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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*,



sically invasive *Pseudomonas aeruginosa*; for patients with low baseline vision; a  
early after the initiation of antibiotics. Fungal ulcers often have worse clinical outc



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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.

### Abbreviations and Acronyms:

[BSCVA](#) (best spectacle-corrected visual acuity), [CMV](#) (cytomegalovirus), [CXL](#) (collagen cross-linking), [HEDS](#) (Herpetic Eye Disease Study), [HSV](#) (herpes simplex virus), [HZO](#) (herpes zoster ophthalmicus), [logMAR](#) (logarithm of the minimum angle of resolution), [MUTT](#) (Mycotic Ulcer Treatment Trial), [SCUT](#) (Steroids for Corneal Ulcer Trial), [VZV](#) (varicella-zoster virus)

Corneal disease remains the leading cause of monocular blindness worldwide, especially affecting marginalized populations.<sup>1</sup> 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.<sup>2, 3</sup> Approximately 2 million people develop a corneal ulcer every year in India alone.<sup>4, 5</sup> In the United States, infectious keratitis often is associated with contact lens wear,<sup>6, 7, 8</sup> but in developing countries it is more commonly caused by ocular trauma sustained during agricultural work.<sup>9, 10, 11, 12</sup> 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.

↔ Mainstay in diagnosis is still Gram stain and culture of corneal samples despite imprecise



sensitivity.<sup>13, 14, 15</sup> 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.<sup>16, 17, 18</sup> 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.<sup>19</sup> Viral keratitis is diagnosed largely on clinical examination because of its characteristic dendritic appearance,<sup>20</sup> but polymerase chain reaction is sometimes used to confirm diagnosis with high sensitivity.<sup>21</sup>

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 *Nocardia* bacteria (Fig 1).<sup>22, 23, 24, 25, 26</sup> 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.<sup>27, 28</sup>

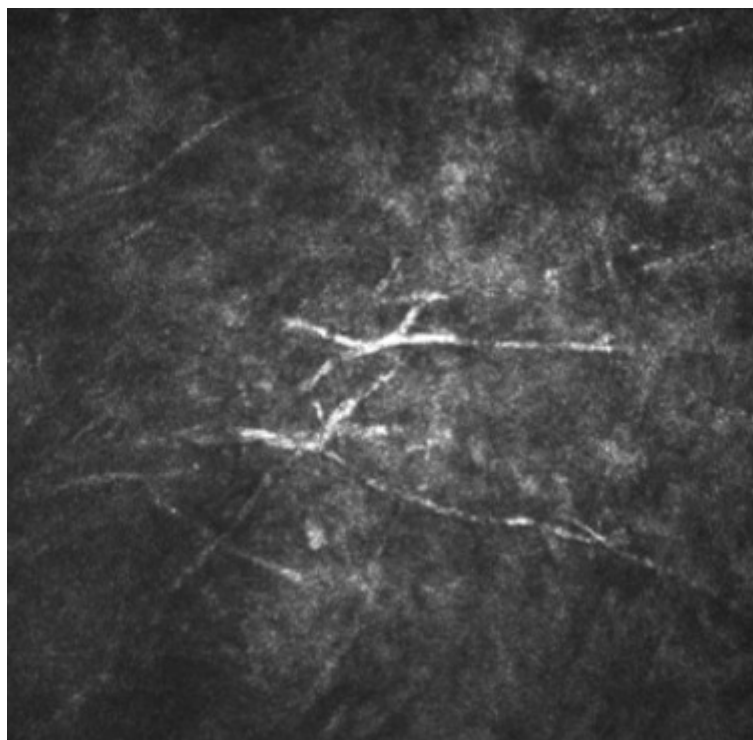


Figure 1 Confocal microscopy image from a patient with filamentous fungal keratitis.



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## Bacterial Keratitis

In the United States, bacterial keratitis is most associated with contact lens use.<sup>19</sup> 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.<sup>29</sup>

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<sup>30</sup> 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.<sup>30, 31, 32, 33, 34</sup>

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.<sup>35</sup> 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.<sup>36, 37, 38</sup> In the Steroids for Corneal Ulcer Trial (SCUT), in vitro susceptibility was correlated with clinical outcomes.<sup>39, 40, 41</sup> 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.<sup>42, 43, 44</sup> 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.<sup>45</sup> In another rabbit study, systemic doxycycline reduced the rate of corneal perforation in pseudomonas ulcers by approximately 50%.<sup>46</sup> 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.<sup>47, 48, 49</sup> Proponents of the use of corticosteroids argue that they improve outcomes by decreasing inflammation, thereby reducing scarring, neovascularization, and stromal melt.<sup>49, 50, 51, 52</sup> However, others argue that corticosteroids delay epithelial healing and may even worsen infection.<sup>53, 54, 55, 56</sup>

A recent Cochrane review of adjuvant topical steroids for bacterial keratitis identified 4 randomized controlled trials comparing adjuvant steroids with topical antibiotics alone.<sup>57</sup> 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.<sup>58, 59, 60</sup> 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.<sup>61</sup>

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,

; Dartmouth-Hitchcock Medical Center in New Hampshire. Patients were randomi

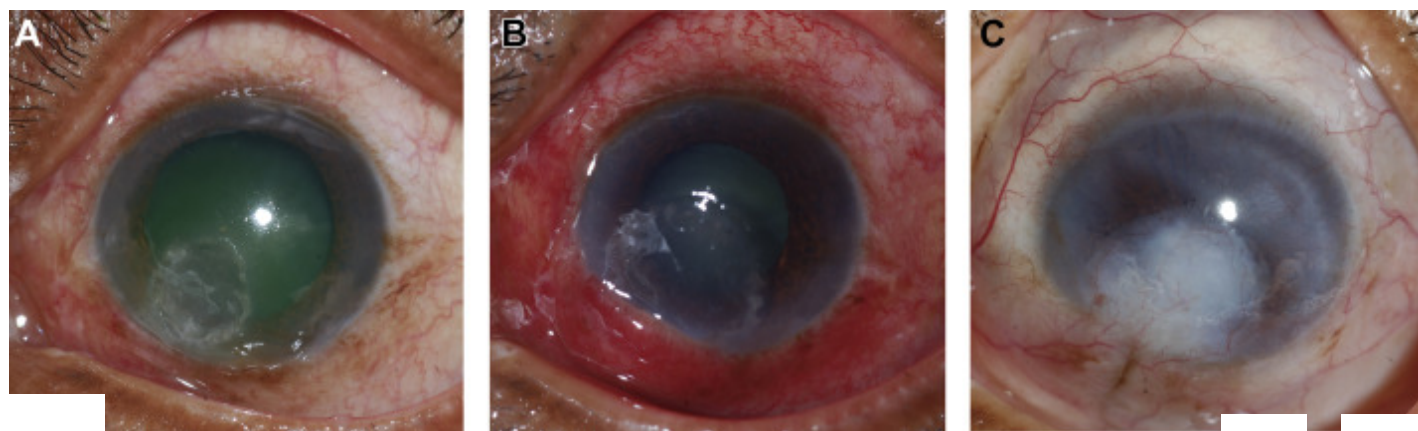
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topical prednisolone sodium phosphate 1.0% or topical placebo starting after a 48-hour course of topical moxifloxacin 0.5%.

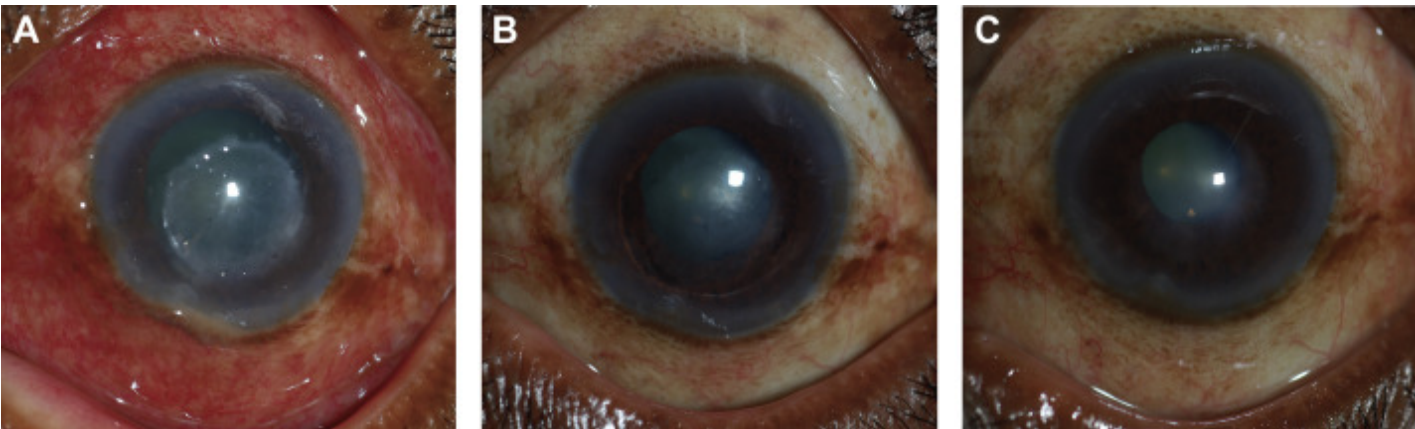
Despite the overall data showing no difference in outcomes such as 3-month visual acuity, 3-month scar size, or rate of perforation between the corticosteroid and placebo groups, subgroup analyses suggested that corticosteroids are beneficial in certain subgroups. Patients with low vision (counting fingers or worse) at baseline had 1.7 lines better vision at 3 months in the corticosteroid group compared with the placebo group ( $P = 0.03$ ). Central ulcers, covering the central 4-mm pupil, that were treated with corticosteroids also had better 3-month best spectacle-corrected visual acuity (BSCVA) compared with placebo ( $\sim 2$  lines better;  $P = 0.02$ ). Likewise, 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 to 3 days of antibiotics having better BSCVA at 3 months than those randomized to placebo ( $\sim 1$  line better BSCVA;  $P = 0.01$ ).<sup>62</sup>

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 ( $P = 0.21$ ) (Fig 2).<sup>63</sup> 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 0.47 mm;  $P = 0.02$ ; no difference in BSCVA).<sup>64</sup> 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 (Fig 3).<sup>65</sup>



**Figure 2** A 64-year-old male manual laborer enrolled in the Steroids for Corneal Ulcer Trial (SCUT) whose ulcer was culture positive for *Nocardia* was randomized to adjuvant corticosteroids. **A**, At enrollment, his visual acuity was logarithm of the minimum angle of resolution (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 light perception).

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**Figure 3** A 67-year-old male manual laborer enrolled in the Steroids for Corneal Ulcer Trial (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 counting fingers). **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.

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The authors of the Cochrane review concluded that there was not enough evidence to support the use of adjuvant steroids, given that of the 4 trials reviewed, only SCUT was sufficiently powered.<sup>57</sup> 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. A summary of relevant randomized clinical trials for bacterial ulcers can be found in [Table 1](#).

**Table 1** Relevant Randomized Clinical Trials



	Sharma et al, 2013 <sup>129</sup>	Moxifloxacin vs. tobramycin/cefazolin	224	Both treatments resulted in similar outcomes and rates of adverse events
	Blair et al, 2011 <sup>58</sup>	Adjuvant steroids vs. placebo	30	Both treatments resulted in similar outcomes and rates of adverse events
Adjuvant steroid trials	Carmichael et al, 1990 <sup>59</sup>	Adjuvant steroids vs. standard therapy	40	Both treatments resulted in similar outcomes and rates of adverse events
	Srinivasan et al, 2009 <sup>60</sup>	Adjuvant steroids vs. placebo	42	Both treatments resulted in similar outcomes and rates of

\* Results may not be generalizable.

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## Fungal Keratitis

Fungal ulcers often have worse outcomes than bacterial ulcers, and there is little evidence to guide treatment.<sup>66</sup> 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

<sup>36, 67, 68</sup> 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

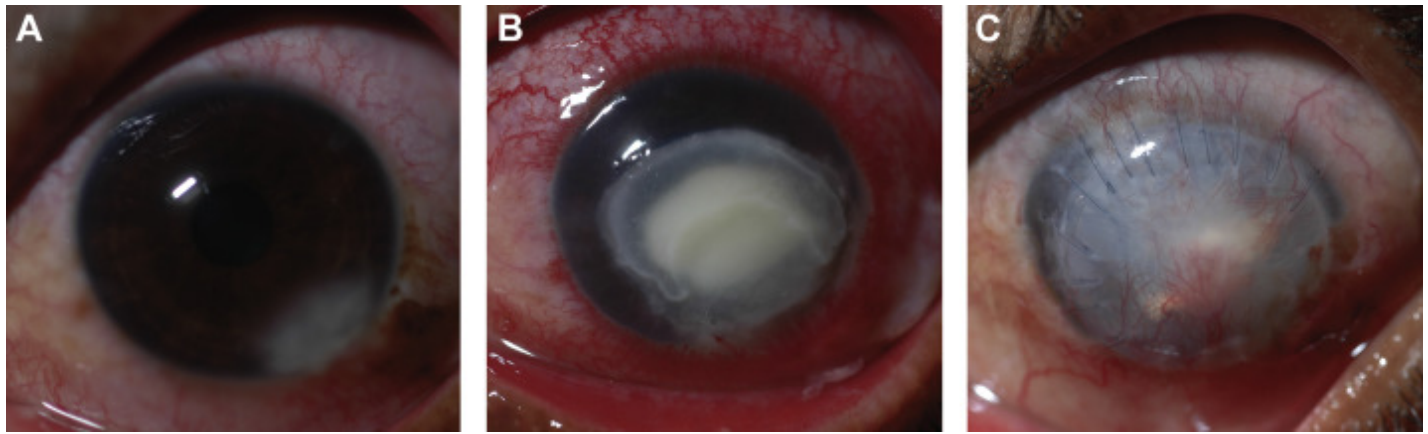


MoistureLoc (Bausch & Lomb, Rochester, NY) contact lens solution.<sup>69, 70, 71, 72</sup> There have been no new Food and Drug Administration–approved treatments since natamycin, a topical polyene, was introduced in the 1960s.

## Topical Treatments

Effective treatment with topical natamycin 5% is limited by its poor penetration into the corneal stroma.<sup>73</sup> 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 because of its excellent ocular penetration.<sup>74</sup> In addition, in an in vitro study by Walsh et al,<sup>75</sup> voriconazole was the only drug tested in which 100% of fungal isolates commonly implicated in keratitis were susceptible.

The MUTT I was a double-masked, randomized controlled clinical trial that compared topical natamycin and topical voriconazole in the treatment of filamentous fungal ulcers.<sup>76</sup> Smear-positive moderate fungal ulcers were enrolled and randomized to receive 1% topical voriconazole or 5% topical natamycin. After enrollment of 323 patients, the Data Safety and Monitoring Committee recommended stopping the trial because those randomized to topical voriconazole had a statistically significant increase in the rate of corneal perforation or therapeutic penetrating keratoplasty than those randomized to natamycin ( $P = 0.009$ ).<sup>76</sup> Those randomized to topical natamycin also had on average 1.8 lines better BSCVA at 3 months compared with the voriconazole group ( $P = 0.006$ ).<sup>76</sup> This difference was particularly notable among *Fusarium* ulcers, which had 4-lines better BSCVA if randomized to natamycin instead of voriconazole ( $P < 0.001$ ) (Fig 4).<sup>76</sup> Three-month scar size was smaller for *Fusarium* ulcers treated with natamycin than those treated with voriconazole (coefficient =  $-1.02$  mm;  $P < 0.001$ ), but not for non-*Fusarium* ulcers (coefficient =  $-0.17$  mm;  $P = 0.42$ ).<sup>76</sup> 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 ( $P < 0.001$ ).<sup>76</sup>



**Figure 4** A 32-year-old male tractor driver enrolled in the Mycotic Ulcer Treatment Trial 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 hand motions). **C**, At 3 months, he had perforated and undergone therapeutic penetrating keratoplasty, and his resulting visual acuity was logMAR 1.9 (Snellen light perception) with contact lens over refraction.

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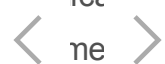
The results of the Mycotic Ulcer Treatment Trial I show a benefit of natamycin over voriconazole for topical treatment of fungal keratitis, and in particular for *Fusarium* keratitis. These results have been confirmed by a second randomized clinical trial<sup>77</sup> and a recent Cochrane review.<sup>78</sup>

## 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 subtherapeutic 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 minimum inhibitory concentration at which 90% of fungal isolates are inhibited (MIC90). In contrast, oral voriconazole provided therapeutic drug levels that remained relatively constant.<sup>79</sup> Of note, in many case reports of successful treatment with topical voriconazole, oral or intravenous voriconazole was used in conjunction with the topical medication.<sup>80, 81</sup>



Mycotic Ulcer Treatment Trial II was a double-masked, randomized, placebo-controlled trial evaluating the effect of adjuvant oral voriconazole versus oral placebo for smear-positive



fungal keratitis.<sup>82</sup> There was no difference in the primary outcome, rate of perforation, or need for therapeutic penetrating keratoplasty between the 2 arms at 3 months (hazard ratio, 0.82;  $P = 0.29$ ).<sup>82</sup> There was also no difference in secondary outcomes, such as visual acuity ( $P = 0.77$ ), scar size ( $P = 0.35$ ), and 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 in the placebo group.<sup>82</sup>

A subsequent subgroup analysis did find a possible benefit to oral voriconazole in *Fusarium* ulcers.<sup>82</sup> Other potential adjuvant treatments for fungal keratitis include intracameral injection of amphotericin with or without hypopyon drainage<sup>83, 84, 85, 86, 87</sup> or intrastromal injection of voriconazole.<sup>88, 89, 90</sup> However, further 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 adjuvant oral voriconazole should be considered if the organism is *Fusarium* (Table 2).

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## Table 2 Relevant Randomized Clinical Trials

Trial	Question	N	Finding	Comment
<i>Fungal Keratitis</i>				
Prajna et al, 2010 <sup>130</sup>	Topical natamycin vs. topical voriconazole	120	No significant difference between treatments	Enrolled exclusively in India*
MUTT I <sup>76</sup>	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 <sup>77</sup>	Topical natamycin vs. topical voriconazole	118	Natamycin resulted in better BSCVA and fewer adverse events	Enrolled exclusively in India*
MUTT II	Adjuvant oral		No benefit of	Only enrolled severe ulcers, enrolled few contact lens-related infections, all

BSCVA = best spectacle-corrected visual acuity; CXL = collagen cross-linking; HEDS = Herpetic Eye Disease Study; HSV = herpes simplex virus; MUTT = Mycotic Ulcer Treatment Trial.

\* Results may not be generalizable.

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## Viral Keratitis

Herpes simplex virus (HSV) keratitis affects an estimated 500 000 people in the United States and an estimated 1.5 million globally.<sup>91</sup> It is the most common cause of unilateral infectious corneal

in much of the developed world.<sup>92</sup> 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 affect quality of life even when patients are not experiencing an active infection.<sup>93</sup> 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.<sup>94</sup> Although trifluridine 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.<sup>95</sup> Topical acyclovir is the first-line treatment for HSV keratitis in Europe because 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 also is effective in treating keratitis caused by CMV.<sup>96</sup> Ganciclovir has been shown to be just as effective as acyclovir, while causing less ocular toxicity. It also may be less likely to promote drug resistance.<sup>96, 97</sup> Northwestern University is currently conducting a large randomized controlled trial investigating ganciclovir for the treatment of VZV keratitis ([NCT02382588](https://clinicaltrials.gov/ct2/show/study/NCT02382588)).

Topical corticosteroids are sometimes used as adjuvant therapy to topical antivirals. The Herpetic Eye Disease Study (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 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 ( $P < 0.001$ ).<sup>98</sup> 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

HEDS I also investigated adjuvant oral acyclovir as a treatment for HSV stromal keratitis. A total of 104 patients receiving both topical trifluridine and corticosteroids were randomized to receive 200 mg oral acyclovir or placebo, to be taken 5 times daily for 10 weeks.<sup>99</sup> 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 visual acuity at 6 months (from 20/400 to 20/200).

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 been shown to be efficacious against VZV keratitis, and the results of HEDS I often are applied similarly to its treatment.

Valacyclovir, a newer antiviral, is well tolerated, and there is some evidence that it may have better ocular penetration.<sup>100, 101</sup> In addition, the treatment dose for valacyclovir is 1 g 3 times daily, as opposed to acyclovir, which is 400 mg 5 times daily (800 mg 5 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.<sup>102</sup>

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, multicenter, 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 ( $P < 0.001$ ).<sup>103</sup>

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 that has been attributed to a lack of passive natural immune boost against the virus.<sup>104</sup> 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 (Table 2).

## 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.<sup>105</sup> Next-generation sequencing may improve on the



stic accuracy of infectious keratitis, particularly for organisms that are difficult to c



conventional methods, such as atypical or anaerobic bacteria.<sup>106</sup> Next-generation sequencing can detect more organisms than 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 cause of infection or antibiotic sensitivity data.<sup>107</sup>

## Collagen Cross-Linking for Bacterial and Fungal Keratitis

Collagen cross-linking (CXL) is a treatment in which photochemically activated riboflavin promotes the formation of covalent bonds between collagen molecules in the cornea. Collagen cross-linking helps strengthen corneal tissue and is currently used to treat keratoconus and other corneal ectatic disorders.<sup>108, 109, 110, 111</sup> Collagen cross-linking may be beneficial in the treatment of infectious ulcers because of its direct antimicrobial effects and its potential to improve the cornea's resistance to enzymatic degradation.<sup>112</sup>

In vitro studies have shown ultraviolet-A light plus riboflavin to be effective against many bacterial pathogens that cause corneal ulcers.<sup>113</sup> A number of case reports have shown CXL to be potentially beneficial in the treatment of recalcitrant bacterial and fungal keratitis, with effects including the improvement of symptoms, the halting of progressive melting, and the resolution of treatment-resistant infections.<sup>107, 114, 115, 116</sup> One small case series treated 16 patients with bacterial keratitis exclusively with CXL.<sup>117</sup> 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.<sup>113, 118</sup> Although there is not as much evidentiary support for using CXL to treat fungal keratitis, it is already used in conjunction with antifungals by some clinicians hoping that it might add any benefit given the poor prognosis for fungal ulcers.

To date, 3 prospective clinical trials have been conducted to assess the effect of CXL in the treatment of infectious keratitis. Bamdad et al<sup>119</sup> randomized 32 patients with moderate bacterial keratitis to receive CXL plus standard therapy or standard therapy alone.<sup>119</sup> 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



Mean treatment duration was 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.<sup>120</sup> Although 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.<sup>121</sup> A third, small randomized clinical trial that 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.<sup>122</sup>

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 ([Table 2](#)). A larger-scale, well-designed randomized clinical trial is needed to fully assess the utility of CXL for the treatment of infectious keratitis.

## Conclusions

Despite having appropriate antimicrobial treatments for most of the pathogens implicated in infectious keratitis, clinical outcomes often are 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, and 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 that ultimately lead to poor vision, may have the greatest potential to improve clinical outcomes.


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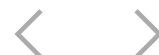
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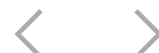
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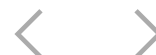
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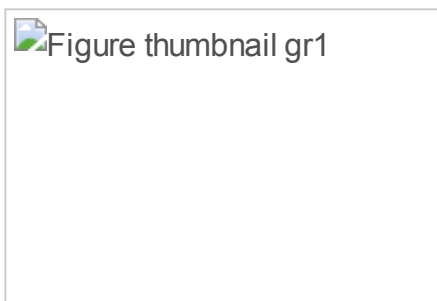
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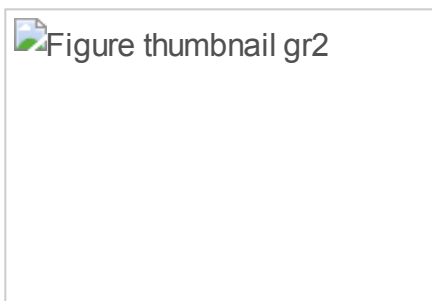
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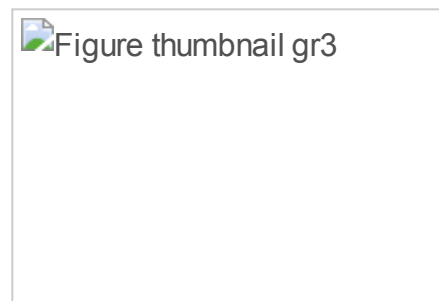
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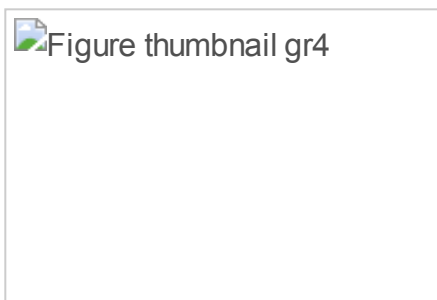
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**Figure 2** A 64-year-old mal...



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**Figure 4** A 32-year-old mal...

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**Table 2: Relevant Randomized Clinical Trials**

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