Herpetic Keratitis Following Laser Refractive Surgery

Herbert E. Kaufman, MD

Recurrence of herpetic keratitis is a rare but potentially serious complication of excimer laser refractive surgery. A pioneer in the development of antiviral drugs, Herbert E. Kaufman presents an approach to the patient at risk.

In the 25 years since its development, excimer laser surgery for vision correction has become the most popular elective procedure in the world. In the US, there are 32 million myopic individuals, and about 400,000 Americans (largely but not exclusively myopes) had laser surgery for correction of refractive error in 2010.

As with any popular procedure, even low-incidence complications have the potential to affect large numbers of people. Reactivation of herpes simplex virus (HSV) is a rare and potentially serious complication of laser refractive surgery that concerns many surgeons. Fortunately, identifying patients at risk for HSV reactivation and appropriately administering antiviral prophylaxis can all but eliminate the HSV reactivation risk associated with this surgical procedures.

Reactivation Risk

Research has shed some light on the link between excimer laser surgery and the potential for reactivation of latent HSV. Animal studies have confirmed that exposure to 193 nm ultraviolet (UV) radiation from the excimer laser can induce ocular reactivation of latent HSV-1. The mechanism of laser-induced HSV reactivation is not completely understood; however, injury to corneal nerves harboring the virus may play a role. Other surgery-related factors such as trauma, stress, and periocular medication use may also contribute to HSV recurrence risk.

Data from animal studies do not necessarily predict events in humans, but there is reason to believe that humans are also at risk for HSV reactivation from corneal laser exposure. Although...
ocular infection is rare, HSV-1 is ubiquitous in the adult population and is commonly shed in tears of asymptomatic individuals.

In a study at our center, 50 healthy adults with no history of HSV-related orobulal or ocular infection were studied for evidence of HSV in tears and saliva. Participants contributed mouth and eye swabs twice daily for 1 month (2800+ tear samples were collected). These were tested by polymerase chain reaction for the presence of HSV-1 DNA. Within this asymptomatic population with no known history of herpes, one might expect viral shedding to be absent or infrequent. However, a full third of tear samples tested positive for HSV-1, and nearly 100% of subjects (49 of 50) shed HSV at least once in either saliva or tears in the course of the month. While we know that the vast majority of individuals never develop ocular complications of HSV, it should be recognized that the virus—or at least HSV DNA—is commonly present in the eye.

**Suspect Post-surgical HSV**

Ordinary corneal HSV recurrences are fairly easy to recognize on slit lamp examination, as they nearly always have the characteristic dendritic appearance (Figure 1). But HSV recurrences following laser refractive surgery or other ocular surgery more commonly have a non-dendritic shape compared to naturally recurring episodes and may easily go unrecognized.

Post-surgical herpetic lesions can be irregular in shape, geographic, or may simply look like a poorly healing epithelial defect. Even in the absence of a typical dendrite, failure of the corneal epithelium to heal following any kind of ocular surgery should arouse suspicion of herpes, and treatment with appropriate antiviral should be considered.

**Putting Risk into Perspective**

The true risk of HSV recurrence as a consequence of excimer laser surgery is not clear. In spite of substantial risk demonstrated in animals, and the
omnipresence of HSV-1 in humans, despite millions of LASIK procedures having been performed to date, few cases of ocular HSV complications have been reported in the literature. Incidence estimates may be falsely low, however, since reporting is not mandatory for this condition. Some of the concern regarding HSV reactivation may simply be a holdover from the period of laser surgery development. The protocol used in the first clinical studies of PRK listed herpes infection as a contraindication. This was due to an overabundance of caution rather than any convincing evidence that HSV reactivation would occur. The FDA now considers a history of herpes a cause for caution but not an absolute contraindication to laser surgery. In my practice, with the exception of patients with a history of stromal herpetic keratitis, I do not consider a history of corneal herpes an absolute contraindication to LASIK.

A Practical Approach

Patients with epithelial herpetic keratitis only (without stromal involvement) may have a reasonably low risk of HSV recurrence in general compared with those who have experienced stromal keratitis. The Herpetic Eye Disease Study (HEDS) demonstrated that, as a group, patients with a history of stromal herpetic keratitis were more likely to experience HSV recurrence when faced with a trigger compared with those with epithelial disease only.8 (In that study the trigger was the use of steroids without simultaneous antiviral prophylaxis.) Because there may be some risk of HSV recurrence, which could lead to permanent scarring, my practice is to use prophylaxis on all refractive surgery patients with a known prior herpes outbreak, whether that was epithelial herpes keratitis or orolabial herpes (“sun blisters”). For those patients, I prescribe a combination of oral valacyclovir (500 mg morning and night beginning a day before surgery, and continuing for a week postoperatively) and topical ganciclovir ophthalmic gel 0.15% (twice daily) for the period beginning a day or two before surgery through 2 weeks after surgery.

Antiviral prophylaxis with systemic valacyclovir has been shown to effectively reduce HSV-1 shedding after ocular laser procedures in animals.4,9

Trifluridine, a drug I developed, was the standard treatment for herpes for many years; however, as a nonselective agent, it can slow wound healing and even cause epithelial keratitis in a significant number of patients. Ganciclovir ophthalmic gel 0.15% is currently my topical agent of choice because it acts selectively on virus-infected cells and thus is much safer.

In Practice

I do not offer elective laser surgery to patients with a history of stromal herpetic disease, which is a contraindication to the procedure for the reasons mentioned above. However, with appropriate prophylaxis, most other patients with a history of HSV can be good candidates for the procedure. In my practice, several dozen patients with a history of corneal HSV have received antiviral prophylaxis prior to laser surgery, and none have experienced HSV reactivation. Others have reported similar success.10

Conclusion

Although the risk of HSV-1 reactivation due to excimer laser surgery appears to be low, antiviral prophylaxis is indicated for some patients to increase the safety of the procedure.

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REFERENCES

Atypical Ocular Infections

Eduardo Alfonso, MD

Travel, climate change, and the abundant use of antibiotics and antiseptics are just a few of the many things stirring the microbial world. As they evolve to meet challenges to their existence, microbial populations move and transform, growing or shrinking in number and changing in pathogenicity, virulence, and resistance. It is not surprising, then, that patterns of ocular infection are changing, creating novel diagnostic challenges for ophthalmologists. Today, when empirical therapy with a potent broad spectrum antibiotic fails, an atypical pathogen may be the cause.

Although outliers exist, most cases of non-viral infectious keratitis are bacterial and caused by a relatively small and well known group of pathogens that includes Staphylococcus aureus, Staphylococcus epidermidis, and Pseudomonas aeruginosa. Indeed, although antibiotic resistance is growing, most of the non-viral corneal infections encountered in everyday practice are caused by common organisms that will respond to a potent fourth-generation fluoroquinolone. But on occasion a corneal infection doesn’t respond; among the possible reasons is an atypical microbe.

Among the less frequently encountered pathogens that cause corneal infection are bacteria (including Escherichia coli and species of Klebsiella and Nocardia), non-tuberculous mycobacteria, fungi (including species of Fusarium, Aspergillus, and Candida), and amoebae (particularly Acanthamoeba). While anyone may acquire an atypical ocular infection, some patient groups are at increased risk (Table 1). In challenging cases, a careful history can reveal risk factors that may assist in pinpointing the cause.

Contact Lenses and Other Vectors

Ocular trauma—including the superficial epithelial disruption associated with contact lens wear—is a set-up for infection, particularly when it takes place in conjunction with exposure to a high pathogen load such as contaminated contact lenses or exposure to water sources like swimming pools/hot tubs, lakes, or even oceans.

Like any other foreign material placed into the body, contact lenses can be vectors that can carry microorganisms. Indeed, anything placed on the lid or in or near the eye—eyeliner, makeup, creams, even lubricating drops and topical ocular medications—can introduce microbes, some of which may be unusual species that cause infection.

Stagnant Water

The incidence of Acanthamoeba keratitis in Miami, where I practice, seems to be increasing. This may relate in part to the frequency of storms and their effects on bodies of water. Stagnant and/or inadequately chlorinated water contains increased numbers of amoebae. In municipal tap water systems, stagnation can occur after a power outage caused by a storm or electrical grid failure. Without power, pumping stations shut down, leading to stagnation of the water supply. (City officials may use excess chlorine as a preventive measure, but pooled water that is far from the point of chlorine addition may already be growing organisms.)

Tap water may become stagnant through inadequate flow, such as from an underused holding tank. In a home supplied by such a tank, water that gains intraepithelial access to the cornea via a surface scratch—such as from washing the face or from a contact lens—could contain amoebae and cause infection.

Climate and Regional Factors

As one might expect, certain pathogens are particularly well adapted to certain climates. For example, there are more fungi in tropical areas than in temperate climates of the north. Among bacteria, Pseudomonas species tend to thrive in warm, humid, watery environments rather than the colder, dryer areas in which staphylococci tend to proliferate. Proximity to urban areas, particularly those with large medical centers, increases exposure to methicillin-resistant staphylococci and other drug-resistant pathogens, which tend to be less prevalent in rural areas.

The bacteria that colonize and sometimes infect us are equally affected by factors specific to their human hosts. Individuals typically develop protective responses to the native flora to which they are continuously exposed. An individual who works in a medical center, for example, may be a carrier.
of methicillin-resistant *Staphylococcus aureus* (MRSA) but may have developed defenses against it and never manifest symptoms of infection. On the other hand, a newly hospitalized patient who has never been exposed to MRSA and who is susceptible to infection may become infected. We see a similar phenomenon among agricultural workers in South America who almost never come down with fungal ocular infections, despite scratching their eyes quite frequently. On the other hand, a contact lens wearing visitor from the north may scratch her eye and develop a fungal infection almost immediately—suggesting (though by no means proving) that regular environmental exposure to pathogens could reduce the likelihood of infection.

Having lived in humid environments all my life, I believe that my own defenses are likely primed to resist *Pseudomonas*. By contrast, individuals from northern climates who come to Miami are far more vulnerable to *Pseudomonas*, because their immune systems do not recognize it and cannot respond as quickly.

**Travel, Antibiotics, and Disrupted Ecosystems**

The extraordinary mobility of human beings today has had a powerful impact on microbial ecosystems throughout the world. No one is safe from any given bug because, even in relatively isolated places, travel has introduced exotic flora.

Travel increases one’s risk of acquiring an unusual pathogen for a variety of reasons. First, as noted, travelers stepping into a novel ecosystem may be exposed to novel pathogens indigenous to that area. These may challenge and overwhelm their naive immune systems. Second, visiting densely populated areas means encountering a greater number and variety of microbes, including atypical pathogens. In places like India, fungal infections are common, due in part to the sheer number of individuals living there.

Thirdly, prophylactic antibiotic or antimalarial medications prescribed to travelers may inadvertently contribute to risk by upsetting the innate microbial flora, potentially suppressing protective bacteria. Studies have found that some microbes in the human biosystem secrete substances that suppress the growth of other microbes in order to maintain balance in the ecosystem and/or the health of the host. For example, lactic acid-producing bacteria have been shown to suppress growth and toxin production by fungi. Thus antibiotic-induced killing of these “friendly” bacteria may contribute to overgrowth of fungal organisms. (In the future, restoration of a balanced bacterial ecosystem following antibiotic administration through prescribing of biologic entities such as probiotics may become commonplace.)

A similar mechanism may also spur emergence of novel pathogens on a larger scale. In addition to selecting for resistant organisms, an unanticipated consequence of the widespread systemic use of broad-spectrum antimicrobials in humans and animals is the selection of atypical bacterial and nonbacterial pathogens due to alterations in ecosystems that would have otherwise kept them in check. This problem is greatly compounded by the now ubiquitous antibacterial products such as hand gels and bar soaps that are marketed as means to kill viruses and bacteria. Antiseptics have much broader coverage than antibiotics, but they often fail to cover pathogens such as *Acanthamoeba*. One worry is that low-dose antiseptic use could kill most of the competing organisms, leaving the *Acanthamoeba* to proliferate and dominate the milieu.

**Practical Considerations**

Microbes are continuously being carried outside of their native environments and are evolving to survive in the face of changing threats, so ophthalmologists must be prepared for the unexpected. With this in mind, it is useful to take a recent travel history in any patients with suspected infection. On a visiting professorship in northern Europe recently, I encountered a patient with severe fungal keratitis who, as it happens, had just spent 2 months on a ranch in Arizona. Fungal pathogens are extremely rare in this part of Europe; it was the travel history that increased the suspicion for a fungal infection and led to starting appropriate therapy quickly.

A poor response to empirical treat-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Risk factors for, and sources of, atypical infections</th>
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<tr>
<td><strong>• Corneal trauma</strong></td>
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<td><strong>• Contact lens wear</strong></td>
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<td><strong>• Make-up and eye creams</strong></td>
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<td><strong>• Ocular medications and moisturizers</strong></td>
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<td><strong>• Exposure to stagnant, standing water</strong></td>
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<td><strong>• Inadequate chlorination of water</strong></td>
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<td><strong>• Hot climate</strong></td>
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<tr>
<td><strong>• Travel</strong></td>
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<tr>
<td><strong>• Antibiotic and antiseptic use</strong></td>
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<tr>
<td><strong>• Impaired immune system</strong></td>
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<td><strong>• Suboptimal hygiene</strong></td>
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**TABLE 2**

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<th>Awareness of atypical pathogens can guide practice</th>
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<td><strong>• Pathogens evolve over time—expect the unexpected</strong></td>
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<tr>
<td><strong>• Take a history of travel and animal contact</strong></td>
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<tr>
<td><strong>• Ask about eye irritation, trauma, saline solutions, eye drops, and cosmetics</strong></td>
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<tr>
<td><strong>• Ask about water exposures, particularly around times of storms or power outages</strong></td>
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<tr>
<td><strong>• Ask about medications and conditions that can affect the flora or the immune system</strong></td>
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<tr>
<td><strong>• Follow closely for response after initiating empirical antibiotic therapy</strong></td>
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<tr>
<td><strong>• When patients do not respond as expected, be vigilant for unusual pathogens (and common pathogens acting in unusual ways)</strong></td>
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ment of a suspected bacterial keratitis (i.e., lack of noticeable improvement 3 to 5 days into treatment) may signal the presence of an unusual pathogenic species. Alternatively, a species that responded well to therapy in the past may have evolved to become more aggressive or more resistant to standard treatments. The fungus *Fusarium*, for example, tends to produce three or four mycotoxins, some of which have changed over time and become increasingly damaging to human cells (Table 2).

**An Eye Toward the Future**

More rapid identification of infecting agents and more targeted control of atypical infections is needed. Our ability to learn from the Human Genome Project and apply genomics to microbiology will greatly enhance our ability to treat corneal infections. Knowledge of microbial gene sequences will allow laboratories to not only identify pathogens more quickly but also to identify a strain’s origin and describe its pathogenic properties.

**Conclusion**

Atypical ocular infections present diagnostic and therapeutic challenges. Awareness of unusual pathogens and the factors that predispose to their acquisition can help clinicians recognize them earlier and prevent subsequent corneal damage.

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**REFERENCES**

1. Which of the following patients may be an appropriate candidate for antiviral prophylaxis prior to excimer laser refractive surgery?
   A. 41-year-old female with history of epithelial herpetic keratitis
   B. 28-year-old female with no history of HSV-related disease
   C. 51-year-old male with history of stromal herpetic keratitis
   D. 39-year-old female with a history of dry eye

2. Which of the following is NOT a risk factor for acquiring an unusual infection during travel?
   A. Antibiotic prophylaxis
   B. Traveling by car
   C. Visiting areas with high population density
   D. Visiting a novel climate

3. HSV-1 may be present in which of the following tissue samples?
   A. Tears of an asymptomatic person with no history of cold sores or ocular herpes
   B. Saliva of an asymptomatic person with no history of cold sores or ocular herpes
   C. Tears of an asymptomatic person with a history of stromal herpetic keratitis
   D. All of the above

4. Which of the following is NOT a potential surgery-associated trigger for HSV reactivation?
   A. Stress
   B. Corticosteroid use
   C. Male gender
   D. Corneal nerve damage

5. Which of the following is an atypical ocular pathogen(s)?
   A. Fusarium species
   B. Staphylococcus aureus
   C. Escherichia coli
   D. Both A and C

6. Travelers who take prophylactic antibiotics may inadvertently increase their risk of infection because these antibiotics may
   A. Suppress protective bacteria
   B. Contribute to resistance
   C. Cause allergic reaction
   D. All of the above

7. Which of the following is characteristic of a prophylaxis regimen of oral valacyclovir and topical ganciclovir?
   A. Moderate risk of corneal toxicity
   B. Potential to suppress reactivation of virus at the trigeminal ganglion
   C. Lack of selectivity for virally infected cells
   D. Poor tolerability

8. Which of the following conditions may allow for amoebic proliferation within a water system?
   A. Hyperchlorination
   B. Home filtration units
   C. Temporary pump station failure
   D. Excessive tap water use in a community

9. Lactic acid-producing bacteria have been shown to
   A. Suppress fungal growth and toxin production
   B. Develop resistance rapidly in warmer climates
   C. Increase the level of Acanthamoeba in stagnant water
   D. Infect travelers to densely populated regions

10. Excimer laser-induced HSV reactivation is concerning to ophthalmologists because:
    A. These lasers trigger HSV reactivation in rabbits
    B. The incidence of HSV recurrences following LASIK is near 10% among infected patients
    C. Cases of ocular HSV following laser refractive surgery have been reported
    D. Both A and C are correct

EVALUATION:
11. Extent to which the activity met the identified Objective 1: 1 2 3 4 5
    Objective 2: 1 2 3 4 5
    Objective 3: 1 2 3 4 5
12. Rate the overall effectiveness of how the activity:
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    Will influence how I practice: 1 2 3 4 5
    Will help me improve patient care: 1 2 3 4 5
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15. How committed are you to making these changes? Yes No
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