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Indecision About Corticosteroids for Bacterial Keratitis

An Evidence-based Update

Kirk R. Wilhelmus, MD, MPH

Purpose: To quantify the effect of topical corticosteroids on bacterial keratitis.

Clinical Relevance: Bacterial keratitis is an economically important infection affecting 1 in 10,000 Americans annually. The predisposing factors, prior ocular health, infecting microorganisms, inflammatory severity, and therapeutic choices can affect the course and outcome. Antibacterial treatment is often curative but does not guarantee good vision. Because many treated patients develop a sight-limiting corneal problem, antiinflammatory therapy has sometimes been recommended.

Literature Reviewed: Publications from 1950 to 2000 that evaluated the effect of corticosteroids on bacterial keratitis in animal experiments, case reports and series, case-comparison and cohort studies, and clinical trials were systematically identified by electronic and manual search strategies.

Results: The use of a topical corticosteroid before the diagnosis of bacterial keratitis significantly predisposed to ulcerative keratitis in eyes with preexisting corneal disease (odds ratio [OR], 2.63; 95% confidence limits [CL], 1.41, 4.91). Once microbial keratitis occurred, prior corticosteroid use significantly increased the odds of antibiotic treatment failure or other infectious complications (OR, 3.75; 95% CL, 2.52, 5.58). However, the effect of a topical corticosteroid with antibiotics after the onset of bacterial keratitis was unclear. Experimental models suggested likely advantages, but clinical studies did not show a significant effect of topical corticosteroid therapy on the outcome of bacterial keratitis (OR, 0.62; 95% CL, 0.25, 1.54).

Conclusions: Topical corticosteroids increase the risk of infectious complications affecting the cornea but may or may not have an effect during antibacterial therapy. The unproven role of corticosteroids in the adjunctive treatment of bacterial keratitis highlights the need to collect prospective information that would guide appropriate management for this common eye disease. *Ophthalmology 2002;109:835–844 © 2002 by the American Academy of Ophthalmology.*

Infections lead to 20% of the world's blindness.[1] Microbial keratitis follows only trachoma and herpes simplex virus eye disease as a leading cause of serious corneal inflammation.[2] Recognized for centuries, acute corneal ulceration remains prevalent.[3]

Bacterial keratitis accounts for 3 of every 1000 patients seen by some ophthalmologists.[4] Among older Americans, keratitis is the eleventh most common eye disorder[5] and leads to nearly a quarter million office visits each year.[6] Extrapolations of population-based incidence data from the community[7] and among contact lens wearers[8–10] indicate that 30,000 Americans have microbial keratitis annually. The rate of corneal infection is higher among certain occupations and in agrarian communities. At a district in southern India, the incidence of corneal ulceration was 113/100,000/year.[11] Using a conservative estimate of 5 to 10 cases/100,000/year, 500,000 persons develop ulcerative keratitis annually around the world.

Bacterial keratitis frequently impairs vision. Before the antibiotic era, corneal infection commonly caused serious complications.[12] Despite the development of broad-spectrum antibacterial agents, sight-limiting scarring still occurs. Of patients with contact lens-related microbial keratitis, one half are left with vision less than 20/60, and a quarter stay 20/200 or worse.[13] Some people lose their eye.[14] Approximately 100,000 Americans have a vision-limiting opacity because of previous bacterial keratitis. The impact of bacterial keratitis on corneal blindness in developing nations is much greater.[15,16] Globally, more than 1 million people are visually disabled in one eye because of microbial corneal infection.

Bacterial keratitis is costly to individuals and to society.

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From the Sid W. Richardson Ocular Microbiology Laboratory, Department of Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston, Texas.

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Reprint request to K. R. Wilhelmus, MD, 6565 Fannin Street, Suite NC205, Houston, TX 77030.

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Medical expenditures range from $50 to $662/patient.[17] Surgery is sometimes needed for a perforation or an opacity: bacterial keratitis accounts for nearly 1% of corneal transplants performed in the United States and Canada.[18] Approximately $15 to $20 million is spent each year in the United States for the diagnosis and treatment of bacterial keratitis.[7] Furthermore, keratitis blunts the quality of life. Many patients are young, working adults who develop an unexpected infection from contact lenses or other injury. Any intervention that shortens the duration of disability, reduces the severity of corneal scarring, and lessens the need for surgery would produce considerable savings and enhance the public health.

Rationale and Purpose

The goals of treating bacterial keratitis are to eliminate the causative organisms, to suppress the destructive reactions, to restore normal ocular structure, and to restore vision. Antibacterial treatment often cures the infection, but many are left impaired. Understanding the microbial, cellular, and molecular pathogenesis of bacterial keratitis "may lead to fewer complications and the development of novel therapeutic strategies."[19]

Neutrophils and other leukocytes are involved in the cornea's inflammatory response to microbial proliferation and invasion. These host reactions account for much of the edematous, infiltrative, and necrotizing changes of bacterial keratitis.[20] Both proinflammatory and antiinflammatory processes take place, involving chemoattractants, adhesion molecules, and other mediators.[3] At present, only corticosteroids are widely available for inhibiting leukocytes, down-regulating proinflammatory cytokines, affecting metalloproteinase production, and modifying wound healing in the inflamed cornea.

Several ophthalmic corticosteroids are commercially available.[21] Topical solutions and suspensions in North America include prednisolone phosphate, prednisolone acetate, dexamethasone phosphate, dexamethasone alcohol, rimexolone alcohol, loteprednol etabonate, fluorometholone alcohol, fluorometholone acetate, and medrysone. Fixed combinations of corticosteroid–antibiotic preparations are also marketed. Bioavailability and antiinflammatory effects are similar whether the corticosteroid is applied to the eye just before or after an antibiotic drop.[22] Concurrent corticosteroid and antibiotic administration achieves good corneal levels,[22] although drug interactions can occur in the solution[23,24] and on the eye.[25]

The discovery and development of antibiotics is one of the great therapeutic legacies of the 20th century. Further advances in preventing complications from infection will come from ways to control the host's response. Whether corticosteroids, added to appropriate antibacterial therapy, are safe and effective in shortening disease, reducing complications, or improving outcome is an issue deserving of further study.

Studies evaluating systemic corticosteroids have shown effects in several infections.[26–28] Clinical trials of patients with sepsis have not established a benefit of corticosteroids except, possibly, for gram-negative bacteremia.[29,30] In bacterial meningitis, corticosteroid therapy prevents hearing loss and possibly other neurologic deficits.[31–33] Few trials have assessed local corticosteroids in corneal[34–37] and intraocular[38] infections, so observational studies are relied on.

Material and Methods

Electronic searching of MEDLINE and EMBASE through 2000 used the text words *keratitis* or *corneal ulcer* combined with *corticosteroid*, *cortisone*, *dexamethasone*, or *prednisolone*, without language restrictions. Studies were also identified by manually searching Index Medicus from 1960 through 1965, Excerpta Medica Ophthalmology from 1960 to 1973, and Ophthalmic Literature from 1950 to 1999. The reference lists of primary reports, review articles, and corneal textbooks were searched for additional relevant articles dating from 1950.

Bacterial keratitis was defined as a stromal infiltrate with an overlying epithelial defect that warranted intensive antibacterial therapy.[39] Laboratory criteria[4] based on the results of smears and cultures from corneal specimens were used when possible. The role of a topical corticosteroid in fungal or protozoal keratitis was not part of this systematic review. Ophthalmic studies were selected that provided data on animals or patients with bacterial keratitis for which corticosteroids were used, with or without antibacterial therapy. All topical corticosteroid preparations were considered equivalent for this overview. Retrieved articles were copied and translated as needed. One unmasked reviewer abstracted information from the full articles, including data for determining a relative effect measure of association.

The results of laboratory experiments were qualitatively categorized into three levels of effect: beneficial, adverse, or neutral. Human studies were quantitatively expressed. Each clinical report's odds ratio (OR) with 95% confidence limits (CL) was calculated from accessible data using Intercooled Stata 6.0 (Stata Corporation, College Station, TX, 1999). Statistical homogeneity among studies was examined with the chi-square test; a P value < 0.15 indicated heterogeneity. Pooled estimates were graphically displayed using RevMan 4.1 (Update Software, Oxford, England, 2000). Superscripts (A, B, or C; and I, II, or III, respectively) were used to show the author's qualitative interpretation of the clinical importance and evidential strength for each summary recommendation.[40]

Results

Corticosteroids before Diagnosis

Topical corticosteroids, used without an antibiotic, generally have a deleterious effect on experimental models of bacterial keratitis.[41–45] A corticosteroid can enhance the stromal growth of some bacteria, such as *Pseudomonas aeruginosa*, but may not produce detectable effects after inoculation with staphylococci or streptococci.[46–48]

One observational study evaluated how a topical corticosteroid might affect the risk of corneal infection in susceptible eyes. In a retrospective series, ulcerative keratitis developed in 5% of 918 patients with pseudophakic or aphakic corneal edema, and a topical corticosteroid significantly increased the risk (OR, 2.63; 95% CL, 1.41, 4.91).[49] Other retrospective studies determined how corticosteroid use before the onset of bacterial keratitis affected subsequent outcome,[50–55] such as antibacterial treatment failure, the occurrence of corneal perforation, or another complication leading to keratoplasty or gluing. Pooling was not limited by

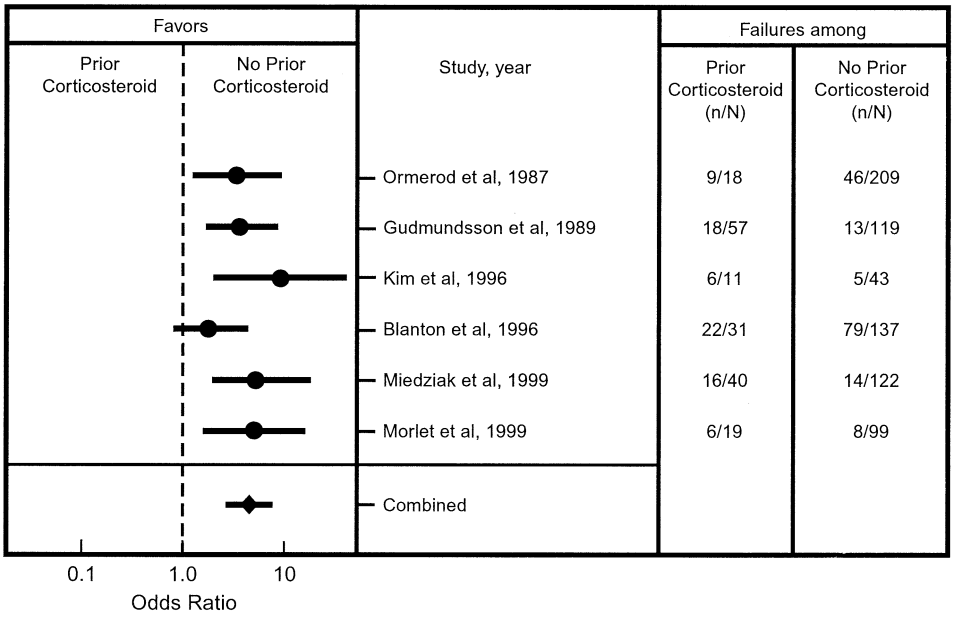

Figure 1. Unadjusted relative risk estimates with 95% confidence intervals (CI) for the relative effect of topical corticosteroid pretreatment before diagnosis on treatment failure and complications requiring surgery among antibiotic-treated patients. The DerSimonian-Laird random-effects estimate of the summary odds ratio (OR) is displayed (OR, 3.75; 95% CI, 2.52, 5.58). The Mantel-Haenszel fixed-effects estimate of the pooled studies was similar (OR, 3.59; 95% CI, 2.42, 5.35). Criteria for treatment failure varied among studies.

heterogeneity ($P = 0.4$), although studies varied in outcome assessment. Patients who received a corticosteroid before diagnosis had a significantly ($P < 0.001$) greater chance of antibiotic treatment failure and infectious complications (Fig 1).

Corticosteroids after Diagnosis

Several experiments on rats, rabbits, and guinea pigs evaluated whether a corticosteroid affects outcome when used in combination with antibacterial therapy.[42,46–48,56–68] Corticosteroids were typically administered concomitantly with antibiotic therapy that was started within 48 hours after bacterial inoculation. Outcome measurements included bacterial counts, leukocytic counts, and ordinal scoring of visible corneal inflammation. Three experiments studied *Streptococcus pneumoniae* keratitis, two examined *Staphylococcus aureus* keratitis, and 19 evaluated *Pseudomonas aeruginosa* keratitis (Table 1). By classifying each of the 24 antibiotic–corticosteroid experiments with regard to the overall effect of corticosteroid, 9 (37.5%) showed a beneficial effect, 3 (12.5%) had an adverse effect, and 12 (50%) were neutral. Of the adverse outcomes, one experiment used a *P. aeruginosa* strain resistant to the antibiotic (gentamicin) that was applied to the eye,[60] and another used a low antibiotic dosage (0.4% tobramycin four times daily).[63] Considered collectively, these models are not conclusive with regard to the effect of corticosteroid on antibiotic-treated bacterial keratitis.

Veterinarians are cautious about using corticosteroids for treating microbial keratitis in dogs, horses, and other animals;[69] but their recommendations rely on experience more than experiment. One randomized trial among cattle showed that dexamethasone did not alter the size or severity of penicillin-treated *Moraxella bovis* keratitis.[70]

Observational studies of bacterial keratitis in humans have not shown a beneficial effect of a topical corticosteroid on bacterial keratitis. An Australian series of culture-confirmed patients shows the difficulties in determining the effects of topical corticosteroid therapy.[71] Fewer corticosteroid-treated eyes were judged successes, but severely involved eyes were more likely to be treated with corticosteroids. This bias may also explain why recrudescent infection occurred in 13% of the corticosteroid group but in none of the patients who did not receive a corticosteroid.

In a nonrandomized multicenter series using ciprofloxacin ointment,[72] a topical corticosteroid was used at the discretion of the treating investigator in 19% of evaluable patients who had a positive bacterial culture, used no other antimicrobial agent, followed the dosing regimen, and returned for reexamination after completing treatment. In another prospective study, patients were randomly assigned to ciprofloxacin solution or to combined cefazolin and tobramycin treatment,[73] and a topical corticosteroid was used at the discretion of the investigator in 22% of the evaluable patients. Corticosteroid-treated patients were just as likely to achieve cure or improvement as those who did not receive a corticosteroid. Similarly, no differences between the patients who did or did not receive corticosteroids were found for time until cure or for final visual acuity. Noncomparability of the treatment groups may have affected the results; for example, initial infiltrates tended to be larger in the corticosteroid-treated groups. Confounding by severity, organism, and other factors was plausible.

One randomized, controlled clinical trial conducted in South Africa evaluated the effect of topical corticosteroids in antibiotic-treated bacterial keratitis.[36] Patients were initially treated with intensive topical and subconjunctival antimicrobial therapy and randomly assigned to receive either dexamethasone 0.1% solution four times daily started on the following day, or to a control group. No detrimental effect of corticosteroids was noted between the two groups with respect to healing rate or complications. The visual outcome of the two groups seemed similar, although a subgroup reanalysis of patients with pretreatment visual acuity of 20/200 or worse shows that visual improvement occurred about twice as often in the corticosteroid group (OR, 2.31; 95% CL, 0.87, 6.09). This trial's inconclusive result had a relatively high probability of type II error. Another limitation was the imbalance with respect to bacterial species (e.g., gram-negative rods accounted for fewer patients in the steroid group than in the control group) and to clinical severity (e.g., 25% more patients with a hypopyon and 67% more patients with deep corneal involvement were in the steroid group than among the controls). An effect of corticosteroid cannot be excluded in this underpowered study with incomplete follow-up.

The combined results of cohort studies and the clinical trial did not show a consistent or significant ($P = 0.15$) effect of corticosteroids on outcome (Fig 2), but pooling was limited by clinical and statistical heterogeneity ($P = 0.04$). Available clinical reports

Table 1. Experimental Animal Models Evaluating Corticosteroids with Antibacterial Agents in Bacterial Keratitis

Reference	Antibiotic	Corticosteroid	Corticosteroid Effect
Streptococcus pneumoniae			
Lepri, 1952[56]	Penicillin G or tetracycline	Cortisone acetate	Beneficial
Badenoch, 1985[47]	Penicillin G, cephradine, or gentamicin	Prednisolone acetate	Beneficial
Gritz, 1992[57]	Penicillin G	Prednisolone phosphate	Neutral
Staphylococcus aureus			
Leibowitz, 1980[46]	Neomycin or gentamicin	Prednisolone acetate	Neutral
Badenoch, 1985[47]	Cephradine or gentamicin	Prednisolone acetate	Beneficial
Pseudomonas aeruginosa			
Suie, 1956[42]	Polymyxin B	Cortisone acetate	Neutral
Bohigian, 1977[58]	Gentamicin	Dexamethasone	Neutral
Davis, 1978[59]	Tobramycin or carbenicillin	Prednisolone acetate or methylprednisolone	Neutral
Leibowitz, 1980[46]	Gentamicin or polymyxin B	Prednisolone acetate	Neutral
Stern, 1980[60]	Gentamicin	Triamcinolone acetonide	Adverse
Smolin, 1980[61]	Gentamicin then tobramycin	Triamcinolone acetonide	Neutral
Behrens-Baumann, 1981[62]	Tobramycin	Dexamethasone	Neutral
Badenoch, 1985[47]	Gentamicin	Prednisolone acetate	Beneficial
Fraser-Smith, 1988[63]	Tobramycin	Dexamethasone	Adverse
Gritz, 1990[48]	Tobramycin	Prednisolone phosphate	Neutral
Ohadi, 1992[64]	Ofloxacin	Prednisolone phosphate	Neutral
Gritz, 1992[57]	Tobramycin	Methylprednisolone acetate	Adverse
Hobden, 1992[65]	Ciprofloxacin	Prednisolone phosphate	Beneficial
Hobden, 1993[66]	Ciprofloxacin	Prednisolone acetate with flurbiprofen	Beneficial
Hobden, 1993[67]	Ciprofloxacin	Prednisolone acetate	Beneficial
Hobden, 1993[67]	Ciprofloxacin	Prednisolone phosphate	Beneficial
Engel, 1995[68]	Tobramycin	Prednisolone acetate	Neutral
Engel, 1995[68]	Tobramycin	Prednisolone phosphate	Beneficial
Engel, 1995[68]	Ciprofloxacin	Dexamethasone	Neutral

cannot reliably conclude how corticosteroids affect the outcome of antibiotic-treated bacterial keratitis.

Discussion

Debate over topical corticosteroids began soon after cortisone's introduction at the middle of the 20th century. Some felt strongly that corticosteroids helped to resolve corneal inflammation; to facilitate epithelial and stromal healing; and to minimize corneal opacification, neovascularization, and destruction. Others opposed corticosteroid use because of concerns about potentiating microbial replication and promoting recrudescence. With ineffective antibiotics corticosteroids could slow recovery, accelerate stromal loss, and increase the risk of perforation in infectious keratitis. Conflict over whether and how to use ophthalmic steroids has persisted for 50 years.

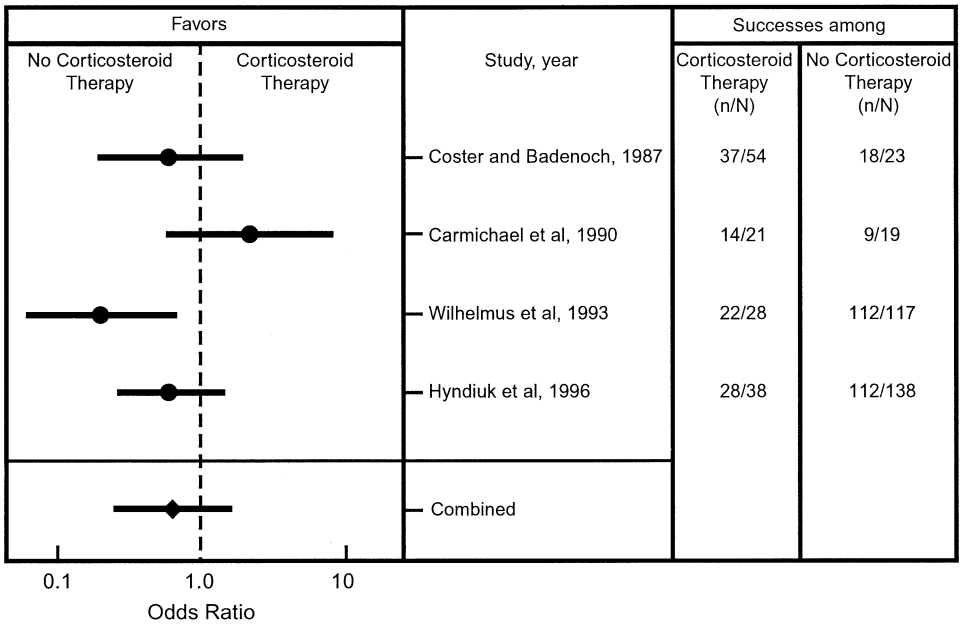

Figure 2. Unadjusted relative risk estimates with 95% confidence intervals (CI) for the relative effect of topical corticosteroid treatment after diagnosis on successful cure or improvement among antibiotic-treated patients. The random-effects estimate of the summary odds ratio (OR) is displayed (OR, 0.62; 95% CI, 0.25, 1.54). The fixed-effects estimate of the pooled studies was also calculated (OR, 0.65; 95% CI, 0.38, 1.11). Criteria for successful outcome varied among studies.

Ophthalmology's Steroid War

Cortisone was first tried for "hypopyon keratitis" a few months after its introduction in 1950. Within a year, Duke-Elder summarized the brief literature on the use of corticosteroids in keratitis and laid down the basic premise for corticosteroid use in ocular inflammatory disease: "The ideal therapeusis is the control of the deleterious aspects of the inflammatory response until such time as the infective or other causal agent is eliminated by other means."[74] Soon afterward, Thygeson and his coworkers[75] reiterated that "great care should be examined in the use of cortisone and hydrocortisone in central corneal ulcers and that bacteriologic diagnosis should be made before employment of these hormones."

This dictum of deferring corticosteroid use until the infecting agent was identified and subdued became a mantra for many clinicians. Adverse experience led Sorsby to warn in 1960, "To combine the corticosteroids with an antibiotic, as is a common practice, is to convert two useful agents into one bad compound and to indulge in blunderbuss therapy of a particularly objectionable type."[76] During this first decade of exploring cortisone's role, many clinicians generally agreed with this advice, although some believed that certain patients might derive benefit.[77–80]

Opinions jelled into beliefs, based largely on anecdotal experience. Then, in 1969, patient data were used to argue that topically administered corticosteroids could limit structural damage in the infected cornea when given in combination with bactericidal agents.[77–81] As subsequently noted by O'Day,[82] this article "brought to a boil a controversy that had been simmering for a number of years. Individuals and even institutions were lined up on one side or the other, and it requires little exaggeration to compare the controversy waged among infectious disease experts to a holy war in which the fundamental belief in question was the use or forswearing of corticosteroids in the therapy of infections." The double-edged effects of corticosteroid therapy provoked vigorous dialogue.[83–88]

The Two Sides of Corticosteroids

Potential adverse effects of corticosteroids include secondary glaucoma, cataract formation, inhibition of corneal wound healing, and enhancement of microbial growth. Corticosteroids increase the chance of infection in eyes with corneal surface disease,[49,89–91] possibly by suppressing innate corneal epithelial defenses (unpublished data; Djalilian AR et al, Invest Ophthalmol Vis Sci 2001;42(4):S575 and Terai K et al, Invest Ophthalmol Vis Sci 2001;42(4):S586). They are the most common factor conducive to infectious crystalline keratopathy. When in use before the occurrence of bacterial keratitis, corticosteroids more than triple the risk of subsequent complications, which can include treatment failure,[52] progressive infection,[54] indolent ulceration,[55] perforation,[51,54] and endophthalmitis.[92]

Corticosteroids impair phagocytosis and intracellular killing of bacteria and, with incomplete antibacterial therapy, allow bacterial survival. Case reports have incriminated corticosteroids in recrudescent infection with bacterial invaders such as *P. aeruginosa* that fully tax the host's defenses.[93,94] Situations in which corticosteroids might increase the risk of complications are the lack of culture isolates or susceptibility results, doubt about the bactericidal effects of topical antibacterial treatment, and poor compliance.

Reasons to use a corticosteroid in the treatment of bacterial keratitis are to dampen local inflammation and its structural complications, to modulate stromal regeneration, and to enable epithelial reformation. Corticosteroids curb leukocyte recruitment and activation and affect the function and genetic transcription of corneal cells. Corticosteroids possibly reduce stromal loss and opacification,[31] although an effect on corneal thinning or scarring in treated bacterial keratitis is not proven.

Corticosteroids have various effects on epithelial healing[95] and could be useful for managing a persistent epithelial defect over inflamed stroma. Some who prefer not to use a corticosteroid during the early antibiotic treatment of bacterial keratitis acknowledge its role against continued stromal inflammation to encourage reepithelialization.

Equipoise in Clinical Practice

The efficacy and safety for the optimal use of a topical corticosteroid in bacterial keratitis have not been determined. Notions about the merit of corticosteroids in bacterial keratitis vary, and advice in ophthalmic textbooks lacks a uniform recommendation. The current Preferred Practice Pattern on bacterial keratitis from the American Academy of Ophthalmology states that "there is no conclusive scientific evidence that shows that steroids alter clinical outcome."[96] Equipoise—the "legitimate uncertainty or indecision as to choice or course of action because of a balance of potential gains versus losses"[97]—affects the issue of corticosteroid use in bacterial keratitis.

Though available for a half century, a window of opportunity for human experimentation remains open. Both the application and avoidance of corticosteroids in bacterial keratitis can be medically and ethically justified. Corneal specialists do use a topical corticosteroid in the management of bacterial keratitis: 69% of respondents in a 1995 survey of the Castroviejo Society[4] and 81% in a 1997 survey of the Ocular Microbiology and Immunology Group (Schwab IR, presented at the OMIG annual meeting, October 25, 1997). Yet ongoing uncertainty points toward the need for prospective studies.[44,82,98] Clinical trial protocols have been planned (Cohen EJ, personal communication; Alfonso EC, personal communication), but a large randomized study has not been done.

Conclusions

Caveats for using a topical corticosteroid during bacterial keratitis have been proposed.[98–101] The following management suggestions are based on the collated evidence.

- Be wary of poor outcome and complications leading to corneal surgery for patients with bacterial keratitis who used a topical corticosteroid before corneal infection began. (B,II)

- Avoid a topical corticosteroid if the causative microorganisms are unknown and effective antibacterial therapy cannot be provided. (A,II)
- Minimize corticosteroid use if inflammation is not near the visual axis and the corneal wound is healing adequately. (C,III)
- Continue a topical corticosteroid, usually at a lower frequency or concentration, for patients already justifiably using a topical corticosteroid for another serious ocular condition or inflammatory disease. (C,III)
- Consider adding a topical corticosteroid to antibacterial therapy for bacterial keratitis after the offending microorganisms are identified and after sensitivities, using clinical or laboratory criteria, are determined when it is judged important to aid reepithelialization or to minimize stromal alteration. (A,II) The corticosteroid may be started after 1 or more days of antibiotic therapy, when no worsening or some improvement is observed. (B,III) Starting a topical corticosteroid with initial antibiotic therapy is credible only if the effectiveness of chosen treatment is confidently assured. (C,III)
- Consider a topical corticosteroid for a persistent epithelial defect caused by ongoing sterile stromal inflammation. (B,III)

Despite these recommendations, clinical ophthalmologists cannot adequately determine which patients might benefit from adjunctive corticosteroid treatment and which could be put at risk. Even less is known about when to start, and how to modify, and when to stop corticosteroids. Although maximal antiinflammatory effects are achieved by beginning a corticosteroid right away, many defer it until a clinical response to antibacterial therapy is determined and initial laboratory information is available. Whether outcome differs by an early versus delayed start of a corticosteroid has not been critically studied. In tapering, some clinicians prefer to adjust its frequency and concentration in step with the antibacterial regimen or according to perceived disease severity. No one has yet established a standard treatment schedule. If corticosteroids are shown worthwhile at any stage in the treatment of bacterial keratitis, a decision-making protocol for corticosteroid selection and dosage would need to be created.

Corneal ulceration is an important public health problem. Information on the role of corticosteroids in bacterial keratitis is insufficient. Better studies of microbial keratitis would aid clinicians in practicing evidence-guided ophthalmology.

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