

UPDATED EDITION

# Diagnostic & Treatment Algorithms for Ocular Surface Disease States

# Keratitis

*Part four of an ongoing series*

New paradigms in the understanding and  
management of keratitis.

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Dear Colleagues:

Thus far in the 2011 update to our series of monographs, we have examined ocular allergy, conjunctivitis and dry eye. As the others in this series did for the aforementioned ocular surface disease states, this monograph will comprehensively review new and existing information as it relates to the understanding and management

of keratitis. It also offers a consensus on the most effective ways to address and manage this condition.

This series has been made possible because of the generous support of Bausch + Lomb. The next and last installment in this series will provide an in-depth look at a new topic, nutrition, by a fresh panel of doctors.

— The Authors

## About the Authors



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## PART I: Epidemiology and Etiology of Keratitis

Keratitis, or inflammation of the cornea, is the most serious of the ocular surface disorders we have explored in this series. It can be sight-threatening and in severe cases, can even lead to loss of the eye. Both sterile and microbial forms of keratitis have been associated with contact lens wear. Other types include chemical, phlyctenular and herpetic keratitis.

### Contact Lenses and Keratitis

Contact lens wear contributes to keratitis risk in several ways. First, wearing contact

lenses, particularly hydrogel lenses, increases carbon dioxide accumulation and decreases oxygen availability under the lens, which reduces the metabolic activity of the epithelium.<sup>1</sup> Through mechanical trauma, hypoxia or as-yet-undiscovered mechanisms, contact lens wear may, in rare cases, also damage the limbal epithelial stem cells.

New silicone hydrogel contact lens materials have significantly reduced or eliminated negative effects on corneal homeostasis and lens-induced hypoxia for most wearers, but

their effect on tear film structure and physiology is similar to that found with other types of soft lenses.<sup>2</sup> As the turnover of the corneal epithelium slows down with lens wear, tear evaporation and thinning increases, and tear break-up time and lipid layer thickness decrease.<sup>2</sup>

In addition, contact lens wear interrupts and slows down the normal rate of tear exchange, which is necessary for the removal of debris, bacteria and antigens from the ocular surface. Silicone hydrogel lenses promote better

tear exchange than hydrogel lenses.<sup>3,4</sup> Regardless of material, overnight wear of lenses poses the greatest risk of complications. Patients who want to sleep in their contact lenses should be wearing lenses made from healthier silicone hydrogel materials, but they need to be aware that this material does not limit their risk of infection.<sup>5</sup>

Practitioners should be particularly cautious about recommending extended wear for patients with other risk factors for microbial keratitis, such as ocular surface disease, ocular trauma, smoking and older age. Unsupervised or uninstructed wear, as in the use of cosmetic contact lenses from unlicensed vendors or lens sharing among friends, also increases the risk of infection.<sup>6,7</sup> All contact lens patients—especially those who sleep in lenses—should be counseled about appropriate lens care and wear.

The latest evidence also suggests that microbial contamination of contact lens cases is a significant and probably underappreciated risk factor in contact lens-related keratitis.<sup>8-10</sup> Despite expectations that cases should be cleaned daily, 33% of patients say they only clean their cases once per month (or less often) and the majority expose their lenses to tap water in the process.<sup>11</sup> One recent paper suggests digital rubbing, rinsing with solution, tissue wiping and air drying as a better cleaning method.<sup>12</sup> In any case, practitioners would do well to emphasize the importance of case cleaning and

## Clinical Pearl

*As part of your patient education efforts, refer contact lens wearers to this Food and Drug Administration web site for a teaching video and additional information about lens care:*

*[www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ContactLenses/default.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ContactLenses/default.htm)*

regular replacement as a critical component of good contact lens care.

## Sterile Keratitis

Marginal infiltrative keratitis, also called hypersensitivity keratitis, contact lens acute red eye (CLARE) or sterile infiltrative keratitis, is the most common contact lens-related form of keratitis. Overnight or extended wear, poor hygiene, protein buildup, a fit that is too tight and contact lens solution hypersensitivity may all be contributing factors. The condition is typically not sight-threatening, but symptoms may be acute and involve significant morbidity.

Rather than a direct bacterial infection, sterile keratitis is thought to be the result of a host-immune response to bacterial exotoxins.<sup>13</sup> It may also be associated with lid disease, collagen vascular diseases or viral eye infections.

Neither silicone hydrogel materials nor daily disposable lens modalities have reduced the overall risk of acute non-ulcerative sterile keratitis.<sup>14</sup> In fact, certain silicone hydrogel lenses were recently associated with a two-fold increased

risk of sterile keratitis, perhaps because greater comfort encourages overwear. There appear to be significant differences among daily disposable brands, with some lens brands increasing risk and others decreasing it.<sup>14</sup>

Clinicians may also see a sterile form of keratitis in post-LASIK eyes. Diffuse lamellar keratitis (DLK) is an inflammatory condition associated with epithelial trauma that usually occurs within a few days after LASIK surgery. The incidence of DLK has been declining, but continued outbreaks associated with improper equipment sterilization have been identified.

## Microbial Keratitis

When the cornea's defenses are weakened from contact lens wear or trauma, opportunistic bacteria can more easily infect the cornea. The infection may be followed by stromal inflammation, which can be as damaging as the infectious process itself and may result in a permanent scar.

In a retrospective review of more than 1 million patient records, Jeng and colleagues determined that the rate of

ulcerative keratitis is 27.6 per 100,000 person-years, which is higher than previously reported.<sup>15</sup> The relative risk for contact lens wearers vs. non-lens wearers is 9.31.

The leading pathogens implicated in microbial keratitis (MK) include Gram-positive *Staphylococcus* and *Streptococcus* species and Gram-negative organisms such as *Pseudomonas aeruginosa*. *Pseudomonas* is the most frequently identified pathogen in contact lens-related MK, but is unusual in trauma cases.<sup>16-18</sup> The bacteria colonize soft contact lenses and often, the lens cases.<sup>10,19</sup> *Pseudomonas* and other Gram-negative species can quickly perforate the cornea, especially in the presence of an epithelial basement membrane defect.

In a large retrospective records review, 31.7% of MK patients lost more than two lines of vision and 1.6% lost 10 or more lines of vision, with ocular trauma and contact lens wear being the major predisposing factors.<sup>20</sup> In recent years, researchers have attempted to determine the relative risks of different types of contact lens wear. In large, prospective, post-market clinical trials of low-Dk/t extended wear disposable lenses, Holden and colleagues<sup>21</sup> found an annualized incidence of 57 cases of MK per 10,000 wearers—or 1 in 173 wearers per year of lens wear. (This was higher than the rate of keratitis seen previously in retrospective population studies.)

Stapleton and colleagues<sup>22</sup> published the following inci-

dence of MK by contact lens type from a one-year prospective study in Australia:

# MK cases per 10,000	Contact Lens Type
1.9	Hydrogel daily wear
11.9	Silicone hydrogel daily wear
2.0	Daily disposable wear
19.5	Hydrogel extended wear
25.4	Silicone hydrogel extended wear

• **Recent contact lens-related outbreaks.** Pathogens once considered much less common have become the subject of increasing concern in the United States contact lens community after two major outbreaks of contact lens-related keratitis. In 2006, an outbreak of *Fusarium* keratitis among contact lens wearers was linked to the use of a particular contact lens solution (ReNu with MoistureLoc, Bausch + Lomb) that was subsequently withdrawn from the market by the manufacturer. Lens care compliance was also thought to have been a factor. Research shows that 50% to 99% of contact lens wearers are noncompliant, with case care compliance being among the worst.<sup>23,24</sup>

Prior to this outbreak, fungal keratitis (caused by *Fusarium*, *Candida*, *Aspergillus* and other filamentous or dematiaceous fungi) was considered very rare in the United States, accounting for perhaps only 5% of corneal infections. It is much more common in tropical climates. Risk factors for fungal keratitis include ocular trauma (especially when associated with soil or

plant matter), diabetes mellitus, chronic topical medication use and topical steroids.

In 2007, an outbreak of *Acanthamoeba* contact lens-related keratitis was linked to another contact lens solution (Complete MoisturePlus, AMO), which was also recalled. Patient noncompliance was once again a factor, as was exposure to non-sterile water (e.g., tap, lake, pool, etc).

*Acanthamoeba* is a water-borne parasite that has both a cyst and trophozoite form. The cysts are very resistant to treatment. In this case, components of the lens care solution may have actually encouraged encystment of the organism.<sup>25</sup> Like *Fusarium* keratitis, *Acanthamoeba* corneal infections often go on to keratoplasty and poor visual outcomes.

Years after the recalls, rates of both *Acanthamoeba* and fungal keratitis remain elevated and have not returned to pre-outbreak levels.<sup>26,27</sup> These two serious contact lens-related keratitis outbreaks in the United States should serve as a reminder of the importance of educating patients about contact lens wearing schedules, hygiene and care. They also highlight the need for ongo-

ing development of contact lens disinfecting solutions. Fortunately, as multipurpose solutions (MPSs) continue to evolve, they are beginning to offer better disinfection against fungi, *Acanthamoeba* and other atypical organisms, particularly in combination with new silicone hydrogel materials.

#### • **Post-LASIK MK.**

Infectious keratitis is also seen as a rare but potentially devastating complication of laser refractive surgery. In 2001, the American Society of Cataract and Refractive Surgery reported the incidence of post-LASIK keratitis as about 1 in 3000 cases.<sup>28</sup> Cases tend to be clustered in mini-epidemics. When the onset is soon after surgery, the most likely pathogens are *Staphylococcus* species. Late-onset cases are more likely to be caused by fungi, *Nocardia* or atypical Mycobacteria.<sup>28</sup>

For the clinician, it is critical to differentiate sterile from infectious keratitis and fungal from bacterial so that appropriate management can be initiated. Inappropriate management delays resolution of the infection, increases cost and the duration of care and may result in vision loss and lasting ocular damage.

### **Recurrent Corneal Erosion Syndrome**

Recurrent corneal erosion syndrome (RCES) is characterized by recurrent episodes of nighttime eye pain or pain upon awakening, accompanied by redness and photophobia. The sudden onset of pain is caused by



Courtesy of Paul Karpecki, O.D.

Recurrent corneal erosion.

sloughing of the epithelium in one or more spots where it fails to adhere properly. It is believed that damage to superficial squamous cells of the epithelium due to corneal exposure is responsible for RCES.<sup>29</sup>

In 20% to 30% of cases, this syndrome is primary, related to epithelial basement membrane dystrophy (EBMD) or other dystrophies.<sup>29,30</sup> In the majority of cases (46% to 71%),<sup>30,31</sup> however, RCES is secondary to corneal trauma, such as a fingernail scratch or paper cut. It may also be secondary to ocular infection, lid pathology or systemic causes. There is a strong association between recurrent erosions and increasing age, as well as with sleep apnea-related dryness.<sup>32</sup>

### **Herpetic Keratitis**

Herpes simplex virus (HSV) stromal keratitis is a recurrent, corneal manifestation of the herpes simplex virus and a leading cause of corneal opacification.<sup>33</sup> Most (95%) ocular herpes infections, other than neonatal cases, are caused by HSV-1.<sup>34</sup> The incidence has been estimated at 8.4 to 13.2 new cases per 100,000 person-years,<sup>33</sup> with the elderly and immunocompromised more likely to suffer from this condition. Recurrences are common. Exactly what triggers these recur-

rences is poorly understood. They have long been thought to be linked to stress, but at least one study found no evidence of an association with stress.<sup>35</sup>

Immune stromal keratitis (ISK, often called disciform keratitis in the past), although also caused by herpes simplex, is a stromal immune response to the prior viral antigen exposure. It does not, therefore, present as an active stromal infection, but there may be some live virus concurrent with the immune keratitis.

Herpes zoster ophthalmicus (HZO) also often leads to corneal involvement. HZO forms of keratitis include infectious epithelial pseudodendrites, neurotrophic ulcers or persistent epithelial defects and stromal immune reaction.<sup>36</sup>

### **Phlyctenular Keratitis**

Phlyctenular keratitis is thought to be a delayed hypersensitivity response to microbial infection, often *Mycobacterium tuberculosis* or *S. aureus*. Recently, it has been shown that *Propionibacterium acnes* is also implicated.<sup>37</sup> More prevalent in young females, the condition and its severity are often closely associated with meibomitis.<sup>37</sup>

### **Chemical Keratitis**

Chemical injury rapidly destroys the epithelium and can cause significant damage to the cornea. Acidic agents cause more surface damage, while alkali agents tend to penetrate more aggressively, causing stromal scarring, ectasia and progressive damage.<sup>38</sup>

# PART 2: Diagnosis and Management of Keratitis

## Sterile Keratitis

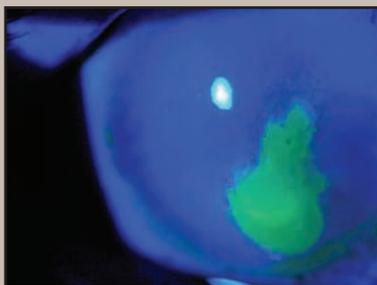
Sterile peripheral corneal infiltrates are commonly seen in optometric practice. Upon examination, the clinician typically sees grayish-white infiltrates in the peripheral cornea, with a clear zone separating the infiltrates from the limbus.

The standard of care in the treatment of peripheral infiltrates is to treat empirically with a combination antibiotic/steroid such as tobramycin/loteprednol etabonate (Zylet, Bausch & Lomb). The medication should be instilled every 2 hours while awake for the first 24 to 48 hours, then reduced to q.i.d. for 3 to 5 more days. With this regimen, the combination therapy can address the most likely culprit, sterile corneal inflammation, and will

### When to Culture

- Infiltrate on or near the visual axis
- Large infiltrate (>3 mm)
- Significant decrease in vision
- Post-surgical eye
- Monocular patient
- History of immunocompromise
- Ocular steroid use
- Older patient
- Diabetic patient
- Patient who works in a nosocomial or health-care setting.

Courtesy of Paul Karpecki, O.D.



In infectious keratitis, the infiltrate is often accompanied by an overlying epithelial defect approximating the size of the stromal infiltrate.

often be sufficient to treat any pathogenic bacteria should there be an early infection.

The risk that the infiltrates are infectious and could be worsened by the steroid is very low. However, if other risk factors, such as a diffuse red eye, cells in the anterior chamber or severe pain are present, a broad-spectrum fluoroquinolone should be used as initial therapy. Patients should be followed closely to ensure improvement with treatment.

Sterile diffuse lamellar keratitis (DLK) may also occur post-LASIK or other refractive surgery. Topical corticosteroids are appropriate for the treatment of DLK, unless the clinician sees clumping of the cells. In the presence of this sign, a corneal melt is possible, and oral corticosteroid therapy should be added.<sup>39</sup>

## Microbial Keratitis

In contrast to the non-infectious conditions described above, MK is characterized by more central, rather than periph-

eral ulcers, more anterior chamber reaction and is often accompanied by an overlying epithelial defect approximating the size of the stromal infiltrate (see sidebar “Differential Diagnosis: Sterile Infiltrative Events vs. Microbial Keratitis” on the next page).

The typical presentation of MK includes a significantly red eye with acute onset. The patient will typically experience more pain and discharge from an infectious ulcer compared to a sterile infiltrate. Severe pain, while not diagnostic, should raise the clinician’s suspicion of infection. Decreased vision is virtually pathognomonic for an infectious process. Vision may be affected even when the infiltrate is relatively small and not located on the visual axis.

In examining a patient with suspected MK, look for the characteristic epithelial defect overlying the infiltrate. Careful assessment of the tear film and discharge is essential. The discharge may be subtle and micro-particulate rather than purulent. Clinicians will often see cells and some flare in the anterior chamber, as well.

Although there is some suggestion in the literature that Gram-negative infections tend to be more diffuse and “wetter” in appearance, visual assessment of the lesion is not sufficient to determine whether the infectious agent is Gram-negative or Gram-positive. Larger, more centrally located or more aggressive infiltrates

## Mini-Tip Cultures are available from multiple sources, including the following:

- eGeneral Medical, Inc., in Raleigh, N.C., (919) 844-9402 or [www.egeneralmedical.com](http://www.egeneralmedical.com)
- Hardy Diagnostics in Santa Maria, Calif., (805) 346-2766 or [www.hardydiagnostics.com](http://www.hardydiagnostics.com)

must be cultured to guide therapy.

Direct culture plating is complex and unlikely to be performed often enough to be reliable in a primary eye-care setting. Pre-packaged mini-tip culture kits have been shown to be as sensitive and specific as direct plating.<sup>40</sup> They are simple and have a relatively long shelf life compared to other culturing materials.

For the most accurate result,

a deep swab of the infiltrate is needed, so anesthetic eye drops (ideally non-preserved) should be instilled. We recommend swabbing the infiltrate itself or around the perimeter of the epithelial defect, rather than attempting to culture the discharge, as discharge does not always contain active bacteria.

A gram stain is also relatively simple and can provide valuable information about whether the causative bacteria

are Gram-negative or Gram-positive.

Medical therapy of MK has changed dramatically over the last decade or so. Prior to the 1990s, the standard of care was fortified cefazolin or vancomycin for Gram-positive ulcers and tobramycin or gentamicin for Gram-negative ulcers. Many corneal specialists still adhere to that regimen today. But research data and clinical experience suggest that smaller, superficial, off-axis lesions can be treated empirically with fluoroquinolone monotherapy.<sup>41</sup>

As with the decision of whether or not to culture, the size of the defect and the likelihood of threatening vision must also be taken into account

## Differential Diagnosis: Sterile Infiltrative Events vs. Microbial Keratitis

	Sterile Corneal Infiltrates	Microbial Keratitis
<b>Symptoms</b>	Minimal pain and photophobia	Moderately severe pain and photophobia
<b>Conjunctival Injection</b>	Minimal, possibly sectoral	Moderate to severe, most likely diffuse
<b>Lid Edema</b>	None or minimal	Moderate
<b>Visual Acuity</b>	Normal	Decreased
<b>Location</b>	Usually mid-peripheral to peripheral, subepithelial	Random with deeper involvement, tend to be more central
<b>Size</b>	Usually 1 to 1.5mm, tend to remain small	> 1.5mm, enlarges over 24-36 hours
<b>NaFl Staining</b>	None or minimal	Moderate to extensive
<b>Anterior Chamber Reaction</b>	None or minimal	Moderate
<b>Stromal edema</b>	None or minimal	Moderate
<b>Number of Infiltrates</b>	Tend to be multiple (>1)	Single
<b>Clear Zone at Limbus</b>	Positive	Negative
<b>Shape</b>	Oval	Any
<b>Purulent Discharge</b>	Negative	Positive

when deciding between fortified and commercially available antibiotic therapy. With severe infections, aggressive and appropriate initial therapy is key to avoiding poor outcomes.<sup>42</sup> The Wills Eye Manual chart on fortified antibiotics and the chapter on the same subject in Ophthalmic Drug Facts<sup>43</sup> are helpful resources.

The only topical ophthalmic antibiotics approved for the treatment of MK are ciprofloxacin, ofloxacin, and levofloxacin. On-label does not, however, mean effective. Resistance to ciprofloxacin, in particular, has been increasing. As standards of care have evolved, newer fluoroquinolones such as moxifloxacin and gatifloxacin have been utilized off-label.

The latest iterations of these fluoroquinolones, Zymaxid (Allergan) and Moxeza (Alcon) include higher antibiotic concentrations, but the active ingredients (gatifloxacin and moxifloxacin, respectively) are the same.

The newest fluoroquinolone, besifloxacin (Besivance, Bausch + Lomb), while also not labeled for keratitis, has demonstrated broad-spectrum in vitro activity against both Gram-positive and Gram-negative pathogens, including those resistant to other fluoroquinolones.<sup>44</sup> In recent rabbit model studies, besifloxacin has been shown to be very effective against *Pseudomonas* keratitis and methicillin-resistant *Staphylococcus aureus* (MRSA) keratitis.<sup>45-47</sup> After treatment, significantly fewer colony-forming units were recovered

from the besifloxacin-treated eyes than from those treated with gatifloxacin, moxifloxacin, or saline (controls). The minimum inhibitory concentrations (MICs) for besifloxacin were at least 8-fold lower than those for the other fluoroquinolones. Besifloxacin may also have some anti-inflammatory properties.<sup>48</sup>

Treatment of suspected MK with topical fluoroquinolones should be much more aggressive than the typical q.i.d. dosing for postoperative prophylaxis or routine corneal presentations. Achieving compliance with some of the dosing recommendations in the medication package inserts (every 15 minutes for six hours, then every 30 minutes for 18 hours, for example) is very challenging. A more realistic schedule is a loading dose of one drop every minute for five minutes given in the office, then drops every hour while awake. At bedtime, the patient can apply an ointment such as bacitracin or bacitracin-polymyxin B, although some clinicians may prefer for them to awaken for drops every 2 hours the first night. Daytime fluoroquinolone treatment should be continued at least hourly, and patients should be examined daily until clinical resolution has occurred.

In sight-threatening cases where vision loss is a concern, q30-minute dosing may be required, and topical fluoroquinolones alternated with fortified antibiotics may be desirable.

With increasing concerns about MRSA, some clinicians

have added trimethoprim-polymyxin B (Polytrim) q2h to fluoroquinolone therapy to provide additional protection against resistant organisms, especially *S. aureus*. Besifloxacin may be able to provide similar coverage to these two drugs in a single medication. In addition to the evidence from the MRSA rabbit studies described above,<sup>46,47</sup> the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study provides important information about differences in the potency of commonly used antibiotics against clinical isolates.<sup>49,50</sup>

For example, according to their MIC<sub>90</sub> values, besifloxacin, vancomycin and imipenem were the most potent against *S. aureus* isolates, while ciprofloxacin, tobramycin and azithromycin were the least potent. Against MRSA, besifloxacin maintained potency with an MIC<sub>50</sub>/MIC<sub>90</sub> of 0.5/1 µg/mL (moxifloxacin: 2/8 µg/mL; ciprofloxacin: 8/256 µg/mL).<sup>49</sup> Imipenem, besifloxacin and vancomycin were the most potent agents against coagulase-negative *Staphylococci* (CNS), while levofloxacin, trimethoprim and azithromycin were the least potent.

Again, the aggressiveness of therapy should be titrated somewhat to the degree of risk, using the same factors one uses in determining whether to culture and whether to use fortified antibiotics.

Eradicating the microbes must be the first priority; adjunctive agents can then help to suppress tissue inflammation and reduce

discomfort. A topical cycloplegic agent such as homatropine, scopolamine or cyclopentolate given at each office visit dramatically reduces the pain level for the patient. Due to the risk of corneal melts, we avoid topical NSAIDs for pain in MK cases, but oral ibuprofen or opioid analgesics can be helpful.

Steroids are effective in treating inflammation but must be used wisely. They should not be given until culture results are available and there is a significant response to treatment—preferably re-epithelialization. This will usually be at least two days after commencing treatment of Gram-positive organisms, and at least three days with Gram-negative organisms. Provided one is certain that the etiology is not fungal or herpetic, it is prudent and reasonable at that point to add two to four times daily dosing of corticosteroid anti-inflammatory therapy such as loteprednol etabonate (Lotemax, Bausch + Lomb) or difluprednate (Durezol, Alcon) to decrease the potential for scarring, particularly if the lesion is para-central. One very recent study showed no benefit to using steroids in combination with antibiotic therapy in the treatment of corneal ulcers.<sup>51</sup> However, the authors also suggested that the early addition of steroids to the antibiotic treatment of corneal ulcers does not seem to be harmful when employed in a closely monitored clinical setting. A national study on the role of steroids in the treatment of infectious keratitis

is underway.<sup>52</sup> Oral doxycycline to minimize the potential for collagenase activity may also be considered.<sup>53</sup>

With Gram-negative infections, it is not uncommon for the infiltrate to appear the same and the epithelial defect to appear even larger after the first day of treatment.<sup>54</sup> This sometimes mistakenly leads clinicians to change the course of treatment too soon. If culture results suggest the selected therapy is correct, give therapy a little longer to begin to show results.



Contact lens wearers are also at increased risk for developing *Acanthamoeba* keratitis, particularly following exposure of lenses to contaminated water. In the early stages, there is sometimes a gelatinous appearance to the cornea; in the later stages, it is commonly misdiagnosed as herpes simplex keratitis.

• **Contact lens-associated MK.** Contact lens wearers are at increased risk for both sterile and microbial keratitis, including some particularly virulent or unusual pathogens. In making the differential diagnosis in a contact lens wearer, the location of the lesion is very important. In a sterile event, the contact lens wearer typically would have smaller and more peripherally located

lesions, classically at the limbus with a clear zone, while an infectious etiology is more likely to produce a single, larger, and more centrally located lesion. Other differentiating features are described above and in the table on page 7.

Contact lens wearers are also at increased risk for development of *Acanthamoeba* keratitis, particularly following exposure of contact lenses to contaminated water (e.g., swimming pools, hot tubs, tap water). In the early stages, there is sometimes a gelatinous appearance to the cornea. Later, one will see perineural infiltrates that look very similar to linear or dendritic herpetic lesions and often lead to misdiagnosis as herpes simplex keratitis. Patients with *Acanthamoeba* keratitis usually, but not always, complain of significant pain. Typically, the eye appears to be getting better, then suddenly flares back up between days 10 and 14. If MK does not improve after 14 days of treatment, reconsider your diagnosis and treatment.

Polyhexamethylene biguanide (PHMB) is generally the preferred agent for treatment of *Acanthamoeba* keratitis. Other agents, used in combination or alone, include propamidine and chlorhexidine. A corneal consult is recommended.

Contact lens-related keratitis is often seen in patients who are noncompliant with lens care and wearing schedules. In particular, we know that the risk of infiltrates and ulcers is highest among those who sleep in contact lenses.

Unfortunately, such patients may also be noncompliant with medical therapy to treat the infection. It is very important to emphasize to the noncompliant lens wearer the potential consequences of not using the prescribed drops. They must be made aware of the risk of blindness, corneal scars and other long-term sequelae.

A compliant patient can be wearing contact lenses again within a week or 10 days of full resolution of the infection. When there is chronic noncompliance or poor hygiene, keeping the patient out of lenses a little longer and working on modification of behaviors or wearing schedules is advisable. The practitioner may consider a switch to daily wear or daily disposable lenses or re-fitting with a looser lens.

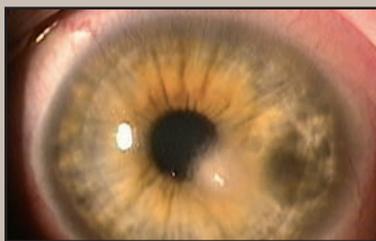
• **Fungal keratitis.** This form of keratitis is exceedingly rare in the United States, but the possibility of a fungal etiology cannot be ignored, particularly if there is a history of vegetative abrasions or agricultural work. The 2006 *Fusarium* outbreak described earlier also demonstrated that contact lens solutions or lens hygiene may be implicated, even without other corneal trauma.

Fungal keratitis is characterized by conjunctival injection and gray or yellow-white infiltrates with irregular, dry, feathery margins.<sup>55</sup> The lesions may be slightly raised above the plane of the corneal epithelium. Satellite lesions and endothelial plaque formation may be more common in fungal keratitis than in bacterial cases.

Culture scrapings will be brittle rather than wet. However, all these distinctions are subtle ones that may be difficult to discern.

If a fungal etiology is suspected, a spatula scraping is preferred over a mini-tip culturette; however, the latter may still isolate the fungal pathogen. Although they tend to develop more slowly

Courtesy of Randall Thomas, O.D.



Fungal (*Fusarium*) infection with stromal infiltrate.

than typical bacterial keratitis, *Fusarium* and other fungal infections are very challenging to treat. Outcomes and response to medical therapy have historically been poor.<sup>56,57</sup>

The standard approach to treatment is topically administered natamycin. If the eye doesn't respond, amphotericin B, flucytosine, fluconazole or a new-generation triazole may be added.<sup>57-60</sup> Antifungal medications have significant side effect profiles, so even if there is a strong suspicion of a fungal etiology, the ulcer should be treated with fortified antibiotics until positive culture results are obtained. Serious consideration should be given to referring to or co-managing with a corneal specialist, given the substantial risks of morbidity, visual loss, corneal scarring and corneal perforation.

## Post-Refractive Surgery Keratitis

MRSA is the most commonly cultured pathogen in post-LASIK keratitis.<sup>61</sup> Although the MRSA pathogen is still relatively rare in non-institutionalized patients, MRSA keratitis following refractive surgery has been reported in the literature, including a series of 13 cases in New York.<sup>62-64</sup>

A large national surveillance program, ARMOR, has recently shown that the incidence of MRSA may be on the rise,<sup>49,50</sup> so clinicians should maintain a healthy awareness of the potential for MRSA and be prepared to treat suspected cases.

Post-refractive surgery keratitis generally occurs within a few days of the laser procedure and should be cultured and treated quickly. In choosing an antibiotic to treat MRSA, the clinician must consider more than just the drug's minimum inhibitory concentration (MIC) value, which is established for the active ingredient and doesn't necessarily reflect the efficacy of a given formulation in a clinical setting, when factors such as washout and pH come into play. The clinician should consider antimicrobial potency as well as tissue penetration of the antibiotic selected to treat MRSA.

The ARMOR data have demonstrated that the new fluoroquinolone besifloxacin, along with some older antibiotics, remain highly efficacious against pathogens that have developed resistance to other drugs. When MRSA is diagnosed or suspected, it is appropriate to add besifloxacin and/or trimethoprim with polymyxin B to your regimen. In post-operative manage-

ment of suspected MRSA infection, fortified vancomycin may also be considered.

## Recurrent Corneal Erosion Syndrome

Acute, unilateral morning pain and redness are hallmarks of RCES. The erosions are usually found on the inferior cornea. Macroform erosions result in significant symptomatology and are usually clearly visible to the clinician. Microform erosions, however, dissipate within 30 minutes to a few hours and must be diagnosed by history. Clinically, the clinician may see negative staining patterns or poor wetting at the site where the epithelium is breaking down, even if the erosion has healed by the time of presentation.

Although often associated with ocular trauma, such as a fingernail scratch, corneal erosion can be spontaneous. In such cases, look closely for subtle signs of epithelial basement membrane dystrophy (EBMD), such as rapid tear film break up in the same spot. After applying a topical anesthetic, gently touch the cornea (typically the inferior cornea) with a Weck cell sponge. In eyes with EBMD, the epithelium heaps up like a loose carpet rather than staying tight as it should. When underlying EBMD is present, it takes very little to cause recurrent epithelial problems.

RCES is relatively easy to diagnose, but there are many different approaches to managing these patients clinically. The standard baseline treatment for RCES is lubrication, ideally with

hypertonic sodium chloride solution (Muro 128 5%, Bausch + Lomb) used q.i.d., plus the same medication in an ointment form at bedtime. Research shows that sodium chloride has a therapeutic effect beyond just lubrication.<sup>65</sup> To be effective, however, therapy should be continued for at least six to eight weeks to draw fluid from the epithelium, keeping it apposed to Bowman's membrane and thereby promoting adherence. This allows for normalization of the basal cells, epithelial basement membrane and stromal corneal tissue complex. (After the first month, clinicians may substitute a non-hypertonic artificial tear ointment at night).

Bandage contact lens therapy for three months or longer is a viable option for the management of patients with recurrent corneal erosion.<sup>66,67</sup> A low-powered refractive lens, whether approved as a bandage lens or not, serves this purpose quite well. Phototherapeutic keratectomy (PTK)<sup>68</sup> and autologous serum<sup>69</sup> have also been shown to have long-term efficacy in treating this condition. Other possible interventions include alcohol delamination or mechanical debridement of the epithelium. Patching is rarely necessary.<sup>70</sup>

For recalcitrant cases, inhibition of matrix metalloproteinase-9, the enzyme responsible for epithelial cleaving, with topical steroids plus oral doxycycline appears to be quite successful.<sup>71,72</sup>

In such cases, we recommend a "cocktail" that includes hypertonic sodium chloride 5% t.i.d. to q.i.d. daily for two months; Muro 128 ointment at bedtime;

Lotemax q.i.d. for two to four weeks, then b.i.d. for six weeks; and 20 mg to 50 mg of doxycycline b.i.d. for two months. Anterior stromal puncture, as pioneered by Rubinfeld, is also very effective.<sup>73</sup>

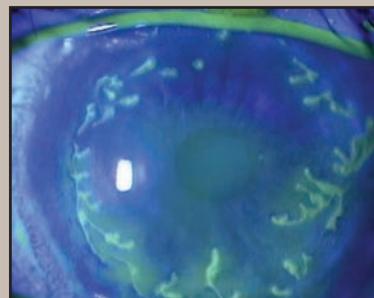
Long-term management demands ongoing lubrication of the eye with artificial tears and possibly supplementation with omega-3 fatty acids. Patients should be counseled to avoid ceiling fans, especially at night. Concomitant blepharitis should also be treated appropriately to help prevent recurrences.

## Herpetic Keratitis

• **Herpes simplex.** Herpes simplex keratitis is seen commonly in clinical eye-care practice. Most people have been exposed to the herpes simplex virus as children, often without ever being diagnosed or treated, as the initial exposure presents as transient mild fever, malaise and chills. Primary herpetic disease



Herpes simplex keratitis.



Herpes simplex keratitis.

Courtesy of Randall Thomas, O.D.

Courtesy of Randall Thomas, O.D.

## Differential Diagnosis of Herpes Simplex and Herpes Zoster

	Herpes Simplex	Herpes Zoster
<b>Dermatomal distribution</b>	Not applicable	Respects the dermatome
<b>Pain</b>	Mild to moderate	Severe
<b>Dendrite appearance</b>	Larger, more branching, discrete, delicate pattern, more central	Smaller, less branching, coarse, blunted pattern, usually peripheral
<b>Epithelium</b>	Ulcerated	Blunted dendrite with slightly raised edges
<b>NaFl staining</b>	Prominent	Dull and irregular
<b>End bulbs</b>	Present	Absent
<b>Scarring of skin</b>	Rare	Common
<b>Postherpetic neuralgia</b>	Rare	Common
<b>Iris atrophy</b>	Rare	Common
<b>Recurrence</b>	Common	Rare

Adapted from Nichols B, Ed. Basic and clinical science course. External disease and the cornea, Section 7, American Academy of Ophthalmology, San Francisco CA 1990.

often has ocular manifestations such as periocular vesicles or ulcerative blepharitis.

Herpes simplex keratitis usually builds up over two to five days, rather than presenting acutely, and is almost always unilateral. Patients typically have some corneal desensitization, little pain and mild photophobia—certainly not the extreme photophobia that clinicians see with infiltrative ulcers or iritis.

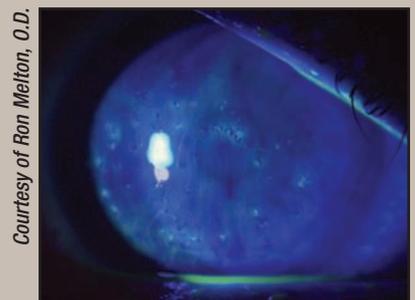
The classic hallmark of herpes simplex is the dendritic ulcer. In the early stages, clinicians might see some focal superficial punctate keratitis (SPK) without the typical dendritic configuration. But even early herpetic lesions will tend to be linear in shape, rather than the round or oval shape common to sterile or bacterial infiltrates. The terminal end bulbs that are also characteristic of herpes simplex keratitis may not be apparent at early

stages, but can be revealed even in small lesions with rose bengal or lissamine green dye. In more advanced stages, the lesions may take on a broader, more geographic appearance.

In the differential diagnosis of HSV keratitis (see table above), one must also rule out conditions that can mimic it, including a rare toxic response to topical latanoprost<sup>74</sup> and Thygeson's SPK.<sup>75</sup> About 20% of all Thygeson's cases are unilateral, such as HSV keratitis. However, Thygeson's typically presents with sudden onset, more photophobia and normal corneal sensitivity. Additionally, the lesions look quite different. Thygeson's lesions are granular, punctate and very well defined. Occasionally, there may be some anterior chamber reaction to herpes simplex, but never to Thygeson's. Also, the lesions for Thygeson's tend to be relatively

uniform throughout the cornea and individual rather than overlapping or coalesced.

A new antiviral, ganciclovir ophthalmic gel (Zirgan, Bausch + Lomb) has replaced trifluridine (Viroptic, Monarch) as the



Courtesy of Ron Melton, O.D.

In Thygeson's SPK, the lesions look quite different from those of herpes simplex keratitis. They are granular, punctate, and well-defined.

standard of care for herpetic keratitis. Ganciclovir ophthalmic gel is as effective in treating established HSV-1 herpetic keratitis in the rabbit as trifluridine<sup>76</sup> but is more convenient and tolerable

for patients than other options<sup>77</sup>,<sup>78</sup> (See “Topical Antiviral Options”). Zirgan is dosed five times a day until the ulcer is healed, followed by three times a day for seven days.

It is important to emphasize to patients that there is a 40% to 50% chance of recurrence with HSV keratitis. Adjunctive, prophylactic oral antivirals can reduce the chance of re-activation.<sup>79</sup> Landmark clinical trials recommend ongoing prophylactic use of acyclovir 400 mg b.i.d. or valacyclovir 500 mg once daily to prevent future recurrences.<sup>80,81</sup> Additionally, anyone with a history of herpes simplex keratitis should be prophylactically treated with oral antivirals before and after undergoing corneal surgery. The adult dosage of acyclovir is easy to remember: 400 mg (half that for herpes zoster) five times daily for a week. Oral antivirals may also be a good first-line choice for children or others who have trouble with eye drops.<sup>82</sup> Permanent punctal occlusion by thermal cautery with topical cyclosporine has also been suggested to reduce recurrences of stromal HSV keratitis.<sup>83</sup>

The management of ISK can be more challenging. Corticosteroids will quickly resolve the stromal edema. However, steroid therapy may at the same time activate or exacerbate the epithelial disease, so a concomitant topical antiviral, dosed q.i.d., is needed. As the steroid is tapered, the antiviral can be reduced or eliminated.

Additionally, a key difference in the treatment of ISK compared to epithelial herpetic kera-

## Topical Antiviral Options

### Trifluridine

- Old drug
- Nonselective toxicity
- Potentially toxic
- More frequent dosing
- Refrigerate until opened
- Thimerosal preserved
- Solution (7.5 ml bottle)
- Viroptic and generic
- Samples not available

### Ganciclovir

- New drug
- Infected cell-specific
- Very low toxicity
- Less frequent dosing
- No refrigeration needed
- BAK preserved
- Gel (5 gram tube)
- Zirgan by B+L
- Samples available

titis is that the steroid treatment must usually be continued over several months, with a long, slow taper. Some people may even need once-daily steroid therapy for life. Loteprednol is ideal for these cases because of its reduced propensity to elevate IOP or cause cataracts.

Both forms have a tendency to recur and may be reactivated by ultraviolet exposure, trauma and possibly stress. The triggers are difficult to determine and are highly variable.

• **Herpes zoster ophthalmicus.** Ocular involvement is common with first division trigeminal herpes zoster ophthalmicus (HZO). The ocular involvement is typically inflammatory keratitis or uveitis, but occasionally episcleritis. In milder cases without uveitic involvement, oral antivirals alone may be used to treat HZO keratitis. But according

to one study, 45% of all cases of herpes zoster have significant iritis, while 36% also go on to develop glaucoma within a 10-year period of time,<sup>84</sup> so it is very important to evaluate for uveitis.

If uveitis or significant stromal disease is present, aggressive topical corticosteroid inflammatory suppression is needed. Clinicians may see a secondary sharp increase in IOP, but rather than stopping the steroid, treat the IOP spike by getting the inflammation under control.

### Phlyctenular Keratitis

Phlyctenular keratitis is seen most often in younger children, especially girls. The position of the lesion—straddling or perpendicular to the limbus—can help to distinguish phlyctenular keratitis from a marginal infiltrate. The lesion will have a raised appearance, and if the lesion is on the cornea, one can usually see a leash of blood vessels continuous with the phlyctenule, which is quite different from a clear or lucid interval in the setting of a peripheral infiltrate. The patient may report significant foreign body sensation if the phlyctenule migrates onto the cornea.

There is often associated



Herpes zoster.

Courtesy of Paul Karpecki, O.D.

blepharitis, given that phlyctenular keratitis is usually the result of staphylococcal hypersensitivity. However, it may also be caused by tuberculosis (TB). Though rare in the United States, TB exposure can occur unnoticed in health-care settings, foreign travel, or on Native American reservations. Patients with phlyctenular keratitis and no obvious blepharitis should be referred for a TB test to rule out a

Courtesy of Randall Thomas, O.D.



The position of the lesion—straddling or perpendicular to the limbus—can help to distinguish phlyctenular keratitis from a marginal infiltrate.

tubercular etiology, particularly if they have been in an area where TB is active.

Phlyctenular keratitis should be treated with topical steroids, given every 2 hours for two or three days, then tapered to q.i.d. for a week. The patient should see improvement within just a day or two. If there is significant epithelial compromise, with its attendant risk of superficial infection, the clinician can use an antibiotic/steroid combination agent such as Zylet. Doxycycline can be used to treat the associated lid disease and improve meibomian gland functioning to prevent recurrences. This drug, however,

must be avoided in children under 12 years of age.

## Chemical Keratoconjunctivitis

With chemical keratitis, which typically involves the conjunctiva as well, the patient has often been pre-treated in an emergent care setting. For the eye-care provider, it is important to know the nature of the agent and any pre-treatment that has occurred. Then, after determining the extent of the injury, the immediate goals are to minimize ulceration and inflammation and promote re-epithelialization.

Ocular exposure to cyanoacrylate (fingernail glue) is common and can be very frightening for the patient but is actually minimally toxic and fairly benign. Using a wet gauze pad and light pressure pads, keep the area wet for 24 hours before peeling off the dried glue.

Aminoglycosides, particularly gentamicin, have been known to cause chemical keratitis, as have proparacaine and tetracaine. Contact lens solutions, hydrogen peroxide and facial lotions can also cause chemical injury to the eye. Lavage the eye to flush out any remaining chemicals.

A litmus test strip can be helpful for those cases when the exact source of chemical injury is not known. If there is no known accidental cause, stop any topical medications. If the chemical agent is highly alkali, use aggressive lavage and check the pH again after flushing out the eye. If the pH has normalized, the eye may be fine, but with continued high

pH, significant blanching or limbal ischemia, the eye may require corneal transplantation. Consultation with a cornea specialist is recommended.

In less severe cases, non-preserved artificial tears are the first line of therapy, but the clinician should also consider antibiotic and/or steroid therapy. Treat with a topical antibiotic alone if there's a fair amount of epithelial compromise, or a combination antibiotic/steroid, depending on the nature of the corneal presentation, the offending agent and the inflammatory response. A cycloplegic is also very helpful for controlling ocular pain.

## Conclusion

Primary eyecare providers routinely see sterile corneal infiltrates, herpetic keratitis and other forms of corneal inflammation and infection, and should be able to recognize and treat rarer, but potentially more devastating forms of keratitis as well. This monograph is intended to serve as a guide to differential diagnosis and management of various corneal disorders.

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