms that traditional culture techniques, and provide us with large volumes of information about the microbiome of the ocular surface. However, it is not clear whether these approaches can be used to effectively determine the etiology of infection or antibiotic sensitivity data.[107]

Collagen Cross-Linking for Bacterial and Fungal Keratitis

Collagen cross-linking (CXL) is a treatment in which photo-chemically activated riboflavin promotes the formation of covalent bonds between collagen molecules in the cornea. CXL helps strengthen corneal tissue, and is currently used to treat keratoconus and other corneal ectatic disorders.[108–111] CXL may be beneficial in the treatment of infectious ulcers due to

its direct antimicrobial effects and its potential to improve the cornea's resistance to enzymatic degradation.[112]

In vitro studies have shown UV-A light plus riboflavin to be effective against many bacterial pathogens that cause corneal ulcers.[113] Additionally, a number of case reports have shown CXL to be potentially beneficial in the treatment of recalcitrant bacterial and fungal keratitis, with effects including improvement of symptoms, the halting of progressive melting, and the resolution of treatment-resistant infections.[107,114–116] One small case series treated 16 patients with bacterial keratitis exclusively with CXL.[117] Fourteen of those patients' ulcers resolved with no further treatment; only 2 required topical antibiotics to clear the infection. If CXL could be used in place of antibiotic treatment this could help treat drug resistant infections and avoid ocular surface toxicity that currently can complicate the treatment of bacterial ulcers.

There is less robust evidence to support the use of CXL in treating filamentous fungal keratitis. *In vitro* CXL alone has not been shown to inactivate fungus, although one *in vitro* study did find CXL plus amphotericin to improve inhibition of fungal pathogens over amphotericin alone.[113,118] Though there is not as much evidentiary support for using CXL to treat fungal keratitis, it is already in use in conjunction with antifungals by some clinicians hoping that it might add any benefit given the poor prognosis for fungal ulcers.

To date, three prospective clinical trials have been conducted to assess the effect of CXL in the treatment of infectious keratitis. Bamdad et al randomized 32 patients with moderate bacterial keratitis to receive either CXL plus standard therapy or standard therapy alone.[119] Two weeks after the treatment, those receiving CXL had a lower mean grade of ulcer (0.69 vs 1.70; P=0.001), smaller area of epithelial defects (P=0.001), and smaller area of infiltrate (P<0.001) than those receiving the standard therapy alone. Mean treatment duration was also shorter in the CXL group (P<0.001).

Another trial randomized patients with bacterial, fungal, *Acanthamoeba*, or mixed origin keratitis to CXL versus antimicrobial treatment alone.[120] While this trial found no difference between groups, it had multiple issues, including inappropriate randomization, inclusion of patients with any kind of keratitis, and insufficient power.[121] A third, small randomized clinical trial investigated cross-linking as adjuvant therapy for deep fungal ulcers at Aravind Eye Hospital in Madurai, India suggested that CXL could increase the rate of perforation in fungal ulcers.[122]

Given the limitations of these clinical trials and mixed results, it is not known whether CXL is a beneficial adjuvant therapy for infectious keratitis. To date, the strongest case currently can be made for the use of CXL in treating bacterial keratitis. A larger scale, well-designed randomized clinical trial is needed in order to fully assess the utility of CXL for the treatment of infectious keratitis.

CONCLUSION

Despite having appropriate antimicrobial treatments for most of the pathogens implicated in infectious keratitis, clinical outcomes are often poor. Strategies to reduce the morbidity

associated with this condition are likely going to have to be multidimensional involving corneal ulcer prevention, improved early and accurate diagnostics techniques such as next generation sequencing as well as novel antimicrobial agents to address the development of drug resistance. Adjuvant therapies that focus on modifying the immune response to the infection thereby reducing the corneal melting and scarring which ultimately leads to poor vision, may have the greatest potential to improve clinical outcomes.

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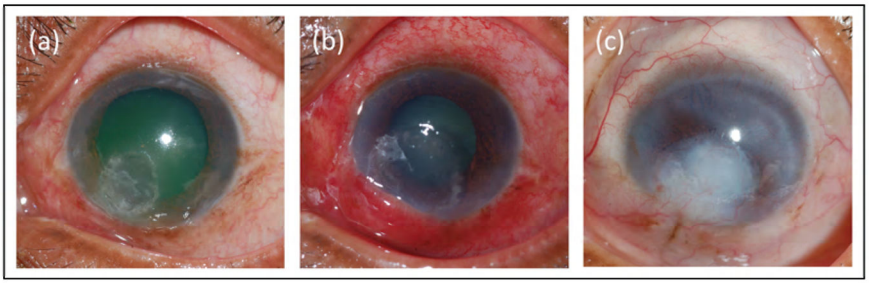

Figure 1.

A 64-year-old male manual laborer enrolled in SCUT whose ulcer was culture positive for *Nocardia* was randomized to adjuvant corticosteroids. (a) at enrollment his visual acuity was logMAR 1.2 (Snellen ~ 20/317); (b) at 3 weeks his visual acuity was logMAR 1.46 (Snellen ~20/577); (c) at 12 months his visual acuity continued to decline to 1.9 logMAR (Snellen LP).

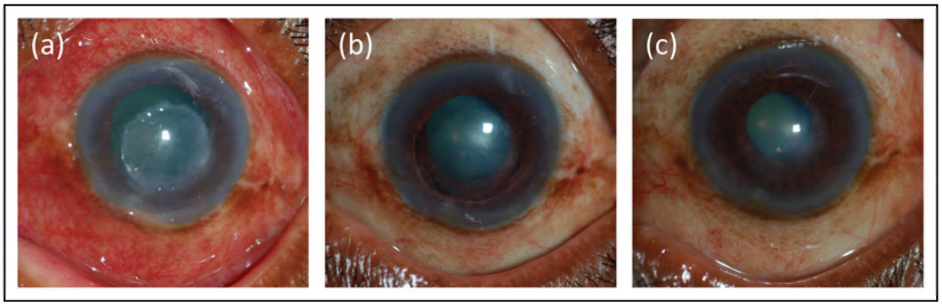

Figure 2.

A 67-year-old male manual laborer enrolled in SCUT whose ulcer was culture positive for *Pseudomonas aeruginosa* was randomized to adjuvant corticosteroids. (a) at enrollment his visual acuity was logMAR 1.7 (Snellen CF); (b) at 3 weeks his visual acuity was logMAR 0.62 (Snellen ~20/83); (c) at 12 months his visual acuity further improved to 0.24 logMAR (Snellen ~20/35) with contact lens over refraction.

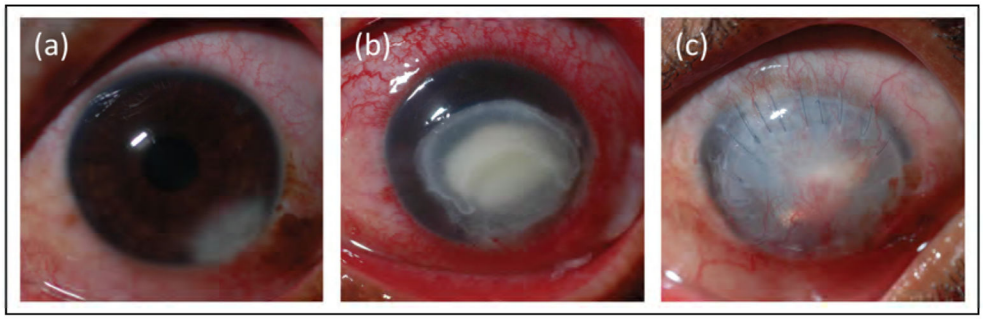

Figure 3.

A 32-year-old male tractor driver enrolled in MUTT I whose ulcer was culture positive for *Fusarium* was randomized to receive topical voriconazole. (a) at enrollment his visual acuity was logMAR 0.1 (Snellen ~20/25); (b) at 3 weeks his visual acuity was logMAR 1.8 (Snellen HM); (c) at 3 months he had perforated and undergone therapeutic penetrating keratoplasty, and his resulting visual acuity was logMAR 1.9 (Snellen LP) with contact lens over refraction.

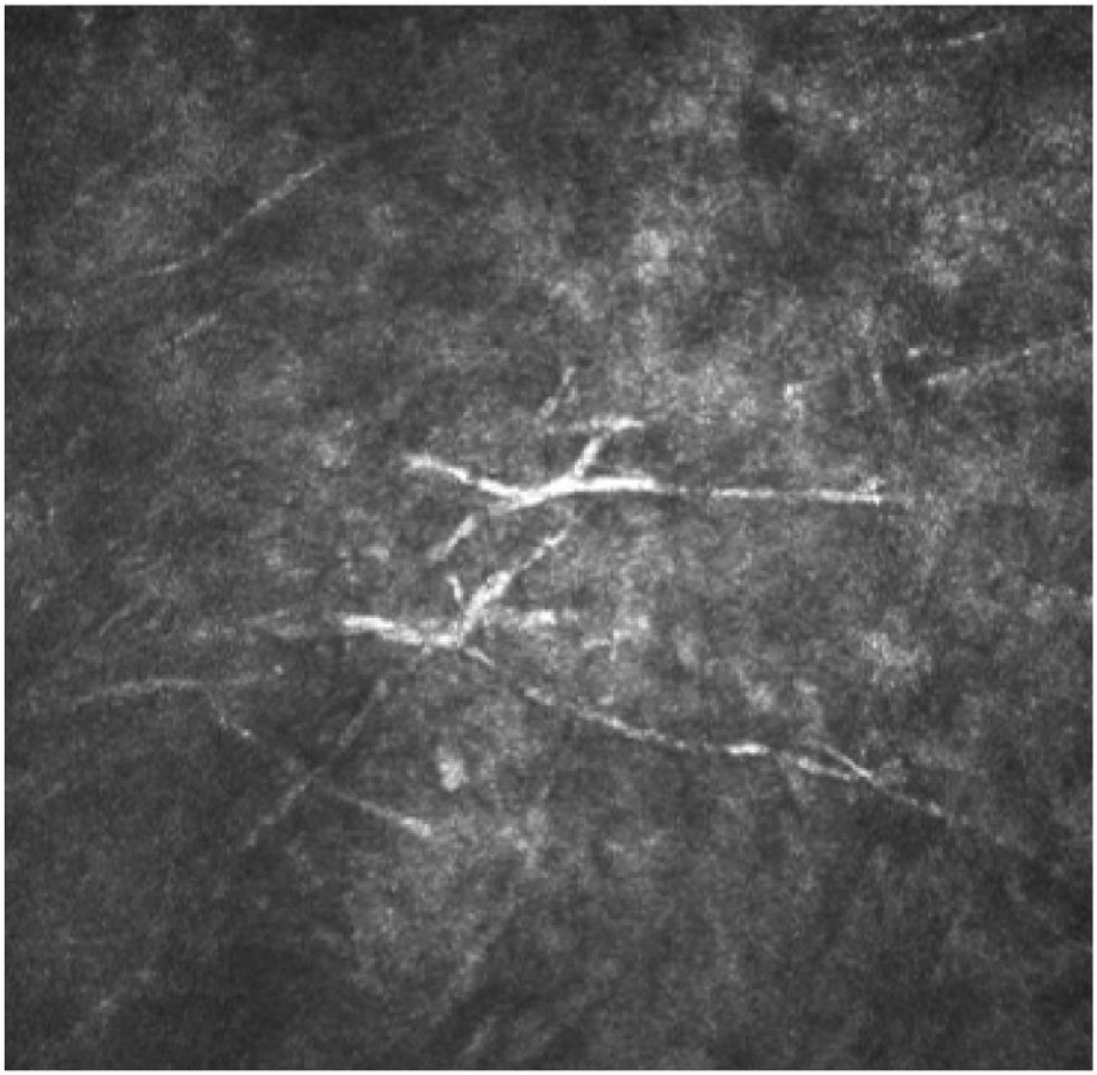

Image 1.
Confocal microscopy image from a patient with filamentous fungal keratitis.

Table 1a

Relevant randomized clinical trials (English-language, full text available online)

	Trial	Question	*N*	Finding	Comment
	Bacterial Keratitis				
Antibiotic Treatment Trials	Constantinou et al., 2007[31]	Moxifloxacin vs ofloxacin vs tobramycin/cefazolin	229	All treatments resulted in similar outcomes and rates of adverse events	Single-masked, vague primary outcome
	Dehghani et al., 2009[124]	Cefazolin/gentamicin vs vancomycin/ceftazidime	89	Vancomycin/ceftazidime led to better outcomes and was better tolerated	Randomization method unclear, masking method unclear
	Hyndiuk et al., 1996[33]	Ciprofloxacin vs tobramycin/cefazolin	324	Both treatments resulted in similar outcomes, but ciprofloxacin resulted in fewer adverse events and less discomfort	No intent to treat analysis, uneven enrollment between arms
	Kasetsuwan et al., 2011[126]	Levofloxacin vs cefazolin/amikacin	71	Both treatments resulted in similar outcomes and rates of adverse events	Low baseline culture positivity, no intent to treat analysis, enrolled exclusively in Thailand *
	O'Brien et al., 1995[32]	Ofloxacin vs tobramycin/cefazolin	248	Both treatments resulted in similar outcomes, but ofloxacin led to less discomfort	No intent to treat analysis
	Panda et al., 1999[128]	Ofloxacin vs tobramycin/cefazolin	30	Both treatments resulted in similar outcomes and rates of adverse events	Small sample size, randomization method unclear, enrolled exclusively in Southeast Asia *
	Parmar et al., 2006[129]	Gatifloxacin vs ciprofloxacin	104	Gatifloxacin resulted in complete healing more often than ciprofloxacin, and was more effective against	Enrolled exclusively in India *
	Pavesio et al., 1997[34]	Ofloxacin vs gentamicin/cefuroxime	122	Both treatments resulted in similar outcomes but ofloxacin resulted in less toxicity	Partially unmasked, enrolled exclusively in the United Kingdom *
	Prajna et al., 2001[130]	Ofloxacin vs ciprofloxacin	217	Both treatments resulted in similar outcomes and rates of adverse events	Vague primary outcome, enrolled exclusively in South India *
	Shah et al., 2010[131]	Moxifloxacin vs gatifloxacin vs tobramycin/cefazolin	61	All treatments resulted in similar outcomes and rates of adverse events	Unmasked, small sample size, low baseline culture positivity, enrolled exclusively in India *
	Sharma et al., 2013[132]	Moxifloxacin vs tobramycin/cefazolin	224	Both treatments resulted in similar outcomes and rates of adverse events	Single-masked, unclear inclusion criteria, randomization allocation, and statistical analysis, enrolled exclusively in India *
Adjuvant Steroid Trials	Blair et al., 2011[58]	Adjuvant steroids vs placebo	30	Both treatments resulted in similar outcomes and rates of adverse events	Small sample size, conflicting results based on measurement methodology, enrolled exclusively in Canada *

	Trial	Question	*N*	Finding	Comment
	Carmichael et al., 1990[59]	Adjuvant steroids vs standard therapy	40	Both treatments resulted in similar outcomes and rates of adverse events	Small sample size, enrolled exclusively in South Africa *
	Srinivasan et al., 2009[60]	Adjuvant steroids vs placebo	42	Both treatments resulted in similar outcomes and rates of adverse events	Small sample size, enrolled exclusively in India *
	SCUT[61]	Adjuvant steroids vs placebo	500	No benefit of steroids overall; steroids did improve outcomes for those with low vision, central ulcers, deep ulcers, non-*Nocardia* or classically invasive *P. aeruginosa* ulcers, or early steroid administration	Enrolled few contact lens-related infections and enrolledexclusively in Southeast Asia *

* results may not be generalizable

Table 1b

Relevant randomized clinical trials (English-language, full text available online)

Trial	Question	*N*	Finding	Comment
Fungal Keratitis				
Prajna et al., 2010[133]	Topical natamycin vs topical voriconazole	120	No significant difference between treatments	Enrolled exclusively in India *
MUTT I[76]	Topical natamycin vs topical voriconazole	323	Natamycin resulted in better BSCVA and fewer adverse events	Enrolled no contact lens-related infections and all patients were enrolled in South India *
Sharma et al., 2015[77]	Topical natamycin vs topical voriconazole	118	Natamycin resulted in better BSCVA and fewer adverse events	Enrolled exclusively in India *
MUTT II[82]	Adjuvant oral voriconazole vs placebo	240	No benefit of adjuvant oral voriconazole	Only enrolled severe ulcers, enrolled few contact lens-related infections and all patients were enrolled in Southeast Asia *, regimen of topical drops changed during trial
Viral Keratitis				
HEDS I[98]	Adjuvant topical steroids vs placebo	106	Adjuvant corticosteroids resulted in faster resolution of infection and longer time to treatment failure	Only studied stromal HSV keratitis so unclear if results apply to other types of ocular HSV
HEDS I[99]	Adjuvant oral acyclovir vs placebo	104	Oral acyclovir did not improve time to treatment failure, but did improve BSCVA at 6 months over placebo	Only studied stromal HSV keratitis so unclear if results apply to other types of ocular HSV
HEDS II[103]	Prophylactic oral acyclovir vs placebo	703	Prophylactic oral acyclovir resulted in lower rates of recurrence	Unclear how results should be applied to superficial ocular HSV
Future Directions				
Bamdad et al., 2015[119]	Adjuvant CXL vs standard therapy for moderate bacterial keratitis	32	Adjuvant CXL shortened the treatment course and resulted in improved outcomes	Small sample size, investigator was partially unmasked, enrolled exclusively in Iran *
Said et al., 2014[120]	Adjuvant CXL vs standard therapy for bacterial, fungal, *Acanthamoeba*, or mixed keratitis	40	No benefit of adjuvant CXL	Inappropriate randomization, inclusion of multiple types of keratitis and mixed keratitis, small sample size, enrolled exclusively in Egypt *
Uddaraju et al., 2015[122]	Adjuvant CXL vs standard therapy for deep fungal keratitis	13	Adjuvant CXL resulted in an increased rate of perforation	Small sample size, inclusion of only severe fungal ulcers, enrolled exclusively in South India *

* results may not be generalizable