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Steroids in the management of infectious keratitis

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Introduction

The key objective of infectious keratitis treatment is to clear the causative organism with appropriate antimicrobial therapy. However, corneal infections are invariably accompanied by a host immune response, leading to corneal scarring, corneal thinning, corneal neovascularization, and subsequent vision loss. Corticosteroids are a consideration in the management of infectious keratitis given their potent anti-inflammatory activity, which in theory could reduce corneal scarring and thinning and improve visual outcomes, while concomitantly reducing ocular pain and discomfort. However, use of corticosteroids in infectious keratitis is controversial. In vitro studies have found that corticosteroids can promote growth of certain pathogens, and some animal studies have reported worse clinical outcomes when corticosteroids were administered in the absence of appropriate antimicrobial therapy. Moreover, topical corticosteroids can result in ocular hypertension and other adverse effects. The indications for topical corticosteroids in the management of infectious keratitis have been more definitively established for some clinical situations than others. As reviewed here, the role of corticosteroids depends to a large extent on the causative pathogen and the efficacy and timing of antimicrobial therapy.

Bacterial Keratitis

The role of corticosteroids for bacterial keratitis was once highly controversial.[1] Animal models demonstrated that corticosteroids used in the absence of antibiotics could promote the growth of some organisms, including *Pseudomonas aeruginosa*.[2] Observational clinical studies found that patients treated with topical corticosteroids prior to diagnosis of bacterial keratitis had worse clinical outcomes, including perforation and penetrating keratoplasty.[1] Animal and human studies investigating the impact of corticosteroids when instituted after starting antibiotic therapy had mixed results, with some showing worse clinical outcomes and others showing no difference or better outcomes.[1] Several preliminary randomized trials

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found no difference in those treated with steroids, although these studies could not provide a definitive answer due to their small sample size.[3–5]

The Steroids for Corneal Ulcers Trial (SCUT) was a large double-masked randomized trial funded by the National Eye Institute that greatly expanded the understanding of the role of corticosteroids for bacterial keratitis.[6] In SCUT, participants with culture-positive bacterial keratitis who had received ≥48 hours of hourly topical moxifloxacin were randomized to a 3-week course of prednisolone sodium phosphate, 1%, or to an identical-appearing placebo eye drop, with each applied 4 times daily for 1 week, then 2 times daily for 1 week, then once daily for 1 week. Of 500 participants enrolled, the vast majority (n=485) were from the Aravind Eye Care System in South India, and very few (n=8) were contact lens wearers. The pre-specified primary outcome, best spectacle corrected visual acuity at 3 months, was not significantly different between treatment arms (−0.009 logMAR, 95%CI −0.085 to 0.068 [i.e., less than a 1-letter difference, with 95% confidence interval ranging from approximately 4 letters better in the steroid group to 3 letters worse]).[6] Scar size at 3 months was also not significantly different between the two arms (0.06 mm larger in steroid group, 95%CI −0.07 to 0.17). Time to re-epithelialization was likewise not significantly different (hazard ratio [HR] 0.92, 95%CI 0.76–1.12), although more participants had an epithelial defect at 21 days in the steroid group (18% vs. 11%; $P = 0.04$). Importantly, rates of serious adverse events such as perforation were not different between the two treatment arms, although IOP elevations were more likely in those who received placebo.

Several pre-specified subgroup analyses of SCUT added evidence regarding which types of bacterial keratitis might be likely to benefit from institution of topical corticosteroids. In general, ulcers with worse severity at presentation were more likely to benefit from steroids. For example, steroids were beneficial for central ulcers (~ 2 lines better; $P = 0.02$), deep ulcers (~1.5 lines better for those with involvement of the posterior third of the cornea; $P = 0.07$), large ulcers (~1.5 lines better for largest quartile; $P = 0.07$), and ulcers with poor vision (~1.5 lines better for those with a baseline visual acuity of Counting Fingers or worse; $P = 0.03$).[6] The effect of steroids was similar for the *Pseudomonas* keratitis subgroup, with similar vision outcomes compared with other pathogens and no increase in corneal perforation (2% of *Pseudomonas* ulcers perforated in each group).[7] In contrast, steroids appeared to be harmful when administered for *Nocardia* keratitis in SCUT, with a 3-month scar size 0.4 mm larger in the *Nocardia* group ($P = 0.03$) and 3-month visual acuity ~1.5 lines worse ($P = 0.21$).[8] Another subgroup analysis suggested that steroids may be more effective when given earlier in the treatment course: steroids resulted in a 1-line improvement in 3-month visual acuity in the subgroup given study drug 2–3 days after starting antibiotics ($P = 0.01$), but not in the subgroup given study drug ≥ 4 days after starting antibiotics (1 line worse in steroid group, $P = 0.14$).[9]

Although the primary outcomes of SCUT were at 3 months, participants were also monitored at 12 months. Overall, results of the secondary 12-month endpoint were similar to the primary 3-month outcomes. However, in non-pre-specified analyses, non-*Nocardia* ulcers treated with steroids experienced a 1-line improvement in 12-month visual acuity (95%CI 2-letter to 2-line improvement; $P = 0.02$) and a slight but non-significant reduction in scar size (−0.06 mm, 95%CI −0.21 to 0.10; $P = 0.46$) relative to the placebo group.[10]

Thus, when synthesizing the available data, SCUT did not demonstrate a benefit of topical corticosteroids for culture-proven bacterial keratitis in its primary pre-specified analyses, but several pre-specified and non-prespecified subgroup analyses suggest that steroids may have a benefit when used promptly (i.e., within 2–3 days) for ulcers not due to *Nocardia*, and especially for severe ulcers (i.e., large, deep, central ulcers).

An ongoing randomized trial will expand on the findings of SCUT. The SCUT II trial (clinicaltrials.gov NCT04097730) is a double-masked trial enrolling patients with bacterial keratitis due to typical bacteria (i.e., not due to *Nocardia* or *Mycobacteria*) with moderate to severe vision loss (i.e., 20/40 or worse). Participants are treated with moxifloxacin and then randomized to one of three groups: difluprednate 0.05%, corneal crosslinking (i.e., ultraviolet-A and riboflavin) plus difluprednate 0.05%, or neither. (Topical placebo and sham crosslinking are provided to the treatment groups not randomized to these treatments to maintain masking.) Part of the rationale of the crosslinking arm stems from the possibility that crosslinking may immediately reduce the burden of organisms, thus making corticosteroid therapy safer.[11] Compared with SCUT I, the steroids in SCUT II are administered at a higher concentration and started 24 hours earlier.

Fungal keratitis

Corticosteroids are thought to be detrimental in the management of fungal keratitis by the vast majority of ophthalmologists, although the evidence base for this belief is weak. No randomized trials have assessed the role of corticosteroids for fungal keratitis, so current practice patterns are based on the results of in vitro studies, animal studies, and observational studies of humans.[12]

Animal models have been the primary source of evidence regarding the role of corticosteroids for fungal keratitis. Corticosteroids have been shown to promote fungal growth in the animal cornea when used without antifungals. Indeed, animal models often require local application of a corticosteroid in order to establish and maintain a fungal infection, and several studies have shown greater rates of fungal keratitis – both for molds and yeast – in animals treated with steroids.[13, 14] Recovery of fungal organisms has been shown to be greater when animals are pre-treated with subconjunctival triamcinolone, with consistent findings for *Candida*, *Aspergillus*, and *Fusarium* keratitis.[15] Corticosteroids have also been shown to alter outcomes of antifungal treatment in animal models, especially when used before antifungal therapy or at the same time antifungal therapy is started or when used at higher concentrations:

- In one study of *Candida albicans* keratitis in rabbits, eyes were treated with antifungal medications 10 times per day for 48 hours, and then the corneas were removed and the efficacy of treatment assessed by measuring the number of colony forming units (CFU) recovered in culture.[16] *Candida* recovery was greatly reduced when ulcers were treated with amphotericin B, and moderately reduced when treated with natamycin. In experiments in which prednisolone acetate 1% was used four times daily in addition to the antifungals, the steroid did not affect the antifungal activity of amphotericin B 0.5% or amphotericin B

0.15%, but non-significantly reduced the efficacy of amphotericin B 0.075%, and significantly reduced the efficacy of natamycin.

- In a different rabbit study, *Aspergillus* keratitis was treated with 5% pimaricin and 2% potassium iodide every 2–3 hours, and the effect of varying concentrations of dexamethasone, 4 times daily, were assessed.[17] Dexamethasone at higher concentrations (0.1% and 0.01%) initially reduced the signs of inflammation but eventually (i.e., from days 12–19) led to an increase in ulcer size and worsening inflammation. In contrast, a low concentration of dexamethasone (0.001%) resulted in less corneal inflammation compared with eyes treated with antifungals alone, and did not cause progression of the ulcer over 19 days of observation.
- In a study of *C albicans* keratitis in rabbits, ulcers treated with topical fluconazole 10 times per day were allocated to early-, mid-, or late-onset steroids (i.e., started at the same time as the antifungal, 6 days later, or 12 days later, respectively).[18] After 3 weeks of treatment, *C albicans* was recovered from approximately two-thirds of eyes given early-onset steroids, one-third of eyes given mid- or late-onset steroids, and one-fifth of control eyes not treated with steroids. Corneal clouding initially decreased in the early steroid group, but then increased after a week of therapy. Corneal clouding and neovascularization were lowest in the group receiving steroids 6 days after fluconazole.

Human studies that have investigated the role of corticosteroids on fungal keratitis have mostly been observational studies of risk factors, and have shown that use of topical steroids prior to diagnosis of fungal keratitis is associated with poorer outcomes.[19] Case series have demonstrated that abrupt discontinuation of topical steroids in a patient with fungal keratitis can lead to inflammatory complications including perforation.[20, 21] Few studies have reported on patients intentionally treated with topical corticosteroids following a diagnosis of fungal keratitis, although one retrospective study reported use of topical steroids in 16 patients with fungal keratitis, started a mean of 42 days (range 13–100 days) after starting topical antifungal therapy, and found recurrence in only one patient.[22, 23] Adjuvant steroid therapy has typically been avoided for fungal keratitis in trials studying the efficacy of antifungal medications or surgical procedures such as crosslinking.[24, 25] Some have advocated treating inflammation with topical calcineurin inhibitors such as cyclosporine or tacrolimus instead of steroids, especially given in vitro reports demonstrating that cyclosporine inhibits growth of several species of *Fusarium*.[26] However, human studies of calcineurin inhibitors for fungal keratitis are limited.[27] The role of corticosteroids after therapeutic penetrating keratoplasty (TPK) for fungal keratitis is unclear since steroids may help prevent immune rejection but may also increase the risk of recurrent infection. Several reports advocate withholding steroids for 1–2 weeks after surgery and only instituting steroid treatment if no signs of recurrent infection have developed during that period.[28] In one case series that started steroids 1 week post-TPK, only 3 of 244 (1%) eyes had a recurrence of infection.[29] Despite the lack of research, the vast majority of clinicians refrain from using steroids in fungal keratitis.

Amoebic keratitis

The role of corticosteroids remains controversial for acanthamoeba keratitis. Acanthamoeba has a biphasic life cycle, with a dormant cyst form that is resistant to treatment, and a motile, replicating trophozoite form. In vitro studies have shown that application of dexamethasone causes excystment of acanthamoeba cysts into the trophozoite form, and marked proliferation of trophozoites.[30] Animal studies of acanthamoeba keratitis have found that systemic steroids administered during the first week of infection resulted in longer and more severe infections, and that topical steroids increased the severity of keratitis in animals inoculated with a mixture of acanthamoeba and *P aeruginosa*.[30, 31] These animal studies suggest caution when using topical corticosteroids for acanthamoeba keratitis.

Several relatively large observational studies of humans have shown poorer outcomes for patients that received topical corticosteroids prior to antiamoebic therapy, although poorer outcomes have not been demonstrated for patients started on corticosteroids after institution of antiamoebic agents. For example, a British study of 174 eyes with acanthamoeba keratitis found that steroid use prior to diagnosis was associated with a nearly 4-fold increased risk of poor outcomes (OR 3.9, 95%CI 1.8–8.6).[32] However, a multivariable analysis of 129 eyes from the same institution found that corticosteroids started after diagnosis were not associated with poor outcomes (OR 1.1, 95%CI 0.4–3.0; median time to starting steroids: 16 days after antiamoebics, interquartile range 4–33 days).[33] A similar result was found in a study of 65 eyes from Chicago, which found that disease severity at presentation was significantly associated with a poor outcome, but post-diagnosis corticosteroid use was not.[34] This latter study found a strong relationship between post-diagnosis corticosteroid use and poor outcomes in the univariable analysis, suggesting that corticosteroid use is very likely subject to confounding by indication. Topical corticosteroids have also been used for acanthamoeba sclerokeratitis. In one report of 36 eyes with acanthamoeba scleritis, topical corticosteroids were effective for controlling pain and inflammation in approximately one-third of cases.[35] Systemic steroids or other immunosuppressive agents were required in the remaining two-thirds of cases. Other retrospective case series have also documented that corticosteroids can be effective for relief of pain, even allowing for withdrawal of narcotics.[36] Most clinicians start topical corticosteroids when treating acanthamoeba keratitis with oral miltefosine, since this anti-amoebic agent has been reported to cause an exuberant inflammatory response.[37] In addition, some routinely start topical corticosteroids after the newly described surgical procedure of Rose Bengal Photodynamic Antimicrobial Therapy (RB-PDAT), although others insist on withholding steroids after this treatment (personal communication, Guillermo Amescua).[38] The evidence base for miltefosine and RB-PDAT – including the benefit of adjuvant steroids and their optimal timing, duration, and dosing – is weak. In general, although it is unclear if and when it is safe to start topical corticosteroids, some reports have suggested waiting for at least 2 weeks following initiation of anti-amoebic therapy with a biguanide agent.[33] A randomized trial would be helpful to clarify the role of topical corticosteroids in acanthamoeba keratitis.

Viral keratitis

Although a wide variety of viruses can cause corneal infections, this discussion is limited to the human herpes viruses and adenoviruses, which are among the most common viral causes of keratitis and are frequently treated with steroids.

Human herpes viruses

Unlike nonviral causes of keratitis, herpes viruses are never cleared from the body but instead establish latency. The host immune system is important for keeping the virus in check, but reactivation of latent virus remains a possibility. For example, in the case of herpes simplex virus (HSV), the virus establishes latency in the trigeminal ganglion. Reactivation is common, leading to retrograde viral shedding along the trigeminal nerve.[39] Reactivated virus can be found in the corneal epithelium, stroma, and endothelium.[40] The host immune response is responsible for clearing virus, but can also result in white blood cell infiltration, edema, and vascularization of the cornea. Thus, the immunosuppressive activity of corticosteroids is a double-edged sword, helping prevent inflammatory complications but also making it more difficult to clear actively replicating virus. Indeed, the use of corticosteroids for herpetic keratitis was once controversial. Case reports published in the 1950s and 1960s—before the era of effective antiviral therapy—found that corticosteroids delayed healing of epithelial keratitis and led to more severe stromal keratitis.[41] Later case series demonstrated that topical corticosteroids may predispose to development of geographic ulcers.[42] However, other case series found that corticosteroids could improve corneal clarity when used with concomitant antiviral therapy. Definitive evidence was provided by a randomized trial performed from 1989 to 1992 as part of the Herpetic Eye Disease Study (HEDS).

HEDS consisted of a series of double-masked randomized trials designed to assess optimal treatment strategies for herpetic keratitis. In one of the trials, participants with herpetic stromal keratitis were randomized to a 10-week course of prednisolone sodium phosphate (starting at a 1% concentration every 8 hours, and tapering to 0.125% once daily) or identical-appearing placebo eyedrops.[43] Both treatment groups were also treated with topical trifluridine for the 10-week treatment regimen. The primary outcome was the time to treatment failure up to a 16-week endpoint, with failure defined as one of the following: a 4-line reduction in visual acuity; increase in the area of keratitis by ≥75%; failure of any clinical improvement over 2 weeks, 2-step increase in cells or 3+ cells for 1 week; IOP > 35 mm Hg and not controlled with antihypertensive treatment for 1 week; active herpetic lesion; or epithelial defect > 1 mm. The trial enrolled 106 participants, and was stopped early after interim analyses found benefit for the steroid group. The corticosteroid group had significantly less treatment failure than the placebo group at the end of the 10-week treatment course (26% failure versus 73% failure), with a median of 89 days (95%CI 81 to >120) until treatment failure in the steroid group versus 17 days (95%CI 14 to 27) in the placebo group. However, once the study medications were discontinued at week 10, the likelihood of treatment failure increased considerably in the steroid group, to 49% at 16 weeks. The relatively high number of treatment failures after discontinuation of treatment suggests that many patients require longer than 2.5 months of topical steroids.

In practice, many patients will require lifelong low-dose topical corticosteroid therapy to prevent recurrence. Once treatment failure occurred in HEDS, further management was at the discretion of the provider. Approximately three-quarters of the control group received topical corticosteroids before resolution, and the total duration of corticosteroid therapy was similar in the two treatment groups by week 16. Visual acuity at 6 months was similar between the two treatment groups—with about 60% achieving ≥ 2 lines improvement—suggesting that the delay in corticosteroid therapy in the control group did not result in substantially worse visual outcomes. The main adverse event was dendritic keratitis, observed in 7% of the steroid group and 2% of the placebo group at week 16. However, the rate of epithelial keratitis likely depends in part on the effectiveness of the antiviral coverage, since a separate HEDS trial found a rate of dendritic keratitis of only 2% over 16 weeks when using same treatment regimen but with the addition of oral acyclovir.[44] Treatment of herpetic endothelial keratitis was not specifically addressed in HEDS, but smaller randomized trials have found that topical corticosteroids are effective for endothelial keratitis when used concomitantly with an antiviral, and that oral acyclovir provides adequate antiviral coverage.[45–47]

HEDS provided high-quality data regarding the benefit of topical corticosteroids for herpetic stromal keratitis. Some of the basic management principles apply to other herpes viruses, including Varicella zoster virus (VZV), Cytomegalovirus (CMV), and Epstein-Barr virus (EBV). In each, steroids are effective for reducing inflammatory complications but also run the risk of reducing the host immune response and thus indirectly promoting viral replication. In the case of VZV, the virus establishes latency in the dorsal root ganglion but asymptomatic viral shedding is uncommon. Zoster stromal keratitis is thought to primarily be an immune-mediated keratitis without active viral replication, and thus corticosteroids are typically used without antiviral coverage. However, case series have found active viral replication in late dendriform corneal epithelial lesions that develop months after acute zoster keratitis, suggesting that corticosteroids should be used with antiviral coverage in some cases.[48, 49] The Zoster Eye Disease Study (ZEDS) is a randomized trial investigating the effectiveness of oral antivirals for zoster keratitis. A subgroup of ZEDS participants will likely be on chronic topical steroids, allowing study of the role of oral antivirals when using steroids for zoster keratitis.[50] Corneal disease from CMV comes primarily in the form of an endotheliitis, caused by active viral replication in the endothelium. Although randomized trials are lacking, steroids appear to be effective in reducing corneal edema and keratic precipitates if accompanied by effective topical or systemic antiviral therapy.[51] Stromal keratitis attributed to EBV, based primarily on consistent serologic testing, has been reported to respond well to topical corticosteroids, usually administered without antiviral coverage since no clinically effective antiviral against EBV currently exists.[52]

Human adenoviruses

Corneal subepithelial infiltrates (SEIs) are a delayed immunological response of epidemic keratoconjunctivitis (EKC) due to adenovirus, typically arising 2–3 weeks following acute infection and lasting for months or years.[53] The host immune response typically clears adenovirus from the ocular surface over a period of 1–2 weeks, although persistent or latent adenovirus infections have been observed in the lymphoid cells of the adenoids and distal

gastrointestinal tract, and also from the ocular surface.[54–56] Corticosteroids may reduce the discomfort and decreased vision associated with corneal inflammation. However, there is evidence from animal models that steroids may prolong clearance of adenoviral infection.[57]

Several randomized trials in humans have assessed the role of corticosteroids in acute epidemic keratoconjunctivitis. In one trial, participants with acute EKC and no SEIs were randomized to a 4-week course of a topical steroid (a preparation that included prednisolone acetate, 1%) or placebo.[58] Participants treated with steroids were less likely to develop SEIs compared with those treated with placebo (38% vs 81%) at the 5-week endpoint, although SEIs appeared in some participants following cessation of the steroids. In a larger trial done in the UK, participants randomized to a 1-week course of dexamethasone developed SEIs at statistically indistinguishable rates as those given placebo (5% vs 13%).[59] There has been speculation that combining a steroid with an antiviral may be a more effective strategy for treatment of EKC, and several trials have assessed the effectiveness of using povidone iodine plus dexamethasone. In one trial, no participants with acute EKC randomized to a 7-day course of povidone iodine 1% plus dexamethasone 0.1% developed SEIs, compared with 40% of those treated with dexamethasone only and 12% of those treated with vehicle.[60] However, a larger trial did not confirm this result: among participants with adenoviral conjunctivitis, SEIs developed in 20% of those randomized to povidone iodine 0.6% plus dexamethasone 0.1% for 5 days, compared with 30% of those randomized to povidone iodine alone and 21% of those randomized to vehicle.[56] Similarly, a trial that randomized participants with acute EKC to a 7-day course of povidone iodine 0.4% plus dexamethasone 0.1% or artificial tears found no difference in the proportion of eyes developing SEIs over the 30-day observation period.[61]

Fewer randomized trials have assessed the effectiveness of topical steroids for established SEIs. In one of the reports mentioned above, participants with chronic SEIs that were still present 9–12 months following acute EKC were again randomized to a 4-week course of steroids or placebo.[58] Resolution of SEIs was observed in 81% of the steroid group and 7% of the placebo group. However, SEIs reappeared upon cessation of topical corticosteroids in half the participants treated with topical steroids. Another trial that randomized participants with SEIs to a 6-month course of either fluorometholone or 0.5% cyclosporine found that SEIs were more likely to resolve in the steroid group at 3 months (39% vs 13%) and 6 months (70% vs 47%), although with wide confidence intervals.[62] Recurrence of SEIs 1 month after discontinuation of therapy was observed in 16% of the steroid group and 9% of the cyclosporine group. Thus, although the role of topical steroids for EKC has not been fully established, trials have not consistently found a benefit for preventing SEIs when used in acute EKC. In contrast, most evidence suggests corticosteroids are effective for treating existing SEIs, although long treatment courses are frequently necessary given the high likelihood of recurrence upon discontinuation of therapy.

Conclusions

Although at times a subject of controversy, topical corticosteroids have an important role in the treatment of infectious keratitis. The manner in which steroids are used should be tailored to the underlying pathogen, but some general principles apply. First, the

main rationale for using a topical corticosteroid in a corneal infection is to reduce the host inflammatory response in order to prevent or limit corneal scarring, thinning, and neovascularization, as well as to treat ocular pain associated with inflammation. Second, and especially for fungal and acanthamoeba keratitis, steroids started prior to treatment have consistently been shown to be associated with poorer outcomes. However, studies have not convincingly shown that corticosteroids started after a suitably long period of antimicrobial therapy are harmful. Third, when used during an acute infection, corticosteroids should be used concomitantly with an antimicrobial. The in vitro and clinical efficacy of the antimicrobial is crucial when deciding how to administer steroids. Corticosteroids reduce the ability of the host immune system to clear the infection, and thus if used without an antimicrobial, or with an ineffective antimicrobial, or with an antimicrobial that has poor corneal penetration, corticosteroids could enhance pathogen replication and lead to deeper, more advanced infections. For bacterial keratitis and herpetic keratitis, highly effective antimicrobials exist, and thus corticosteroids can be used safely. Antifungal and antiamoebic drugs are less effective, and thus corticosteroids present a greater risk in these infections. Finally, randomized trials have proven instrumental in our understanding of the role of corticosteroids in bacterial and herpetic keratitis. Additional randomized trials are important to better define the role of steroids for other causes of infectious keratitis.

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