Fighting Corneal Invaders

Experts explain how to eradicate the pathogens that cause infectious keratitis.

• Understanding Corneal Infection Care
• Fungi and Protozoa in Contact Lens Wearers
• How to Fend off Herpes and Varicella Zoster
• Critical Questions in Disease Management
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Cover design by Ashley Schmouder. Illustrations by Gina Urwin. Design ©Jobsonhealthcare.
Accelerated CXL Protocol, New Imaging Aid Keratoconus Care

The advent of corneal collagen crosslinking (CXL) using ultraviolet A (UV-A) redefined the progressive keratoconus (KC) treatment paradigm from one of management to one of active, non-invasive intervention. Accelerated CXL, one variation of the Dresden protocol, uses higher levels of UV light over shorter durations of time, in effect administering the same UV dosage as conventional CXL treatments while providing for reduced procedure time.

Although duration and level of irradiance are important aspects of CXL, follow-up time in prospective CXL studies are integral to proving the efficacy and safety of accelerated CXL protocols. A new study in the journal Cornea looked at the impact of accelerated CXL, mediated by exposure to a UV-A irradiance of 18 (mW/cm²) for a period of five minutes, on progressive keratoconus. The study examined the effects of the CXL protocol through follow-up visits over the course of up to 21.7 months. According to researchers at the University of Muenster Medical Center, the indexes of surface variance and height decentration, which are the most sensitive and specific criteria by which efficacy of CXL is determined, were shown to match those of standard CXL. Importantly, corneal complications did not occur in any subjects of the study.

The new accelerated CXL protocol matched the efficacy and safety of standard CXL protocols, as demonstrated by looking at keratoconus and corneal health indices over acceptable follow-up times.

NEW TECHNOLOGIES

Early detection of keratoconus before laser-based surgery, in which subclinical KC may lead to full ectasia post-surgery, is a major priority. Researchers used a new in vivo, noncontact corneal biomechanical analysis device called the Corvis ST (Oculus) in addition to new indicators of early KC called application length level and deflection length level, to improve subclinical KC detection. Currently, subclinical keratoconus is difficult to detect because distinguishing a normal eye from a keratoconic eye has not been device-independent; by using the keratoconus percentage index (KISA%) and commonly used topographic patterns, the study was able to better define KC, which may be used in the future to detect early KC more often.

Also, a new form of OCT called swept-source Fourier-domain optical coherence tomography (SS-OCT) uses a special mathematical analysis to detect subclinical KC, which puts prospective laser-based surgical patients at high risk for post-surgical ectasia. Using the KISA% along with SS-OCT, researchers were able to detect subclinical KC to a high degree of accuracy. All new early KC detection technologies become more accurate when using device-independent indices to differentiate between normal and keratoconic eyes.

IN BRIEF

- There may be a connection between serologic markers and conjunctival damage in patients with Sjögren’s syndrome, reports a study in Cornea. Researchers evaluated 64 patients diagnosed with primary Sjögren’s according to the 2012 Sjögren’s International Collaborative Clinico-Rheumatologic Assessment (SICCA) criteria. Serum anti-Ro/SSA, anti-La/SSB, rheumatoid factor (RF), antinuclear antibody (ANA) levels, Ocular Surface Disease Index (OSDI), Schirmer I test values, tear breakup time and SICCA ocular staining score (OSS) were determined. A strong correlation between serum RF and ANA levels and conjunctival staining scores and the total OSS was identified, suggesting conjunctival damage. Further study is needed to investigate the OSDI and SICCA OSS at multiple time points after treatment.


- Dry eye patients exhibit varied but diminished corneal sensitivity (CoS), suggesting there are different states of ocular surface compensation for the disease. Researchers measured the CoS and evaluated the tear films of forty-six patients with DES four times over the course of three months, and observed a statistically significant change in sensitivity values, especially with more severe disease. CoS severity was highly variable. “Normal sensitivity values, measured once, cannot exclude future changes in sensitivity,” the authors wrote. Although patients were separated into etiologic subgroups—hormonal, immunologic, toxic, neural and environmental—no statistically significant differences were found among them, likely due to small sample size.


- A new tear-infused lens material technology from Johnson & Johnson Vision Care is designed to help wearers tolerate their lenses longer. The Acuvue Oasys Brand Contact Lenses 1-Day with HydraLuxe mimic the body’s natural mucins to lubricate and moisturize the eye, improving comfort, J&J says.

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Failure to Communicate
The CDC’s latest MMWR reveals that contact lens compliance is embarrassingly low. What can we do about it?

Recently, the Centers for Disease Control’s Morbidity and Mortality Weekly Report (MMWR) highlighted the United States contact lens-wearing public’s abysmal record for contact lens compliance. The results of the survey were both tragic and embarrassing, and should serve as a sobering reminder that we, the contact lens prescribers responsible for our patients’ well-being, may not be doing an adequate enough job educating patients on proper lens care and hygiene.

A population-based estimate of the number of contact lens wearers suggests there are 40.9 million lens wearers in the United States, many of whom are at risk for adverse reactions to contact lens wear. Demographically, the results showed that, overall, contact lens wearers were younger, female and white compared with non-lens wearers.

A WAKE-UP CALL
Researchers used an adapted version of the Contact Lens Risk Survey to help describe lens behaviors.

Approximately 99% of over 1,000 lens wearers surveyed online said they engaged in one or more behaviors identified in previous studies as a risk for infection. Nearly one-third of those surveyed reported a previous contact lens-related red eye, a painful response requiring medical intervention, or both. Some of the reckless behaviors soft lens wearers admitted to:

- Keeping daily wear lenses in overnight (50.2%).
- Napping in their lenses (87.1%).
- Topping off solution in the lens case instead of replacing it daily (55.1%).
- Extending the replacement frequency of lenses (49.9%) or lens cases (82.3%).
- Showering while wearing lenses (84.9%) and swimming while wearing lenses (61.0%).

The majority of GP wearers and about one-third of soft lens wearers also reported using tap water to rinse or store their lenses. This is concerning, as it violates a basic tenet of contact lens wear: exposure to non-sterile water of any type poses a potential risk for devastating microbial events.

Lens cases remain the primary reservoir of microbial contamination. Another recent study showed that over 50% of cases harbor significant amounts of microbes (bacteria and more) that can be a vector for infection in lens wearers. Common pathogens include coagulase-negative Staphylococcus, Bacillus sp., Pseudomonas aeruginosa and Serratia marcescens.

PRACTICE IMPLICATIONS
What’s a prescriber to do in light of these dismal results? There has to be some shared responsibility among manufacturers, practitioners and patients. For our part in the hygiene compliance redux, we must remain focused on continuing to educate patients on proper lens care—and not just early in the wearing experience, but on every single visit. Practitioners should continually emphasize the following recommendations from CDC’s Consensus Panel on Contact Lenses:

1. **Adopt good hygiene habits.** Always thoroughly wash your hands. Never sleep in lenses unless instructed to by your eye care provider. Keep all water away from lenses and case and avoid swimming, using hot tubs or showering in lenses.

2. **Replace contact lenses, solutions and cases.** Replace lenses and cases as recommended by your eye care provider. Discard used solution from lens case and clean with fresh solution, not water.

3. **Seek medical care.** Visit your ECP yearly unless advised otherwise. If you experience any persistent eye pain, discomfort, redness or blurred vision, remove lenses immediately and call your ECP.

4. **Be prepared.** Carry a back-up pair of lenses and glasses, as well as your prescription, with you at all times.

A wise instructor once said that patients provide the highest compliment by seeking guidance through your care. They choose you because they trust you to prescribe and recommend the best care for them. But trust is a two-way street: Do you trust them to listen? Only you can know if they’re getting the message.

Avoiding ‘Tunnel Vision’

Break the habit of narrowly defining patients by their chief complaint and you’ll improve your opportunities to promote contact lens wear.

It’s a busy day in your office. You’re about to see your first patient. Before entering the exam room, however, your assistant alerts you that a last-minute patient has been added to your schedule that morning: a 38-year-old female who requests a regular eye exam, noting a slight change in vision. She currently wears eyeglasses. An ocular health assessment reveals that everything otherwise is healthy. The patient is given a new prescription for glasses and sent on her way.

IS THAT THE FULL STORY?
While electronic medical records (EMRs) have made practice more efficient, they have also narrowed our approach to patient care. Most EMRs include either a type of “short form”—a code used to identify a specific exam, such as a contact lens fitting—or a color used to denote certain kinds of exams or procedures. So, the EMR for a patient in for a glaucoma work-up would likely be colored or coded differently than a patient coming in for a contact lens fitting or an eye exam.

Logic tells us this gives structure to the practice’s schedule, thus making expectations for the day run much smoother. It also provides us with information on the patient ahead of time, allowing us to filter our thought process and focus on the task at hand once we enter the exam room. This system is particularly useful for patients seen for a medical follow-up visit. For example, the practitioner knows ahead of time that the patient coming in for a glaucoma work-up will need certain procedures and diagnostic testing appropriate for the condition. But does this logic hold true for those coming in for their regular examinations, or does it hinder our opportunity to help these patients to the best of our ability?

Consider this scenario: A contact lens wearer comes in for their yearly examination. Their chief complaint is that they “need to update their contact lens prescription and order more lenses.” We assess the lenses, perform an over-refraction and find no prescription change. We remove the lenses, perform a subjective refraction and eye health assessment. Everything appears normal, and the patient reports the lenses are comfortable. We then order the patient a year’s supply of lenses; this is usually the end of the encounter. But, have we done anything to make sure that they have the right prescription for their glasses when they are not wearing contact lenses? If they do have glasses, are they functional and something they would feel comfortable wearing out in public, or are they a 10-year-old pair that’s hanging by a thread? Additionally, have we made sure that the current contact lenses are the best and most comfortable kind for the patient, or does the lack of complaints simply mean that they are “good enough”? Unfortunately, many practitioners do not take the time to explore these questions. Why? Is it the product of a healthcare environment that has forced the concept of efficiency at the expense of understanding all of our patient’s ocular needs?

AN ALTERNATIVE APPROACH
Really, the first step is to mentally remove the patient from the bucket that we may have automatically placed them in based on how they were scheduled. This allows us to think about every patient as a potential contact lens wearer, if appropriate, and also make sure that we discuss glasses with them.

How does this concept relate to the patient discussed at the outset? Odds are that she likely was not asked about her interest in contact lenses. In fact, this patient actually...
used to wear lenses, but discontinued because of comfort issues and her perception that the lenses were inconvenient to care for.

The contact lenses she used to wear were monthly replacement lenses that she wore for “a few months” before replacing them. She used “whatever solution was on sale,” but didn’t really use much because she didn’t replace the solution in her contact lens case as frequently as she was supposed to. She recalls sleeping in her contact lenses a few times a week, even though they weren’t approved for extended wear.

Thus, her perception of lens wear was one of discomfort, likely secondary to her noncompliant habits. She’s also unaware of the benefits of newer contact lens technologies and how they might help her wear lenses more comfortably. She views contact lenses as being pretty much the same, so she never asked about them at her appointment—and we never brought it up because of how the patient was scheduled (as a glasses wearer), our busy schedule and her apparent lack of interest. The result: missed opportunities for us both.

In this case, all that would have been required is for the practitioner to ask the patient if she may be interested in being fit with a new contact lens, and briefly tell her about some of the newer technologies available that may enhance her wearing experience.

**CREATE THE OPPORTUNITY**

How do we avoid being so focused on the type of scheduled appointment that we miss the opportunity to provide our patients with other solutions that may benefit them? First, recognize that it may be happening, and make a point to discuss contact lenses with all patients who are candidates. Though some of these individuals may not be interested in contact lenses, there are certainly a number who will be. Additionally, they may be unaware of new options available today that may not have been available several years ago. It is important to keep in mind that patients are often uninformed regarding the newest lens options.

Of course, one of the major objections to incorporating a discussion of contact lenses with every patient is the additional chair time. In reality, it will only increase the length of the appointment by a small amount—and it’s time spent that is in the patient’s best interest. Educating them about visual options should be at the forefront of a practitioner’s mind in every case. Not all will take advantage of it, but all will appreciate it.

**F**or us personally, we both admit to being so focused on the task at hand and the reason for the visit that we did not always offer contacts as an option to appropriate candidates. When we started to, however, we realized the unmet need that we weren’t tapping into. Only when we changed our habits did we truly cater to the needs of our patients and ultimately grow our contact lens practices. Will you embrace the same opportunity in your practice?
Adenoviral infections remain the number one cause of urgent care visits to eye care practitioners’ offices.

In a typical week at the Urgent Care service of an academic-based clinic, we may see cases as varied and interesting as bilateral disc edema, vitreous hemorrhage from diabetic retinopathy and bilateral granulomatous uveitis. But, by far, the number one reason a patient calls or walks into our clinics is the presence of a red eye. They have an infection and need antibiotics. However, a true bacterial conjunctivitis is rare in adults.

In fact, adenoviral conjunctivitis is the most common cause of red eye in the world. This may partly be due to the viruses’ resilient nature; they are resistant to disinfection and can spread via both direct (i.e., ocular and respiratory secretions) and indirect contact (i.e., inanimate surfaces such as doorknobs, tonometry probes, towels), which allows for them to be unwittingly and easily transmitted to potentially large groups of people during an early asymptomatic incubation period.

WHAT YOU’LL SEE
Adenovirus (ADV) can manifest as one of four clinical conditions: (1) epidemic keratoconjunctivitis, (2) acute hemorrhage conjunctivitis, (3) pharyngoconjunctival fever, and (4) nonspecific follicular conjunctivitis. Patients experience a viral prodromal phase followed by adenopathy, and sometimes fever, pharyngitis and upper respiratory infection.

Epidemic keratoconjunctivitis (EKC), caused by adenoviruses 8, 19 and 37, is the most significant form of adenovirus because of the eventual involvement of the cornea and subsequent impact on vision. The presentation of EKC in its initial acute phase includes subjective complaints of unilateral tearing, redness, photophobia and eyelid edema, along with objective findings of conjunctival chemosis, follicular conjunctivitis and preauricular lymphadenopathy. The second eye usually becomes involved within days. This typically occurs about one week after exposure to the virus, and can last a few weeks.

The viral shedding can cause an intense inflammatory reaction in the conjunctiva that leads to pseudomembrane formation. The appearance of subepithelial corneal infiltrates, usually in the second week, signals the second phase of the infection and is virtually pathognomonic for adenovirus, most often EKC. These infiltrates can account for worsening symptoms and changes in vision, and can persist for anywhere from weeks to years. Severe complications may include chronic dry eye, conjunctival scarring and chronic epiphora. Herpes simplex virus (HSV) may be present with EKC and is indistinguishable from ADV.

It’s clear that early detection of adenovirus is imperative, from both the perspective of providing the correct diagnosis and treatment for your individual patient as well as for the greater issue of public health by taking steps to curb the spread of infection. Rapid assay is available via a 10-minute in-office test (AdenoPlus, RPS) that the manufacturer says has 90% sensitivity and 96% specificity.

For those not using the in-office assay to make the diagnosis, differentials include acute bacterial conjunctivitis, allergic conjunctivitis, episcleritis, angle closure glaucoma, blepharitis/dry eye, uveitis and infectious/inflammatory keratitis.

WHAT TO DO
Once the clinical picture and/or testing confirm the diagnosis, how do you treat EKC? While mild cases are usually self-limited and treatment is mostly supportive (chilled artificial tears, cool compresses, topical antihistamines), and education regarding proper hygiene and

How to Contain an Outbreak
EKC is called an “epidemic” with good reason. Spread of the virus happens fast. A week to 10-day vacation from work is generally recommended, and contact with family members is to be curtailed. Estimates suggest a 20% to 40% likelihood of intrafamilial spread of the virus. Patients need to be carefully educated about what to expect (that their symptoms may get worse before improving) and what actions they need to take to avoid contagion (i.e., avoid physical contact with others and frequently clean touched surfaces and household items).
the contagious nature of the virus, moderate to severe cases involving subepithelial infiltrates and symptomatic pseudomembrane formation warrant intervention.

Sometimes, topical steroids are used for symptomatic relief, though there is always concern over potential side effects such as intraocular pressure rise and the possibility of rebound effect once the steroid is discontinued.7 Zirgan (ganciclovir gel 0.15%, Bausch + Lomb) has been shown to be effective against adenovirus in vitro.12

Bear in mind, however, there are no controlled clinical studies to document its efficacy. Cyclosporine 1%, a steroid-sparing immunosuppressive, has been shown to be effective for the treatment of subepithelial infiltrates associated with EKC in patients resistant to the tapering of, or experiencing side effects from, corticosteroid drops, as has topical tacrolimus 0.03%, which has a similar mechanism of action but is decidedly more potent.13-14

Epidemic keratoconjunctivitis is a serious ocular infection for all concerned: the patient, their families, friends and colleagues, and the doctor entrusted to treat them. Early detection and patient education is mandatory to minimize contamination. Currently, there is no single accepted antiviral treatment—while there are options, none have been widely investigated with large clinical trials. Until such a time is reached, treat each red eye that comes into your office as a virus until proven otherwise, then treat the viral patient according to their signs and symptoms.15

10. Tabbara K, Jarade E. Ganciclovir effects in adenoviral keratoconjunctivitis. 2001 [ARVO abstract 3111 (suppl)].
Microbial keratitis affects an estimated 30,000 Americans annually.\textsuperscript{1} Typically, the event occurs in eyes susceptible to infection by some pre-existing condition and only rarely occurs in an otherwise unaffected eye, due to the cornea’s robust defenses against infection.\textsuperscript{1,2} Any condition that causes, or leads to epithelial corneal damage, in which laceration of the basal laminar layer occurs, increases one’s risk for developing bacterial corneal ulcers, also known as bacterial or ulcerative keratitis.

In general, corneal infections typically arise from the same species of bacteria normally found on the lids, periorcular skin, conjunctival sac or in adjacent nasal passages. The most common organisms found in the uncompromised, healthy cornea include \textit{Staphylococcus}, \textit{Streptococcus}, \textit{Pseudomonas}, \textit{Moraxella} and enterobacteriaceae such as \textit{Serratia marcescens} and \textit{Klebsiella pneumonia}. \textit{Proteus} may also be encountered in a compromised cornea.

Gram-positive \textit{Staphylococcus aureus} is the most common organism identified in North America, while gram-negative \textit{Pseudomonas aeruginosa} is the most common underlying etiology documented in contact lens-associated corneal ulcers. \textit{Streptococcus pneumoniae} is more prevalent in the developing world.\textsuperscript{1,3-4}

Other, less common causes of microbial contact lens-related keratitis include infections resulting from the presence of fungi (i.e., \textit{Fusarium}, \textit{Aspergillus}, \textit{Candida}) and protozoa (i.e., \textit{Acanthamoeba}, microsporidia, rhinosporidia).\textsuperscript{4}

Clinical Infections in the Presentation

Signs and symptoms of bacterial keratitis typically commence within 24 hours of infection. Common symptoms include photophobia, decreased visual acuity, redness, discharge, eyelid swelling, and pain of varying degrees. Patients with a \textit{Moraxella}-associated ulcer or with corneal hypoesthesia may not report significant pain.\textsuperscript{2,4}

A significant number of bacterial keratitis cases result in loss of vision due to corneal scarring and irregularities.\textsuperscript{1} Bacterial ulcers can occur at any location on the cornea, but those that are central or paracentral pose the greatest risk to vision even if the infecting organism is successfully treated.\textsuperscript{1}

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Typically, patients develop moderate to severe lid and conjunctival edema and inflammation, along with a mucopurulent discharge. Often, the stroma exhibits a dense, gray-white infiltrate with indistinct margins, surrounding corneal edema and an overlying, ulcerated, epithelial defect that stains with fluorescein. There may be an associated mild to severe anterior chamber reaction, which could lead to hypopyon formation, elevated IOP, cataract and synechiae (Table 1). Other potential findings include descemetoceles and corneal perforation, with the potential for endophthalmitis to develop and result in loss of the eye.1-4

Clinically, there are some differences in presentation that can aid in determining the causative agent and, subsequently, the best initial treatment. Note, however, a laboratory culture is needed to make a definitive diagnosis. A corneal ulcer caused by Gram-positive organisms, such as *Staphylococcus*, will present with a yellow and gray-white area of infiltration located directly beneath an epithelial defect. Generally, these lesions are well-demarcated, discrete round or oval-shaped “dry” abrasions that may be associated with a severe anterior chamber reaction (Figure 1).

Ulcers caused by Gram-negative bacteria, in contrast, are more diffuse in presentation with a “soupy” or “wet” appearance. The mucopurulent discharge seen in *P. aeruginosa*, for example, is yellow-green and can cling to the ulcer’s surface. Similarly gray-white in color, they initially involve the central cornea, but then progress rapidly outwards to encompass the entire cornea. Quite often, the anterior chamber reaction produced by gram-negative bacteria is intense, with hypopyon formation (Figure 2).2,3

**INVESTIGATING INFILTRATES**

When evaluating a patient with corneal infiltrates, determine whether it is sterile or the result of an infectious process, as the clinical course and prognosis can be quite different. Sterile corneal infiltrates develop from one of a number of insults associated with contact lens wear, including trapped debris, chemical toxicity, hypoxia and hypersensitivity. They may also be the result of an immune reaction to exotoxins from staphylococci colonizing the sebaceous gland openings of the eyelid margin, known as staphylococcal marginal keratitis. A variety of systemic diseases (e.g., rheumatoid arthritis, polyarteritis nodosa and sarcoidosis) may also lead to stromal infiltration. Sterile infiltrates appear as white lesions and represent inflammatory cells within the collagen matrix of the corneal anterior stroma.1-2,4

Patients are usually asymptomatic, although some may present with a small degree of pain, discomfort, tearing or photophobia (Table 1). A careful history regarding contact lens hygiene should be obtained. Successful treatment can be achieved with the initiation of topical corticosteroids and even the concomitant use of topical antibiotics to help control ocular surface and eyelid bacterial flora. It is also recommended that patients refrain from contact lens wear for a short period and brush up on proper eyelid and contact lens hygiene.2,4
UNDERSTANDING CORNEAL INFECTION CARE

CULTURING
Identifying the offending organism in bacterial keratitis is important when determining the appropriate treatment regimen and preventing potentially severe complications. Culturing is the only means of determining sensitivity to antibiotics, which allows for the selection of the most appropriate antibiotic and prevents overuse of ineffective antibiotics.1,3 Having said that, the majority of community-acquired cases of bacterial keratitis are managed without smears or cultures and resolve with empiric therapy.1,4 Some indications for when culture and sensitivity and Gram stain testing should be obtained include: cases that involve a large, central corneal infiltrate that extends to the middle to deep stroma; immunocompromised or hospitalized patients; a history of organic trauma; those that are chronic in nature or unresponsive to broad-spectrum antibiotic therapy; sight-threatening lesions; sclera extension of the majority of community-acquired cases of bacterial keratitis are managed without smears or cultures and resolve with empiric therapy.1,4 Some indications for when culture and sensitivity and Gram stain testing should be obtained include: cases that involve a large, central corneal infiltrate that extends to the middle to deep stroma; immunocompromised or hospitalized patients; a history of organic trauma; those that are chronic in nature or unresponsive to broad-spectrum antibiotic therapy; sight-threatening lesions; sclera extension of the corneal ulcer using a calcium alginate swab moistened with thioglycolate or trypticase soy broth. A new swab should be used for each area cultured. The use of antibiotics is not recommended for conjunctiva or lid margins, as the preservatives may cause a decreased yield of live organisms; however, an agent such as proparacaine hydrochloride 0.5% should be used in obtaining corneal specimens for patient comfort. Cultures can also be obtained using a sterile transport swab in a mini-culture tube (Figure 3). Specimens can then be plated onto culture media and also sterile glass slides for Gram and Giemsa staining. Typically, blood agar is inoculated first, as it readily supports the growth of most corneal pathogens. Other media available include chocolate agar, Sabourand’s agar, thiglycolate broth, and brain-heart infusion broth. Information from cultures is usually available within 24 to 48 hours.1,3 Plates looking for fungal growth should be held for two weeks or longer.

TREATMENT
Initial therapy for the treatment of bacterial keratitis depends on severity and clinical presentation. Studies comparing the efficacy of fluoroquinolones (FQs) with fortified antibiotics have found that empirical treatment with FQs seems to be at least as effective as combined fortified antibiotics in managing bacterial keratitis.5,8 FQs offer the advantage of good ocular penetration, broad-spectrum activity, less risk of ocular discomfort/toxicity, lower dispensing cost and ready availability.6-8 For these reasons, they have become the most widely used options in the treatment of bacterial keratitis, although the newest FQs are not FDA-approved for this purpose.

Further research has delineated that the fourth-generation fluoroquinolones, moxifloxacin and ciprofloxacin, work better for Gram-negative organisms, including *Pseudomonas*.2,9-10 Besifloxacin 0.6%, a chlorofluoroquinolone, is the newest topical antimicrobial available. The gel-forming polymer (i.e., Durasite, InSite Vision) used in its preparation yields greater ocular surface retention time compared with others in its class.

Although currently only approved to treat bacterial conjunctivitis, besifloxacin has been postulated in rabbit models to have some treatment efficacy in bacterial keratitis even in the presence of epithelial disruption.7 In addition, this drug has shown greater in vitro potency compared to other FQs, particularly among MRSA (methicillin-resistant *S. aureus*) and MRSE (methicillin-resistant *S. epidermidis*) species, although further investigation is needed.1,7,11-12 There are some concerns of increased risk of corneal perforation and delay in epithelial closure with fluoroquinolone use, as they may alter corneal

Table 1. Differentiating Sterile and Infectious Infiltrates

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>NUMBER OF LESIONS</th>
<th>LESION SIZE</th>
<th>DEGREE OF STAINING</th>
<th>PAIN LEVEL</th>
<th>INJECTION</th>
<th>A/C REACTION</th>
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<td>Infectious</td>
<td>Typically central 6mm.</td>
<td>Typically single</td>
<td>Greater than 1mm</td>
<td>Staining Equal to Lesion Size</td>
<td>Severe</td>
<td>Diffuse,</td>
</tr>
<tr>
<td>Sterile</td>
<td>Peripheral; located at 2, 4, 8 and 10 o’clock; clear “lucid” zone between cornea and limbus.</td>
<td>Single or Multiple</td>
<td>0.1mm to 1.5mm</td>
<td>Staining Less than Lesion</td>
<td>Mild to Moderate</td>
<td>Localized, Mild to Moderate</td>
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collagen or keratocyte function, however, this has not yet been confirmed via a randomized controlled trial.\textsuperscript{1,13-15}

For suspected or confirmed cases of \textit{Pseudomonas}, gatifloxacin and ciprofloxacin provide better coverage than other FQs.\textsuperscript{1,4,10-11} The use of a fluoroquinolone in conjunction with tobramycin or bacitracin/polymyxin B provides an even broader spectrum of coverage and further decreases the development of resistant bacteria. Cycloplegia agents may be used to decrease synchiae formation and pain, and are indicated when anterior chamber inflammation is present. Topical scopolamine 0.25\%, homatropine 5\% or atropine 1\% can be used two to three times daily.\textsuperscript{1-3,17}

An initial loading dose of antibiotic is critical for any moderate to severe corneal ulcers. Following this, patients should be monitored daily until a positive response to treatment is observed, such as re-epithelialization, reduced pain, smaller ulcer/infiltrate size and depth and/or an improvement in iritis. The IOP may be elevated if there is a secondary iritis, and if so, must be treated. Avoid prostaglandins and miotics, as they can increase inflammation. If a positive response is appreciated, the antibiotic regimen can be tapered, but should not be set below the minimum inhibitory concentration (MIC) for the chosen antibiotic—usually a TID and QID dosing—to decrease the chance of developing resistance. Consider hospitalization in severe cases or if there are concerns of noncompliance.\textsuperscript{2,3,10,18}

If the lesion does not show some improvement in four to seven days, consider other, less common causes of keratitis.\textsuperscript{19}

Although somewhat controversial, adjunctive therapy with topical corticosteroids can be beneficial in the treatment of some bacterial keratitis (avoid steroids if the infectious agent is \textit{Mycobacterium} or \textit{Nocardia}). Subsequent trials and analyses of the Steroids for Corneal Ulcers Trial (SCUT) support the practice of initiating topical steroids early in the course of the disease. After approximately 24 to 48 hours of appropriate antibiotic therapy, a topical corticosteroid (prednisolone acetate 1\%, difluprednate 0.05\%, or loteprednol etabonate 0.5\%) can be started BID to QID to help speed resolution and hopefully reduce corneal scarring.\textsuperscript{2,17,20-21}

**NOVEL THERAPIES**

Given the increasing prevalence of MRSA, as well as resistance to cephalosporins and fluoroquinolones, studies are emerging to find novel targets for antimicrobial therapy. Resistance occurs when there is a single- or multi-step mutation in the genes encoding the target enzymes.\textsuperscript{12} The older fluoroquinolones (i.e., ciprofloxacin and ofloxacin) preferentially inhibit topoisomerase IV of gram-positive bacteria, whereas the newer FQs (i.e., moxifloxacin and gatifloxacin) exhibit a more balanced inhibition of both DNA gyrase and topoisomerase IV. This requires a double step mutation to result in resistance. Agents such as besofloxacin, with only a topical formulation available, are less susceptible to resistance compared with antibiotics with both topical and oral formulations.\textsuperscript{1,10,11,18,22} Finally, some older, less frequently used drugs such as bacitracin, gentamycin and sulfacetamide may prove successful if resistance is encountered.

Topical, fortified vancomycin is the last resort drop for MRSA or any gram-positive resistant bacteria. As noted above, culture and sensitivity should be used to tailor the appropriate therapy.\textsuperscript{19}

Corneal crosslinking uses ultraviolet-A radiation and riboflavin to produce covalent bonds, or “cross-links,” in the corneal stroma by way of photochemical reactions. In vitro experiments have shown that stiffening the corneal stroma in effect stabilizes it and increases its resistance to enzymatic bacteria degradation, avoiding progression to corneal melting. Currently, the indication for this treatment is set aside for those cases that are recurrent or unresponsive to traditional antimicrobial therapy.\textsuperscript{10,23}

Many studies reveal success in using amniotic membrane transplantation (AMT) in the treatment of infectious keratitis and corneal perforation.\textsuperscript{24} The amniotic membrane allows for epithelial cell migration, promotes re-epithelialization, inhibits inflammation and may have an antimicrobial effect. Thus, AMT could be a viable option if medical treatment fails or there is corneal perforation.\textsuperscript{24}
Table 2. Suggested Treatment Based on Lesion Size/Location1,2,4,10,17

<table>
<thead>
<tr>
<th>RISK OF VISION LOSS</th>
<th>LOW</th>
<th>MODERATE</th>
<th>SEVERE AND SIGHT-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Features</strong></td>
<td>Small, non-staining peripheral infiltrate; minimal A/C reaction; (-)discharge.</td>
<td>Peripheral infiltrate 1mm to 1.5mm in size, or smaller infiltrate with associated epithelial defect.</td>
<td>Greater than 1mm to 2mm in size; central; unresponsive to initial therapy.</td>
</tr>
<tr>
<td><strong>Antibiotic(s) to Use</strong></td>
<td>Monotherapy with topical FQL (i.e., moxifloxacin, gatifloxacin, besifloxacin).</td>
<td>Monotherapy with topical FQL.</td>
<td>Combination fortified aminoglycoside-ceramsolin agents.</td>
</tr>
<tr>
<td><strong>Dosing Schedule</strong></td>
<td>One drop every 1-2 hours.</td>
<td>One drop every hour around the clock with loading dose of five drops separated by five minutes each.</td>
<td>Fortified tobramycin or gentamicin (15 mg/mL) alternated with fortified cefazolin (50mg/mL) every 30 minutes.</td>
</tr>
<tr>
<td><strong>Other Considerations</strong></td>
<td>For contact lens wearers, consider antibiotic ointment at nighttime (i.e., tobramycin, bacitracin/polyoxymyxin B). If the lesion is sterile, consider combination ointment (i.e., tobramycin/dexamethasone or neomycin/polyoxymyxin B/dexamethasone).</td>
<td>Consider adding an antibiotic ointment OHS or BID.</td>
<td>Vancomycin can be used instead of cefazolin in resistant or unresponsive keratitis. Also, consider antibiotic ointment QHS or BID.</td>
</tr>
</tbody>
</table>


Bacterial keratitis can be visually devastating if not identified early and treated immediately. In many cases, empiric treatment with fourth-generation fluoroquinolones can be successful, especially when combined with an antibiotic ointment of a different class. Practitioners must always be prudent in determining the causative organism if patients do respond as expected to initial therapy, and should consider culturing in all cases.
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<table>
<thead>
<tr>
<th>Toric Periphery</th>
<th>Large Diameter</th>
<th>Front Toric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toric PC to aid in 3 &amp; 9 compression or impingement, helping patients with 6 &amp; 12 edge lift or stand-off, and for patients in a front toric that need alignment help.</td>
<td>Two larger diameters in 17.0 &amp; 17.5 creates more sagittal depth for the highly irregular corneas.</td>
<td>Front Toric available for patients with residual astigmatism of 1.00 diopter or more.</td>
</tr>
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</table>

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Contact lens wear is the most significant risk factor for infectious microbial keratitis, which can result in significant visual morbidity and permanent vision loss. Historically, disease incidence had been five times higher in extended soft contact lens wearers than in daily soft contact lens wearers—20.9 and 4.1 per 10,000 persons, respectively. Recent literature, however, suggests a rise in both the number and severity of contact lens-related infections. Possible explanations for this change include the increasing number and younger ages of contact lens wearers, expanding popularity of orthokeratology and the shift from use of peroxide-based disinfecting solutions to multipurpose solutions.

Though bacteria are responsible for the majority of cases of contact lens-related microbial keratitis, infections caused by fungal and protozoan organisms are often more difficult to treat, more likely to result in poor clinical outcomes such as corneal perforation, and are more likely to require surgical intervention. Both organisms penetrate deeply into the corneal stroma.

Fungi gain access through an epithelial defect and are capable of crossing an intact Descemet’s membrane to reach the anterior chamber. Fusarium, a filamentous septated fungus, is the most common cause of contact lens-related fungal keratitis, followed by Aspergillus and Candida. In contrast, protozoa like Acanthamoeba gain entry by attaching to the corneal epithelium and producing proteases that destroy corneal tissue. The motile trophozoite can also encyst rapidly into a double-walled configuration that is highly resistant to destruction. These infections are hard to eradicate as a result of both deeper invasion into the cornea and poor penetration of antifungal and amoebicidal medications.

In the recent past, two outbreaks involving Fusarium and Acanthamoeba keratitis were associated with contact lens solutions. More specifically, ReNu with MoistureLoc (Bausch + Lomb) was implicated in the outbreak of Fusarium keratitis in 2006, which was first reported in Singapore and Hong Kong. A year later, Complete MoisturePlus (AMO) was found to have been involved in the outbreak of Acanthamoeba keratitis from 2003 to 2006. With the offending contact lens solutions withdrawn from the market, contact lens-related Fusarium infections declined. Conversely, Acanthamoeba infections remain high. Acanthamoeba keratitis has risen 10-fold from previous estimates of 1.65 to 2.01 cases per one million contact lens wearers to 20 cases per one million contact lens wearers. This increase has prompted the search for yet unidentified risk factors. Recent research, however, has failed to provide any significant insight.

Acanthamoeba keratitis has risen 10-fold from previous estimates of 1.65 to 2.01 cases per one million contact lens wearers to 20 cases per one million contact lens wearers. This increase has prompted the search for yet unidentified risk factors. Recent research, however, has failed to provide any significant insight.

To date, the etiology to explain this rising trend in Acanthamoeba keratitis remains indeterminate.

ABOUT THE AUTHORS

Dr. Cheung is a cornea fellow at Wills Eye Hospital. She graduated medical school from Albert Medical School of Brown University and completed her ophthalmology residency at University Hospitals Case Medical Center.

Dr. Hammersmith is an attending surgeon on the Corneal Service and director of the Cornea Fellowship Program at Wills Eye Hospital. She is also an associate professor at the Jefferson Medical College of Thomas Jefferson University.
Managing these infections can be challenging. Here’s a breakdown of the most important points to remember.

Fungi and Protozoa in Contact Lens Wearers

**RISK FACTORS**
Overnight contact lens wear remains one of the leading causes of corneal ulcers despite advancement in contact lens technology. In a recent Centers for Disease Control (CDC) survey, half of contact lens wearers report sleeping in their lenses overnight. Other risk factors include poor storage case hygiene, infrequent storage case replacement and solution type. Daily disposable contact lens wear may reduce the severity of corneal ulcers and lead to better visual outcomes. Fungal keratitis can also result from trauma, especially trauma with exposure to organic matter. Chronic steroid use with exposure to contaminated water or soil while wearing contact lenses or after trauma can also lead to *Acanthamoeba keratitis*.

**IDENTIFICATION**
A timely diagnosis is beneficial and often leads to a more favorable outcome. However, it is common for a delay to occur in the diagnosis of infections related to fungi or *Acanthamoeba*, as these are often misdiagnosed as bacterial or herpes simplex virus (HSV) infections. Significant delay in diagnosis ranging from 27 to 43 days has been observed particularly in *Acanthamoeba* keratitis. Proper diagnosis is paramount, as delays in treatment coupled with an advanced disease state can lead to poorer visual outcomes and increased need for surgical intervention. Early *Acanthamoeba* keratitis often presents with a dendritiform keratitis or a nonspecific keratitis. As such, two-thirds of these patients are misdiagnosed as having HSV keratitis. Pain out of proportion to clinical findings—a classic indication of *Acanthamoeba* keratitis—can be used to differentiate between the two. However, some patients do not present with such impressive pain. Thus, the possibility of *Acanthamoeba* keratitis should be considered in any patient with a history of contact lens wear and presumed HSV infection. If the patient does not have a typical response to antiviral medications, then the diagnosis of *Acanthamoeba* keratitis should be sought. Radial perineuritis is a finding that greatly enhances the suspicion for *Acanthamoeba* keratitis (Figure 2). A ring infiltrate is a later finding in *Acanthamoeba* keratitis, which has a classic appearance but poorer prognosis than these earlier signs. Fungal keratitis may also present with a dendritiform appearance, multifocal lesions, feathery bordered infiltrates and satellite lesions. The infiltrates may have a leathery
or dry appearance and often are deep in the stroma (Figure 3). Fungal infections often have impressive anterior chamber inflammation with endothelial plaque and hypopyon.8,25 Despite this inflammation, they often have less lid edema and hyperemia than classically seen with bacterial infections.

**WORK-UP PROTOCOLS**

In cases of suspected infectious keratitis, corneal scrapings should be obtained for gram stain and cultures with blood agar, chocolate agar, Sabouraud dextrose agar and thioglycolate broth. If a fungal infection is suspected, corneal scrapings should also be sent for additional Grocott–Gomori methenamine silver stain, potassium hydroxide, lactophenol cotton blue, Giemsa or calcofluor white.8,25 Sabouraud dextrose agar is the preferred medium for fungi, though it can also grow on chocolate agar and blood agar.8,25 Fungal cultures should be kept for a minimum of two weeks.8,25

Corneal scrapings in ulcers suspicious for *Acanthamoeba* should be sent for additional Giemsa, periodic acid-Schiff, hematoxylin and eosin, Wright’s, calcofluor-white or acidine orange stains to identify trophozoites or cysts.27 *Acanthamoeba* is best plated on nonnutrient agar with an *Escherichia coli* or *Enterobacter aerogenes* overlay.27,28 Scrapings and cultures are helpful early in the disease when the infection is more superficial, but once the infection has advanced deeper into the corneal stroma, a corneal biopsy may be necessary to confirm the diagnosis.27 Corneal biopsies may also be useful in monitoring treatment success or complete resolution of the infection, as this can often be difficult to ascertain clinically.

Confocal microscopy, if available, may hasten diagnosis of fungal hyphae and *Acanthamoeba* cysts. It can be particularly useful in cases when the infiltrates are deep and not accessible by corneal scrapings.29 A prospective observational clinical study found the sensitivity and specificity of confocal microscopy to be 88.3% and 99.1%, respectively, when diagnosing either fungal or *Acanthamoeba* keratitis.29 However, equipment expense and necessary staff training can limit use of this technology. Polymerase chain reaction testing is another option for diagnosing both fungal and *Acanthamoeba* infections that may yield results sooner than cultures; however, this test is not yet widely available.20,25

**FUNGAL TREATMENT**

In severe fungal keratitis, consider treatment with multiple medications, such as a combination of two topical antifungal agents or the addition of an oral agent.8,30 Note, however, no consensus exists on the preferred treatment regimens, the best single antifungal agent or best combination therapy.25,31 Natamycin was found in the MUTT trial to be more efficacious than voriconazole in treating filamentous fungi such as *Fusarium* or *Aspergillus*.9 In cases of nonseptated fungal infections such as *Candida*, topical amphotericin B or voriconazole may be preferred. In recalcitrant cases, intrastromal injection of voriconazole...
or intracameral injection of amphotericin B or voriconazole may be considered. Topical cycloplegics can alleviate pain and prevent formation of synechiae in cases when anterior chamber inflammation is pronounced. Coexistent elevation of intraocular pressure or glaucoma portends a worse prognosis and should be aggressively treated.

Therapeutic penetrating keratoplasty (PK) is usually reserved for fungal ulcers that have been refractory to medical treatment or that have resulted in corneal perforation. Tissue adhesives such as cyanoacrylate glue or amniotic membrane may be used in cases of impending perforation to allow antifungal medications to be given for a period of time prior to surgery. Studies show that PK is effective and can result in good vision, but is often plagued by recurrence of fungal infection, a higher rate of graft failure and secondary glaucoma.29

Interest in corneal collagen crosslinking (CXL) as a means to treat infectious keratitis has grown recently, particularly in cases of corneal melting. CXL may be beneficial through its direct cytotoxic action, enhancement of corneal integrity and reduction of the inflammatory response. However, studies suggest no difference between CXL and current treatment modalities in speeding resolution of mycotic keratitis or reducing adverse outcomes like corneal perforation.32,33

<table>
<thead>
<tr>
<th>Table 1. Antifungal Agents</th>
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<table>
<thead>
<tr>
<th>Topical</th>
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<tbody>
<tr>
<td><strong>Natamycin</strong></td>
</tr>
<tr>
<td>5% up to Q1hr</td>
</tr>
<tr>
<td>Polyene</td>
</tr>
<tr>
<td>• More effective against filamentous fungus such as Fusarium and Aspergillus as supported by the Mycotic Ulcer Treatment Trial (MUTT).4</td>
</tr>
<tr>
<td>• Often used as first-line treatment for filamentous fungi.</td>
</tr>
<tr>
<td>• Commercially available.</td>
</tr>
<tr>
<td>• Less toxic than amphotericin B.</td>
</tr>
</tbody>
</table>

| **Amphotericin B**          |
| 0.15% up to Q1hr            |
| Polyene                     |
| • More effective against yeast such as Candida. |

| **Voriconazole**            |
| 1% up to Q1hr               |
| Triazole                    |
| • Effective against filamentous fungus such as Fusarium and yeast such as Candida. |
| • Good alternative to natamycin. |

<table>
<thead>
<tr>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voriconazole</strong></td>
</tr>
<tr>
<td>200mg PO BID</td>
</tr>
<tr>
<td>Azole</td>
</tr>
<tr>
<td>• Broad-spectrum against Fusarium, Aspergillus and Candida species.</td>
</tr>
<tr>
<td>• Requires periodic monitoring of liver function enzymes.</td>
</tr>
</tbody>
</table>

| **Itraconazole**            |
| 200mg to 400mg PO BID       |
| Azole                       |
| • Effective against Aspergillus species. |

| **Fluconazole**             |
| 200mg to 400mg PO BID       |
| Bistriazole                 |
| • Effective against Candida species. |

| **Ketoconazole**            |
| 200mg PO BID                |
| Azole                       |
| • Effective against Aspergillus and Candida. |

<table>
<thead>
<tr>
<th>Intrastromal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voriconazole</strong></td>
</tr>
<tr>
<td>50µg/0.1mL*</td>
</tr>
<tr>
<td>Triazole</td>
</tr>
<tr>
<td>• May be effective in recalcitrant cases, with stromal involvement in Fusarium, Aspergillus.41,42</td>
</tr>
</tbody>
</table>

| **Amphotericin B**          |
| 5µg to 10µg in 1mL of 5% dextrose |
| Polyene                     |
| • Useful in treatment of Aspergillus and natamycin-resistant fungi with progression despite topical treatment.41 |

| **Voriconazole**            |
| 50µg/0.1mL*                 |
| Triazole                    |
| • Adjunctive treatment.     |

*Reconstituted with 2mL of lactated Ringer’s solution to a concentration of 0.5 mg/mL.

**PROTOZOA TREATMENT**
When treating *Acanthamoeba* keratitis, dual coverage—with one antiseptic (e.g., chlorhexidine or PHMB) and one diamidine (e.g., propamidine or hexamindine)—is usually started with hourly around-the-clock dosing for the first few days.27 Frequent dosing early on can help destroy trophozoites before cysts are established, but can also be toxic to the epithelium.20 Treatment should be tapered based on clinical response and tailored individually.27 Cycloplegic agents, oral nonsteroids or oral narcotic medications can be used for pain control.

The use of topical corticosteroids is controversial.20,27,34 Steroids help control inflammation when severe...
pain, scleritis or significant anterior chamber reaction is present. They may reduce pain and improve anterior chamber inflammation without increasing the rate of medical treatment failure in cases when diagnosis of Acanthamoeba keratitis was not delayed and when corticosteroids were initiated in conjunction and after use of amoebicidal medications. Steroids are used cautiously and sparingly because they can weaken the host’s immune system, promote excystment (cyst to trophozoite) and proliferation of trophozoites. It is not clear whether or not steroids prevent encystment (trophozoite to cyst), which may be beneficial in the early stages of treatment.

In our experience, topical corticosteroids are initiated after four to six weeks of amoebicidal treatment and, importantly, without discontinuing the use of amoebicidal agents during use. Amoebicidal agents should be continued for at least a few weeks after topical corticosteroids have been discontinued.

Table 2. Amoebicidal Agents

<table>
<thead>
<tr>
<th></th>
<th>Concentration/Dose</th>
<th>Class</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Chlorhexidine    | 0.02% up to Q1hr   | Antiseptic | • Primary treatment.  
|                  |                    |        | • Best amoebicial and cysticidal activity.                         |
| Polyhexamethylene biguanide (PHMB) | 0.02% up to Q1hr | Antiseptic | • Primary treatment.  
|                  |                    |        | • Best amoebicial and cysticidal activity.                         |
| Propamidine (Brolene) | 0.1% up to Q1hr | Diamidine | • Used in conjunction with an antiseptic agent.  
|                  |                    |        | • Effective against trophozoite and cysts.                         |
| Hexamidine       | 0.1% up to Q1hr    | Diamidine | • Used in conjunction with an antiseptic agent.  
|                  |                    |        | • Effective against trophozoite and cysts.                         |

|                  |                    |        |                                                                      |
| Systemic         |                    |        |                                                                      |
| Voriconazole     | 200mg PO BID       | Azole  | • Adjunctive therapy.  
|                  |                    |        | • Requires periodic monitoring of liver function tests.           |
| Itraconazole     | 200mg to 600mg PO per day (BID dosing) | Azole  | • Adjunctive therapy.  
| Ketoconazole     | 200mg to 600mg PO per day (BID dosing) | Azole  | • Adjunctive therapy.  
| Pentamidine      | 190mg to 400mg/day IV | Diamidine | • May be useful adjunct prior to therapeutic penetrating keratoplasty.  |

In more advanced cases of Acanthamoeba keratitis—e.g., sclerokeratitis—systemic use of oral antifungal agents with anti-amoebic activity such as voriconazole, itraconazole or ketoconazole in addition to oral corticosteroids or systemic immunosuppressants can be used as an adjunct to topical treatment. Persistent epithelial defect is a common problem in severe Acanthamoeba keratitis. The toxicity of topical antiseptic and diamidine to the corneal epithelium is well known. Streptococcus is a common organism associated with bacterial superinfection in Acanthamoeba keratitis. Prophylactic use of antibacterial drugs should be used to prevent bacterial superinfection. Amniotic membrane transplant can help with re-epithelialization.

An Ounce of Prevention...

Improving contact lens hygiene is an important way to decrease the modifiable risk factors of microbial keratitis. Here are the latest contact lens wear and care recommendations for the public put forth by the CDC.

1. Never sleep or nap in contact lenses.
2. Do not wear contact lenses while swimming, or in the hot tub.
3. Wash hands thoroughly before handling lenses.
4. Never rinse lenses or contact lens cases with water. Do not use water as a storage medium for contact lenses.
5. Discard used solution from the contact lens case, rinse case with fresh solution, store case upside down with caps off and store contact lenses in fresh solution.
6. Replace lenses as recommended by eye care provider.
7. Replace contact lens case every three months.
Therapeutic PK is a last resort in cases of corneal perforation or progressive corneal and scleral melt. Success of the graft is typically higher when the infection is localized and inflammation is controlled prior to surgery. Attempts to delay surgery and prolong management with anti-amoebic agents can be achieved at times with amniotic membrane transplant or gluing. It is important for the corneal surgeon to trephine beyond clinical areas of infiltrate and satellite lesions during surgery to ensure organism elimination. Patients should continue to use amoebicidal agents for several months after surgery to kill any residual organisms. Optical PK should be considered for cases of corneal scarring or central irregular astigmatism after infection, as the procedure has a much higher success rate in terms of graft survival and visual outcomes as compared to therapeutic penetrating keratoplasty. Practitioners should monitor for signs of recurrent infection for a minimum of three months after ceasing amoebicidal agents.

Microbial keratitis is an uncommon infection that can result from contact lens wear. Atypical infections from fungal and protozoan organisms are often difficult to diagnose and treat, and have poorer visual outcomes. It is crucial to maintain a high level of suspicion for atypical infections so that the diagnosis is not delayed and treatment can be initiated promptly.

Herpetic eye disease is the number one cause of infectious vision loss in the United States. Though non-corneal manifestations of the disease exist, corneal ulceration, infiltration and scarring are the primary mechanisms through which this group of viruses cause vision loss. As such, viral eye disease is also the primary infectious indication for keratoplasty. While penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK) are effective at re-establishing a clear cornea, eyes with herpetic indication for transplant have an elevated risk of viral reactivation within the donor tissue in the first year postoperatively. This perpetuates the cycle of infection, inflammation and scarring and may prompt a need for retransplant.

In initial episodes, these sorts of severe outcomes may seem only remotely possible and foster a false sense of security when initial medical treatment is successful. However, herpes viruses are capable of remaining dormant within the host and reactivating at a later date; thus, treating these eyes effectively over both the acute and chronic phase of the disease are clinical challenges that must be resolved.

Compounding the therapeutic challenges posed by viral eye disease are some of the common points of confusion in its diagnosis and management—namely, antiviral efficacy, the role of steroids in management, the diagnosis of herpetic iridocyclitis, differences in medication response between herpes simplex and herpes zoster and the effect and role of vaccination in the epidemiology and management of herpes zoster ophthalmicus (HZO).

The purpose of this article is to review some of the more technical considerations regarding herpetic eye disease and how we can apply this to our patients to achieve successful long-term outcomes.

**SIMPLEX: NOT SO SIMPLE**

Herpes simplex 1 and 2 (HSV-1 and HSV-2) and varicella zoster (VZV) are members of the alphaherpesvirinae subfamily of the larger herpesviridae family, to which cytomegalovirus and Epstein Barr virus also belong. HSV is the primary source of viral-induced vision loss affecting approximately 500,000 patients in the United States, with 10% to 20% developing ocular effects. Though the HSV genome is moderately larger than VZV (due to coding repeats), there is a surprising genetic homology for viruses that can result in different pathologies: HSV-1 has only 10 genes that VZV does not, while VSV has only six genes that HSV-1 does not. In addition to their genetic resemblance, the viruses produce similar findings clinically (i.e., dendriform keratitis, disciform endotheliitis, iridocyclitis, retinitis and neurotroph). As such, many practitioners treat these viruses in a similar fashion. There are several problems with this approach, however:

First, the Herpetic Eye Disease Study (HEDS), on which the majority of clinical practices regarding viral eye disease are based, looks only at herpes simplex, not varicella zoster—which limits the patent base to which data from the study can be applied to.

Second, despite the responsiveness of both HSV and VZV to guanosine antivirals, their natural histories, ocular effects and specific antiviral sensitivities can vary significantly. Herpes simplex and herpes zoster both begin as epithelial disease; however, once established...

**ABOUT THE AUTHOR**

Dr. Bronner is a staff optometrist at the Pacific Cataract and Laser Institute of Kennewick, Wash. He has no financial interest in any products or services described in this article.

Knowing how to manage these viral conditions, especially long-term, is key to saving your patients’ vision.

**By Aaron Bronner, OD**
as affecting the cornea, HSV may vacillate freely between epithelial recurrences of infection and immune stromal keratitis as well as iridocyclitis, and may have a tendency towards frequent recurrences. This is in contrast to zoster ophthalmicus, which progresses more typically on a temporal continuum, with some cases resolving early in the process and others progressing to chronic smoldering ocular inflammation. Zoster ophthalmicus also much less frequently involves multiple recurrences. Therefore, while the management of HSV keratitis involves episodic treatments of acute flares-ups, zoster keratitis, while less common, can sometimes take months to effectively clear and may be marked by periodic manifestations of different forms of the disease.

The differing antiviral sensitivity patterns among virus groups also pose problems. Zoster research lags significantly behind that of simplex due to the lack of animal models of the disease and difficulties with experimental reactivation in humans, challenges that HSV research doesn’t face. The second-generation antiviral trifluridine, which is too toxic for systemic dosing, is effective topically in the management of infectious HSV, but is ineffective against VZV. Among the guanosine analog agents (acyclovir, valacyclovir, famciclovir and ganciclovir) one finding remains consistent: HSV has two to four times lower minimum inhibitory concentrations than varicella zoster virus, a fact reflected in the higher dosing strategies of oral antivirals for zoster compared with simplex.

Of this group, ganciclovir, an effective agent that is toxic when dosed systemically, is the only member of this class commercially available as a topical preparation in the United States (i.e., ganciclovir 0.15% gel, Zirgan, Bausch + Lomb).

SUPPRESSION DOSING OF ORAL ANTIVIRALS
One of the most important elements to come out of HEDS was the role of suppression dosing of oral antivirals, which significantly reduce the rate of recurrence of both stromal and epithelial keratitis with HSV infection. Dosing 400mg of acyclovir BID reduced the rate of recurrent stromal disease—the manifestation most likely to lead to corneal transplant among patients who had already had at least one episode of stromal keratitis—from 28% in the placebo group to 14% in the treatment group. Note, this protective effect likely extends after treatment ceases. Further, while years of research indicated that acyclovir-resistant HSV was extremely uncommon in immune competent patient bases, a more recent study concluded that long-term (i.e., greater than one year) suppression dosing was a significant risk factor for promoting acyclovir resistance, even in normal patients. Therefore, using suppression dosing is warranted only when a history of recurrent stromal disease supports it. While this HEDS-based information can’t be applied to the treatment of HZO—a virus with a tendency towards much less recurrence among healthy populations—a handful of smaller studies have demonstrated suppression dosing is effective at reducing incidence of herpes zoster in immune-suppressed populations.

I am comfortable extrapolating this information to my clinical care.
HOW TO FEND OFF HERPES AND VARICELLA ZOSTER

A presentation of classic dendritic keratitis due to HSV.

Clinically, my approach to HSV keratitis is to use a topical or oral antiviral in cases of simple dendritic keratitis. Research shows either approach to be equivalent. When the pathology moves deeper, though, I become more particular about treatment regimens. In cases of inflammatory sub-dendritic, nummular or disciform keratitis, I use a topical corticosteroid paired with an oral antiviral for prophylaxis, as effective penetration of the topically dosed antivirals becomes a concern. When manifestations transition from infectious to inflammatory, I treat the infectious process first and then add a steroid once the cornea has been sterilized, as indicated by re-epithelialization.

Because topical steroids have the potential to make cases of HSV epithelial keratitis worse, their use for all manifestations of HSV keratitis inappropriately has remained somewhat taboo. The good news is we know that while topical corticosteroid use is important to outcomes, their use may prolong episodes and may predispose a patient to further, more severe manifestations of the disease. Because of this controversy, a general prescribing practice of corticosteroids in the management of HZO is to be comfortable using them but only when their absence threatens vision, as in the case of central or severe corneal infiltrates or recrudescent inflammation. Also, as HZO often progresses along many months, it’s important to realize that dosing of steroids may require a several month taper.

THE ROLE OF STEROIDS

The clinical manifestations of herpes simplex keratitis vary from dendritic epithelial disease to sub-dendritic stromal keratitis, nummular keratitis and disciform endothelitis. The generally accepted mechanism of these keratitides is that dendritic disease is actually infectious keratitis characterized by proliferation of live virus within the epithelial margins of the lesion, while stromal and endothelial effects are inflammatory responses to retained non-vital viral proteins. As such, it’s useful to sub-classify HSV keratitis as infectious epithelial keratitis or immune stromal keratitis and treat as the underlying mechanism indicates. For infectious epithelial disease, an antiviral (either oral or topical) is sufficient. For immune stromal disease, topical steroids and a paired prophylactic topical or oral antiviral is appropriate treatment.

However, systemic corticosteroids are used in immune-competent patients during episodes of shingles to reduce associated pain, without concern for disease exacerbation. Mirroring this systemic practice is the use of topical steroids with HZO. Although there are widely accepted manifestations of the disease that are active viral proliferation—the pseudodendrite, for example—corticosteroids are not strictly contraindicated in any HZO presentation. Though widespread, use of corticosteroids in treatment of HZO is not universally accepted. Rather, some practitioners feel their use may prolong episodes and may predispose a patient to further, more severe manifestations of the disease.

HERPETIC UVEITIS

The clinical picture of herpetic uveitis can be quite variable, with fine or granulomatous keratic precipitates that may be distributed diffusely, in Arlt’s triangle or in a linear pattern. Concomitant corneal edema, IOP spikes or sectorial iris atrophy may also appear. While this variability implies there won’t be one classic presentation of viral uveitis, it also gives a number of clinical clues about potential diagnoses.

Equally valuable in arriving at a correct diagnosis for viral uveitis is the patient setting. In cases of anterior uveitis, the most common caus-
We eye care providers focus our attention on zoster-based disease presentations in adulthood, as this is how it presents in our offices. But it behooves us to consider such cases as merely part of the lifelong infection that begins with the first clinical manifestation of varicella—chicken pox—and how that initial infection and subsequent re-exposures shape the immune system’s vigilance to the virus, which in turn affects disease patterns throughout life.

Notably, these relationships were disrupted by the widespread varicella vaccination process begun two decades ago when Varivax (Merck) was added to the recommended childhood vaccination schedule in 1995. This vaccine is made up of a live, albeit attenuated, form of VZV known as the Oka strain. The virus type is more easily contained by the immune system, which reduces disease burden. As such, clinical varicella has been reduced by approximately 70%.22,23

This reduced disease burden, however, may have some unintended consequences for anyone carrying wild-type VZV in latency—namely, all of us whose childhood immunization panels predate the introduction of Varivax. A widely held (though unproven) belief is that a significant part of our immune-boosting capabilities against the virus, which influences our immune vigilance, comes with environmental exposures to children who have varicella.23 The Varivax program thus deprives us of these immune boosters, as children are no longer widely developing chicken pox.

If, as seems likely, highly transmissible varicella provides immune boosters for those with latent VZV, immune vigilance will wane more rapidly, and we could see a sharp rise in shingles among the pre-vaccine generations, possibly including healthy adults. This rise is predicted by mathematical modeling to occur 10 to 20 years after implementation of the vaccine—i.e., now—and could last for 30 to 50 years.24 At this time, efforts to document a potential increase in zoster incidence have been inconsistent.23 My own anecdotal experience has been marked by a spate of otherwise healthy young adults developing zoster.

The long-term projection for shingles is a rosier picture. The Oka strain is more easily contained by the immune system, preventing initial manifestation of chicken pox, and more easily held in latency, which theoretically should reduce zoster incidence in adulthood among those vaccinated. Of course, this effect will not manifest until all pre-vaccination generations have died. Although we won’t be around to see it, one small part of the world we’ll leave our children could be better—less shingles.

For us “great unwashed masses” of pre-vaccination, Zostavax (Merck), which uses the same Oka strain as Varivax but at significantly higher concentrations, offers protection against shingles as in immune booster. It has been shown to reduce incidence of zoster by 50% in susceptible populations. Approved in 2006, the CDC currently recommends Zostavax for all adults over the age of 60. It is approved for use in patients as young as 50.

This gives rise to a common clinical question: “My patient just had shingles; should I send them for Zostavax?” The answer is probably “no.” The episode of shingles is likely to be at least as potent an immune booster as the vaccine, and so vaccination will provide diminishing returns, if any. However, patients who are at risk for shingles and in the absence of an immediate history of the disease should likely be encouraged to receive the booster. For high-risk, immune-suppressed populations with potential for recurrent disease, suppression dosing of antiviral is probably more appropriate than the vaccination.
age of 60 who developed uveitis for the first time, herpes zoster and herpes simplex were the most common non-idiopathic etiologies found, accounting for approximately 18% of uveitis cases. An appropriate differential diagnosis for presumed viral uveitis in this age group would contain other common sources of uveitis, but perhaps more importantly, consideration of the masquerading syndromes of intraocular leukemia or lymphoma, as well as a retained cataract fragment after cataract surgery, should be given. As penetration of topical antivirals into the anterior chamber can be hampered by an intact epithelium, treatment of isolated viral uveitis should include both oral antivirals at the correct treatment dosage for the suspected etiology, and a topical, and in some cases oral, corticosteroid.

The management of viral eye disease, due to its prolonged natural history, relationship with host immunity and varied clinical presentations, is a complex and serious part of eye care. Understanding these subtleties and recognizing the differences between HSV and VZV can improve practitioner confidence and patient care, and lead to better outcomes.

HEDS Up: Three Key Points

The first Herpetic Eye Disease Study (HEDS I) is over 20 years old and—though it is still being presented as such—is no longer new material. At this point, eye care providers must be aware of the following elements of the study:

1. It only applies to herpes simplex; varicella zoster was not studied.
2. Suppression dosing of acyclovir reduces the risk of recurrence of epithelial and stromal keratitis by approximately 50%, though this effect is not as robust in patients without a history of previous stromal keratitis.
3. Topical corticosteroids are safe and effective in treating herpetic stromal keratitis and iridocyclitis. Withholding topical steroids for HSV stromal keratitis can result in worse outcomes.

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- A Guide to Scleral Lens Fitting
- Scleral Lens Fitting Videos
- Scleral Lens Fitting Scales
Bacterial keratitis is a rare yet potentially devastating ophthalmic disease. Acute infections can present with dense corneal infiltrates, edema and subsequent ulceration, which, despite aggressive treatment, may result in long-term, vision-threatening sequelae including corneal scarring, glaucoma and cataract. In fact, corneal opacification due to ulceration is a leading cause of vision loss contributing approximately two million new cases of blindness worldwide each year.

Past research has noted an incidence of ulcerative bacterial keratitis as approximately 11 per 100,000 person-years in the United States, while more recent studies report rates ranging from 20.9 to 27.6 per 100,000 person-years. Unsurprisingly, there is a significant increase in incidence among contact lens wearers, up to 130.4 per 100,000 person-years; in fact, wearing contact lenses, especially overnight, is the greatest risk factor for bacterial keratitis in developed nations. With 40 million contact lens wearers in the United States and the increasing popularity of toric and multifocal lenses, the incidence of bacterial keratitis may well continue to rise.

Aside from contact lens wear, other significant risk factors for bacterial keratitis include surgical and non-surgical trauma; ocular surface disease such as exposure keratopathy, tear-film deficiencies, neurotrophic keratopathy, bullous keratopathy and blepharitis; and systemic conditions such as diabetes, graft-versus-host disease, mucous membrane disorders or immunosuppression. Often, patients exhibit several of these risk factors.

1. WHAT’S THE CAUSE?
In general, it is extremely rare for a healthy eye to develop a spontaneous infection; generally, one or more predisposing factors can be identified in most cases. Recording a thorough contact lens history—including wear time, type of solution, lens hygiene and replacement habits—is critically important. Understanding the nature of the disease course including duration of symptoms, degree of pain, redness, presence of discharge and change in vision can indicate severity as well as help distinguish rapidly evolving infections from those with a more indolent course. Taking a thorough medical and ocular history can also help uncover underlying issues such as immunosuppression, recent illness, prior ocular disease, infections or trauma. Of particular importance is a history of prior herpetic eye disease, which can often leave the cornea neurotrophic and thus more susceptible to bacterial keratitis.

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Though causes of bacterial keratitis vary depending on geography and patient population, most reflect the normal flora of the ocular surface and are largely due to gram-positive organisms such as coagulase-negative Staphylococci, Staphylococcus aureus and Corynebacterium.6,14,16-18 Pseudomonas aeruginosa is generally the most likely causative organism in cases of gram-negative infections.14 Contact lens wear in particular tends to be associated with Pseudomonas, although significant numbers of Serratia marcescens and Moraxella sp. infections have also been reported.14,18-21 Generally, gram-negative organisms result in a rapidly evolving, highly virulent infection that can lead to ocular perforation in just 24 to 48 hours. While certain gram-positive organisms, such as S. aureus or Streptococcus pneumoniae may behave similarly, other gram-positive species such as Streptococcus viridans may have a more indolent course with less dramatic clinical presentations.

2. HOW TO TEST?
Stains and cultures allow for early identification of non-bacterial organisms and provide the basis for eliminating either gram-positive or gram-negative coverage in order to reduce patient eye drop burden and avoid overuse and misuse of antibiotics. However, variations in ability and availability of culture materials and reagents result in the empiric treatment of many cases of community bacterial keratitis.22,23 In fact, the 2013 published preferred practice pattern of bacterial keratitis from the American Academy of Ophthalmology recommends pursuing stains and cultures only in cases in which the ulcer: is particularly large; is centrally located; involves the mid or deep stroma; is an infection that has not been responsive to initial treatment; or has atypical features which may indicate fungal, amoebic or mycobacterial keratitis.24

While traditional culture methods successfully identify a causal organism in only 40% to 60% of cases, in the era of emerging antibiotic resistance it may be prudent to attempt Gram stain and culture of all cases of bacterial keratitis in order to tailor treatment appropriately when possible.16,22,25,26 Of importance, prior treatment with antimicrobials does not necessarily decrease culture yields, although it may take longer to recover pathogens.19,22 Thus, there can be utility in delayed cultures particularly in refractory or chronic cases.

A corneal tissue biopsy is an additional diagnostic approach, particularly when initial results from corneal scrapings are unrevealing.24,30 A recent study identified a causal agent in 42% of cases, either with culture or histopathologic examination of the tissue. Of note, 44% of patients in this series had initial negative cultures from corneal scrapings.30 The advantage of biopsy is that the tissue can be used both for culture and histopathology; the latter of which may have added benefit in identifying Acanthamoeba or fungi, which are more difficult to culture with traditional methods. While biopsy may have some inherent risk to the pa-
CONSIDERING KERATITIS: CRITICAL QUESTIONS

3. WHICH ANTIBIOTIC?
Ideally, treatment should be tailored to the causal organism; however, in the case of a rapidly progressive disease process, patients cannot afford to wait until Gram stain results return prior to initiating treatment. Gram stain may take up to 24 hours to return from the lab while culture data will take several days. In the absence of details from the history or unusual features on clinical exam that could indicate a fungal, amoebic or viral process, first-line empiric treatment should provide broad coverage against both gram-positive and gram-negative organisms.

Fourth-generation fluoroquinolones are considered by many to be mainstays of corneal ulcer treatment, as they provide excellent gram-negative coverage while offering strong protection against gram-positive organisms such as *S. aureus* and coagulase-negative *Staphylococcus sp.* In general, fluoroquinolones are readily available, well tolerated, and effectively penetrate the ocular surface, making these agents an attractive first-line choice in treating keratitis. Gatifloxacin and moxifloxacin, in particular, are often popular choices for initial empiric treatment of bacterial keratitis.

However, increasing rates of antibiotic resistance, particularly among gram-positive organisms, should be considered when initiating treatment. Studies like the Ocular Tracking Resistance in US Today (TRUST) and Antibiotic Resistance Monitoring in Ocular MicRones (ARMOR) have shown that while methicillin-sensitive *S. aureus* (MSSA) susceptibility to all fluoroquinolones is approximatively 80%, methicillin-resistant *S. aureus* (MRSA), susceptibility is only roughly 15%. In addition to MSSA and MRSA, many other gram-positive organisms have developed significant resistance to most commonly used ophthalmic antibiotics, with the efficacy of third generation fluoroquinolones the most affected. Regarding gram-negative organisms, fluoroquinolones continue to provide excellent coverage in most geographic areas, but reports of emerging resistance are on the rise.

Fortified antibiotics offer an increased concentration of drug over commercially available antibiotics and provide more complete coverage of both gram-positive and gram-negative organisms including MRSA and *Pseudomonas.* The fortified antibiotic regimen typically includes a cephalosporin or vancomycin combined with an aminoglycoside such as tobramycin or gentamicin. Though effective in many cases, there are also obvious disadvantages, including access to specialized compounding pharmacies, reduced shelf life, the need for multiple drops and possible increased risk of ocular toxicity. While several studies highlight similar outcomes between fluoroquinolone monotherapy and fortified antibiotics, in an era of significant antibiotic resistance, practitioners should consider either combining a fluoroquinolone with fortified vancomycin or cefazolin, or using a combination fortified regimen for complete coverage, particularly in severe cases. Antibiotic resistance patterns can vary significantly by geography. Thus, local antibiograms should be used to inform treatment choices.

4. WHAT ABOUT STEROIDS?
Debate over whether or not to use steroids in the treatment of bacterial keratitis is ongoing—on one hand, they suppress inflammation, which may in turn reduce the risk of subsequent corneal scarring; on the other, there are a number of disadvantages including higher risk of corneal melting, an increase in infection burden due to local immunosuppression and elevated IOP.

A recent review analyzed four randomized control trials (including the Steroids for Corneal Ulcer Trial (SCUT)) comparing groups treated with antibiotics and topical corticosteroids against antibiotics alone. As three of the four trials were underpowered to detect treatment effect differences, it is difficult to draw definitive conclusions. Nonetheless, there did not appear to be a difference in visual acuity, re-epithelialization time, quality of life or adverse affects between the treatment and control groups.

However, the timing of steroid initiation may be an important consideration. Participants in the Steroids for Corneal Ulcer Trial (SCUT) received steroids anywhere from two to 34 days after starting antibiotic therapy. In a recently published sub-analysis, patients who were given steroids within two to three days of starting antibiotic therapy showed a statistically significant gain in visual acuity at three months, particularly those with severe or moderately severe ulcers. Additionally, the data suggests steroids may actually be detrimental with respect to visual acuity if initiated after four days of antibiotic therapy. Long-term follow-up data from the SCUT also supports corticosteroid use, showing a one-line improvement in visual acuity at 12 months for ulcers not caused by *Nocardia* species.
There are a number of differing approaches and unanswered questions in the diagnosis and management of bacterial keratitis. A thorough history with particular attention to contact lens use, combined with subsequent culture data can help tailor treatment regimens. When possible, cultures and smears should be obtained on initial presentation, although delayed cultures can still be beneficial. Antibiotic resistance is an important consideration when treating empirically, and it is necessary to understand local antibiograms to make rational decisions.

In cases where ulcers are large, centrally located and have begun to invade and destroy the corneal stroma, fortified antibiotics provide the necessary robust gram-positive and gram-negative coverage for adequate treatment. Finally, steroids may provide some benefit with respect to visual acuity if initiated early.

7. Stapleton F, Carnt N. Contact lens-related microbial keratitis: how have epidemiology and genetics helped us with pathogenesis and prophylaxis? Eye (Lond) 26, 185-93 (2012).
**CONSIDERING KERATITIS: CRITICAL QUESTIONS**

**CE TEST - OCTOBER 2015**

1. Cultures are not routinely obtained in patients with significant ulcerative keratitis who exhibit the following:
   a. When an unusual organism is suspected.
   b. Patients who are hospitalized or immunocompromised.
   c. Patients who are not responding to initial, seemingly appropriate treatment.
   d. When ulceration is off-axis and less than 2mm diameter in size.

2. Which of the following is true regarding the use of topical steroids in microbial keratitis?
   a. Their use has shown no benefit in systematic and meta-analysis reviews.
   b. Using topical steroids is safe prior to identifying the organism responsible for infection.
   c. Steroids should be avoided in Nocardia and fungal infections.
   d. The SCUT results show that timing in initiating topical steroids seems to not have an impact on outcomes.

3. A corneal biopsy in suspected infection of the cornea has the following advantage(s):
   a. Tissue can be used for both culture and histopathology.
   b. May provide a causal organism when initial cultures are negative.
   c. Biopsy results are difficult to obtain once topical treatment has been initiated.
   d. A and B are correct.

4. Signs of improvement in treatment of infectious bacterial keratitis include all of the following except:
   a. No growth on a culture (taken after the referring doctor treated the patient with antibiotic drops for three days).
   b. Reduction in cell infiltrate and surrounding edema.
   c. Progressive re-epithelialization.
   d. Reduction in anterior chamber reaction.

5. An appropriate alternative medication for fluoroquinolone-resistant *Pseudomonas aeruginosa* keratitis is:
   a. Amikacin or cefazidime.
   b. Any first or second-generation fortified cefazolinpo.
   c. Fortified vancomycin.
   d. Any sulfonamide, since they haven’t been used much lately.

6. Which of the following is not a risk factor for developing bacterial keratitis?
   a. ICU care.
   b. The use of steroids.
   c. Sleeping with contact lenses.
   d. Aspirin therapy.

7. All of the following are symptoms or signs of corneal infection except:
   a. Pain, redness and photophobia.
   b. Discharge and foreign body sensation.
   c. Anterior chamber reaction.
   d. All are possible signs or symptoms of corneal infection.

8. Which of the following is not a reason to culture corneal ulcers?
   a. Should be a medicolegal component of your record in case the ulcer doesn’t respond to empiric treatment.
   b. Reveals sensitivities of the organism(s).
   c. No single agent is generally effective for most infections.
   d. Effectively treated organisms are difficult to isolate.

9. Currently, the most effective/complete treatment plan for resistant bacterial infection is:
   a. Vancomycin and cefazidime.
   b. Tobramycin and ciprofloxacin.
   c. Gentamycin and cefazolin.
   d. Ofloxacin and erythromycin.

10. All of the following systemic disorders are risk factors for corneal infection except:
    a. Diabetes mellitus.
    b. Nucous membrane disorders.
    c. Graft v. host disease.
    d. All of the above are potential risk factors for infection.

**EXAMINATION ANSWER SHEET**

**Considering Keratitis: Critical Questions in Disease Management**

Valid for credit through October 1, 2018

Online: This exam can also be taken online at [www.reviewofcontactlenses.com](http://www.reviewofcontactlenses.com). Upon passing the exam, you can view your results immediately. You can also view your test history at any time from the website.

Directions: Select one answer for each question in the exam and completely darken the appropriate circle. A minimum score of 70% is required to earn credit.

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**Answers to CE exam:**

1. A B C D  6. A B C D
2. A B C D  7. A B C D
3. A B C D  8. A B C D
5. A B C D  10. A B C D

**Evaluation questions** (1 = Excellent, 2 = Very Good, 3 = Good, 4 = Fair, 5 = Poor)

11. Met the goal statement:
   a. 1 2 3 4 5
12. Related to your practice needs:
   a. 1 2 3 4 5
13. Will help improve patient care:
   a. 1 2 3 4 5
14. Avoided commercial bias/influence:
   a. 1 2 3 4 5
15. How do you rate the overall quality of the material?
   a. 1 2 3 4 5
16. Your knowledge of the subject increased:
   a. 1 2 3 4 5
17. The difficulty of the course was:
   a. Complex  b. Somewhat  c. Basic
18. How long did it take to complete this course?
   a. 1 2 3 4 5
19. Comments on this course:
   __________________________________________

20. Suggested topics for future CE articles:
   __________________________________________

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Business Name: ________________________________

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By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by fraudulent or improper means.

Signature: ________________________________ Date: ______________

Please retain a copy for your records.

LESSON 11842, RO-RCCL-1015
Mucin: Friend or Foe?

Though vital to eye health in many ways, mucus—when overproduced—can interfere with contact lens wear. For good long-term results, reduce excess by targeting goblet cells.

Many patients with inflamed, dry post-surgical eyes also often present with copious mucus. Doctors spend hours, and significant amounts of money, altering contact lens materials and fits in an attempt to ameliorate symptoms of blurred vision caused by a buildup of mucus on or under lenses—often without success, leaving patients frustrated and unhappy. What to do? Perhaps the answer to this dilemma lies in targeting the root of the problem—why this is happening—rather than addressing the issue after the fact.

Goblet cells (which produce mucus) are located throughout our bodies, including the airways and gut as well as our bulbar and palpebral conjunctivae. Goblet cells are vital to maintaining homeostasis of the ocular surface by providing a defense system and lubrication for the surface epithelia. The mucous layer secreted by the goblet cells is essential for clearing away external pathogens and allergens. Goblet cells also secrete cytokines and modulate dendritic cells. In effect, mucus is a friend, not foe, to the ocular surface.

When goblet cells are dysfunctional, however, they can cause significant pathogenesis. In the eye, secretion is induced by stimulation of the afferent nerves in the cornea and conjunctiva, causing a reflex neural arc of the efferent sympathetic and parasympathetic nerves surrounding the goblet cells. A key common feature of goblet cell upregulation, regardless of the initiating event (i.e., dryness, allergy or another disease state), is inflammation and the presence of inflammatory regulators. In some patients, such as scleral lens wearers, this overproduction can have adverse consequences.

ACHIEVING BALANCE

Scleral contact lenses are often indicated for severe dry eye states, including Sjogren’s syndrome, ocular cicatricial pemphigoid, Stevens-Johnson syndrome and neurotrophic keratitis. However, because these and other conditions produce a chronic inflammatory state of the ocular surface that can lead to mucus buildup, many scleral patients complain of “foggy” vision within minutes to hours following lens application. Thus, it is vital to achieve the right balance between mucus levels and the lens. This can be done in one of several ways:

1. **Address all dry eye-related conditions.** This includes improving lid hygiene, lubricating the ocular surface with preservative-free products and prescribing nutritional supplements (i.e., omega fatty acids).

2. **Address any lens fit-related issues.** Instill fluorescein to see if there are any leaks under the lens. Make sure the landing area is wide and tangential to the sclera—avoid focal impingement of the conjunctiva (Figure 1). Limit the central vault to 200 µm to 250µm and make sure there is clearance over the limbus.

3. **Always order scleral lenses in the most highly wettable materials available.** Do not have the patient continually remove the lens and clean it throughout the day (as much as they are tempted to do so). Lens removal will further drive the overproduction problem by inducing a “mucus fishing syndrome” effect. Instead, use saline vials (0.9% sodium chloride inhalation) to “squirt” the mucus out from under the lens. Conditioning solution or lubricant can be used on a plunger to “squeegee” the front surface of the lens and remove deposits. Mucus production will likely downregulate in two to four weeks, once the inflammatory status of the eye improves.

Consider adding an immunomodulator—such as a steroid—for a short course during scleral lens adaptation if mucus is a problem. Use a mucus-eliminating chemical cleaner weekly to keep the lens surface clean and free of scrubbing induced scratches.

Above all, be sure to educate patients on the fact that mucus is a sign of their disease state and not a result of a poor contact lens fit. Steps should be taken for goblet cell protection, rather than mucus elimination. With proper protection, mucus production will decrease.

A Sticky Situation

These tips can help ensure a consistent presentation among all staff members.

"GETTING NEW BEHAVIORS TO STICK ISN’T AS EASY AS WRITING THEM INTO YOUR OFFICE MANUAL."

Once you’ve done this, your team is ready to man the phones. If one of your staff members reverts back to the old, unfriendly “Doctor’s office,” call them aside and have a one-to-one discussion out of earshot of others. Remind them of what was discussed during the staff meeting, and ask if they remember why the staff decided on the approved greeting. Hopefully, they will say yes and remember to stick with the script.

**Give It Time**

As with all tasks that are repeated constantly throughout the day, expect it to take some time for staff members to learn and fully embrace a new habit. Finally, ask staff members who struggle with the new practice protocol if there is anything you can do to help them remember to answer the phones properly. If they are aligned with your mission, they will admit there’s really nothing else you need to do and that they will do a better job from now on.

While these four steps may seem like an inordinate amount of work, they are the most effective path to stickiness. Getting new behaviors to stick isn’t as easy as writing them into your office manual.

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I’m at my wit’s end. I’ve held repeated staff meetings about the proper way to answer the phone. The staff does it correctly for a few days, then reverts back to the old way. I just can’t get it to stick!

Many of us could substitute almost any task for “answer the phone” and feel just as frustrated as this doctor. We’ve all been there. Here’s how to get more consistent staff results—and less frustration:

1. **Acknowledge skill.** Using our telephone example, first acknowledge that your staff members are capable of memorizing something to say on the phone. Though it may not be the greeting you want, recognize that your staff members are at least making an effort. So, step number one is to acknowledge that they have the skill to do the task. Unless you’re asking them to recite the Gettysburg Address when answering phone calls, memory or aptitude shouldn’t be the reason your greeting isn’t being delivered!

2. **Involve staff.** The next step is the most important one. Instead of simply issuing an edict to use the approved script, ask your staff, “How can we answer the phone in a way that conveys what our practice stands for?” If you get blank stares, you’ll have to take a step backwards and start with, “What does our practice stand for?” or, “What’s unique and different about us that we want patients to remember?”

Let’s assume you get an answer such as, “We’re the friendliest doctor’s office there is—not just among local eye doctors, but every doctor on earth!” Ask your staff if answering the phone with a simple, “Doctor’s office,” supports your ultra-friendly mantra. If you don’t get a resounding “No!” you’ll need to consider retraining or rehiring!

3. **Create a script.** From here, share your requested method of answering the phone, such as, “Hi, this is Tara from Friendly Vision. How can we help you today?” Ask your staff if this feels more in line with the practice’s theme. At this point, it is a great idea to have an open-minded brainstorming session to edit and tweak your proposed greeting. Having your phone staff offer opinions here is valuable. If you get good feedback, use it, or at least test it for a few weeks.

4. **Practice, practice, practice.** Once you’ve got a consensus on the best phone greeting, ensure your staff understands the connection between the words and the reasons behind them. From there, practice answering the phone at staff meetings. After each session, ask the receptionists how they feel. Did the greeting feel artificial, forced or natural? Regardless of the response, follow up by asking why. Let those using the script give input on how they feel about the new script and make any edits.

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