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TOPICS IN Ocular Antiinfectives

Culturing Ocular Infections in the 21st Century

Joseph Blondeau, PhD

Even as newer, more exciting modes of pathogen detection become increasingly available, culture remains the fundamental tool for the identification and characterization of most ocular pathogens. Improving one's use of the lab can mean better care for patients.

Prescribing antimicrobials to patients with suspected infections without first obtaining a culture is always something of a gamble. Many patients, including those with superficial ocular infections, respond well to wisely chosen empiric antimicrobial therapies—indeed, the high rate of success with broad spectrum topical ophthalmic antibiotics is a common reason for skipping the culture. And culturing is not without its downsides: including cost, time, and sometimes frustration, as microbiology reports can be ambiguous or even misleading.

However, by the time a patient responds poorly to an empirically chosen agent, the opportunity for collecting a reliable specimen has been missed. Antibiotic exposure alters patient's normal flora and can hinder microbiologic growth in vitro.[1]

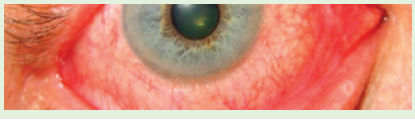
One might expect that, in this era of shifting patterns of antibiotic resistance, clinicians would err increasingly on the side of obtaining a culture prior to instituting antimicrobial treatment for suspected infections. Yet, in my experience, eyecare providers tend to underutilize the microbiology lab, reserving its use for severe or recalcitrant ocular infections. In this brief review, I will look at why that might be and offer some ideas for optimizing ocular cultures.

The Case for Culture

The principle reason for obtaining a culture specimen prior to initiation of antimicrobial therapy is to identify a causative pathogen (if one exists), enabling the clinician to target antimicrobial therapy as precisely as possible, and, should therapy need to be amended, to be able to do so with minimal guesswork. Cultures of superficial ocular infections—including conjunctivitis, blepharitis, and keratoconjunctivitis—can be obtained at the chairside in both children and adults. Of course, patients suspected of having an intraocular infection require immediate culturing of the relevant tissue and empiric antimicrobial treatment covering likely pathogens.

Ocular infections may be caused by a wide range of pathogens, including organisms that make up the normal bacterial flora of periocular skin, conjunctiva, nose, and/or upper airway and may be considered innocuous when isolated from other sites (Table 1). Geographic variability of pathogen species and susceptibility patterns can be marked. Knowledge of and ready access to current susceptibility data—antibiograms—from within one's region of practice (preferably from one's own institution) is

See INSIDE for:
Advances in Managing Adenovirus Ocular Infections
by Shachar Tauber, MD



TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Refine their practice of ocular culture and transport for a range of infection types.
2. Interpret reports from microbiologic laboratory more effectively.
3. Name two factors that distinguish possible treatment options for adenovirus conjunctivitis.

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crucial to optimizing antibiotic selection.

Many centers compile culture and susceptibility data yearly into hospital antibiograms. These may be subdivided by various patients categories, including outpatient pediatric, inpatient pediatric, outpatient adult, inpatient adult, etc. Other groupings of isolates, such as those derived from certain anatomical sites or by certain subspecialty services, may be available at some institutions; certainly, an ophthalmology-specific antibiogram would provide useful information for eyecare providers.

While local, up-to-date, often category-specific antibiograms are great resources, they are not a substitute for the patient-specific information that can be gained only from ocular culture: pathogen identification and antimicrobial minimum inhibitory concentration (MIC) profiles. There is a tendency to think of pathogens as either susceptible or resistant to individual antibiotics, with little appreciation for the gray zone in between. MIC values tell the clinician more than whether an organism is "susceptible" or "resistant" by systemic standards; they can also describe the relative susceptibilities of an isolate to several antibiotics.

This becomes important in topical antimicrobial treatment of superficial ocular infections. It is well known that MIC breakpoints reflect organisms' in vitro susceptibility to systemically administered drugs; there are no breakpoints for determining susceptibility or resistance of a topically administered antibiotic. Pathogens with high MICs (above the breakpoint) are categorized as "resistant"; however, the same pathogen may succumb to the same drug used topically due to high concentrations achievable when antibiotic is applied directly to the infection. Thus, depending on the clinical circumstances, it may be reasonable to choose a topical antibiotic to which the pathogen is technically "resistant." (Assuming equivalent safety, one may want to choose the antibiotic with the lowest MIC—even though the bug is technically "resistant" at this level.)

Barriers to Culture

As mentioned, eyecare providers may forego a pretreatment ophthalmic culture in some patients for several reasons: the availability of safe, broad-spectrum topical antibiotics with good pharmacokinetic properties against

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STATEMENT OF NEED

Ophthalmologists face numerous challenges in optimizing their competencies and clinical practices in the realm of preventing, diagnosing, and treating ocular infections and their sequelae; these challenges include:

- The widespread "off-label" use of topical ophthalmic antibiotics to prevent and treat serious and sight-threatening infections—given the reality that the most widely used topical antibiotics in ophthalmology have FDA approvals restricted to bacterial conjunctivitis.
- The escalating levels of multi-drug resistance in common ocular pathogens.[1]
- The emergence and increasing prevalence of once-atypical infections that may require diagnostic and treatment techniques relatively unfamiliar to comprehensive ophthalmologists.[2]
- The introduction of new and potentially more efficacious and/or safe ophthalmic antiinfectives.[3]
- The introduction of new and potentially more accurate diagnostic techniques for ophthalmic infections.[4]
- Widespread discussion over the efficacy and safety of novel or alternative delivery techniques and vehicles for prophylactic ophthalmic antibiotics (including but not limited to intracameral injection and topical mucoadhesives).[5,6]
- Increased understanding of the inflammatory damage caused by ocular infections and the best ways to prevent/alleviate inflammation without fueling the growth of pathogenic organisms.

Given the continually evolving challenges described above, *Topics in Ocular Antiinfectives* aims to help ophthalmologists update outdated competencies and narrow gaps between actual and optimal clinical practices. As an ongoing resource, this series will support evidence-based and rational antiinfective choices across a range of ophthalmic clinical situations.

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FACULTY AND DISCLOSURE STATEMENTS

Nisha Acharya, MD (Faculty Advisor), is an associate professor of ophthalmology and epidemiology at the University of California, San Francisco and director of the Uveitis Service at the F.I. Proctor Foundation. She states that in the past 12 months, she has not had a financial relationship with any commercial organization that produces, markets, re-sells, or distributes healthcare goods or services consumed by or used on patients.

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common ocular infections and a perception of limited usefulness of culture related to a lack of susceptibility breakpoints for topical antibiotics. A third reason relates to confusion around interpretation of language in some microbiology laboratory reports. For office-based doctors, there is also a hassle factor: they may not have access to a microbiology lab or even have the right supplies for specimen collection. The office may not even know how to bill appropriately.

Unfortunately, some organisms that are considered pathogenic when recovered from eye specimens are considered contaminants when found in other specimens. Unless a lab has a clear understanding of what types of pathogens are associated with ocular infections, it may report "mixed skin organisms" or "likely contaminant" without further differentiation. Such a report holds little value for ophthalmologists, who much prefer lab reporting of the species of isolates, including susceptibility results.

In addition, a report of "no growth" may also be difficult to interpret as it can result from a variety of circumstances, including collection or transport error (a false negative), infection by an unusual or nonbacterial pathogen, or a noninfectious etiology. Whenever there is confusion about laboratory reporting, clinicians should speak directly to lab personnel. It may help to share specific ophthalmologic needs, including requesting identification and susceptibilities of common ocular pathogens and commensals that might otherwise be reported collectively as normal flora.

Tips for Ocular Culture

For conjunctivitis or blepharitis, Gram stains and cultures may be obtained using soft-tipped applicator (eg, cotton, Dacron, or calcium alginate), moistened with nonpreserved sterile medium. Anesthetic is typically not necessary but may be used to enhance patient comfort. To obtain conjunctival culture, gently lower the bottom lid and apply the swab to the lower bulbar conjunctiva for about 5 seconds avoiding the eyelid margin. For blepharitis culture, gently touch the swab to the superior and inferior lid margins and eyelashes.[2] In the case of unilateral disease, obtaining culture and gram stain of the fellow eye can serve as a control.[1]

Conjunctiva and eyelid specimens can be plated together on an agar plate, keeping adequate distance between the streaks and marking the location of the cultures. Most bacteria can be isolated on 5% sheep's blood agar, however some pathogens are better plated on chocolate agar (eg, *Haemophilus* species, *Neisseria* species, and some streptococci). Agar containing mannitol salt is useful for rapid isolation of staphylococcal species. Alternatively, transport swabs, properly marked, can be used. All cultures or transport media should be delivered promptly to the lab, preferably within 2 hours.[1,2] Smears should be stained as appropriate: gram stain for bacteria, calcofluor-white stain for fungi and *Acanthamoeba*, or direct fluorescent antibody for *Chlamydia trachomatis*.[1] Advanced molecular based diagnostic technologies, including polymerase chain reaction (PCR), are replacing culture and/or stained smears for some eye pathogens.

Sample collection from the cornea is a more delicate procedure; it should be performed by experienced hands

CORE CONCEPTS

- Culturing specimens drawn from suspected ocular infections is good clinical care. Specimens collected prior to the initiation of antimicrobials improve the chance for effective treatment.
- In the absence of a culture, local antibiograms and eye-specific microbiologic surveys can help guide antibiotic selection.
- Interpretation of antibiotic susceptibility reports is improved by knowledge of likely pathogens and a sophisticated understanding of MIC values.
- Conjunctival and eyelid cultures are easily performed; they may be plated in the clinic or transported via transport swab.
- A good working relationship between clinical and microbiology-lab teams is critical for optimal culturing, interpretation, and patient care.

TABLE 1 PREVALENT PATHOGENS IN OCULAR INFECTIONS

INFECTION TYPE	COMMON PATHOGENS
Conjunctivitis, adult or child[1,2]	*S. aureus* (including MRSA); *H. influenzae*; *S. pneumoniae*; *Moraxella catarrhalis*
Conjunctivitis, chronic (adult)[2]	Chlamydia
Conjunctivitis, hyperacute[2]	*N. gonorrhea*
Conjunctivitis, viral[2]	Adenovirus
Conjunctivitis, viral acute hemorrhagic[2]	Coxsackie virus, Enterovirus
Blepharitis[2]	*S. aureus* (including MRSA); *S. epidermidis* (including MRSE)
Keratitis, bacterial[2]	*S. aureus* (including MRSA); *P. aeruginosa*; Streptococcus species; *Moraxella* species; *Serratia marcescens*; Gram-negative bacteria; Atypical mycobacteria (post –LASIK)
Keratitis, fungal[2]	Yeast: *Candida*; Filamentous: *Aspergillus*, *Fusarium*
Keratitis, viral[2]	Herpes simplex virus; Varicella zoster virus
Keratitis, amoebic[2]	*Acanthamoeba*
Endophthalmitis (post-operative phacoemulsification, acute)[2,3]	Coagulase-negative staphylococci (including MRSE); *S. aureus* (including MRSA); ß-haemolytic streptococci; *S. pneumoniae*; *E. faecalis*; ∂-haemolytic streptococci (including *S. mitis* and *S. salivarius*); Gram-negative bacteria (including *H. influenzae* and *P. aeruginosa*); Fungi (*Candida* spp., *Aspergillus* spp., *Fusarium* spp.)
Endophthalmitis (post-operative phacoemulsification, delayed or chronic)[2,3]	*P. acnes*; Diphtheroids (including *Corynebacterium* spp.); Coagulase-negative staphylococci (including MRSE); Fungi

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in order to avoid further injuring the corneal surface. After application of topical anesthetic, samples are taken at the leading edge of a corneal ulcer—where the bacterial population is most dense—by soft-tipped swab, spatula, or blade. Scrapings tend to provide more material and are generally preferable to swabs for the diagnosis of keratitis. Proper labeling of specimens and expeditious transport improve the chance for an accurate result.[1] The collection and handling of specimens for the workup of endophthalmitis—aqueous fluid, vitreous fluid, or vitrectomy tissues—is performed by specialists only and is beyond the scope of this article.

When unusual pathogens are suspected (eg, *Neisseria gonorrhea*, anaerobes, fungal pathogens, mycobacteria), clinicians should discuss appropriate collection methods with their laboratory. Yeast—but not filamentous fungi—may grow on routine culture. Viral pathogens may be grown in culture using special viral medium. Although viral culture has been largely replaced by faster methods such as polymerase chain reaction, culture remains important in some instances—for example, when treatment may require systemic antiviral medications to which the virus may be resistant. *Acanthamoeba* may also be cultured in vitro, albeit typically over the course of several weeks.

Two notes of caution when it comes to obtaining cultures: first, microorganisms are susceptible to preservatives in histologic transport media. Thus, when specimens are being sent for both histology and microbiology—such as may be the case in a complicated patient with a broad differential diagnosis—specimens must be transported in separate containers. Ordering cultures and sensitivities as an afterthought on a specimen that was collected for histologic diagnosis is not usually feasible. Most surgeons and eyecare providers are well aware of this distinction; however it bears mentioning as occasional mishandling does occur.

Second, microbiologic specimens should be transported to the lab in the shortest period of time possible so that they are still viable when plated for growth. If specimen transport can't be accomplished in fewer than 4 to 6 hours, specimens should be refrigerated until they can be transported. If left unrefrigerated for longer periods of time—due to unanticipated delays or a failure in communication—fastidious organisms such as *Haemophilus influenza* and *Streptococcus pneumoniae* may lose viability, and results may be skewed toward hardier species such as *Staphylococcus aureus* and *S. epidermidis*.

Conclusion

Cultures are the foundation of infectious diseases diagnosis and remain vital to the care of patients with ophthalmic infections. While numerous advances in molecular diagnostic technology have been made, a viable organism is still required to determine antimicrobial susceptibility or resistance profiles. Simple steps may be taken to improve culture collection practice in many clinics.

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Advances in Managing Adenovirus Ocular Infections

Shachar Tauber, MD

Adenoviruses are the infectious agents most commonly involved in external ocular infections. Their ubiquity and their ability to generate epidemics make them a significant public health issue. Follicular conjunctivitis is the most common form of adenoviral ocular disease. Epidemic keratoconjunctivitis is the most contagious.[1]

As a group, adenoviruses rank among the most transmissible of microbes, with infection rates of 10% to 50% between close contacts, such as those sharing a home or dormitory.[2] Among the factors that enable such transmissibility is the very large number of adenovirus serotypes, with more than 50 reported to date. The resulting antigenic variability produces extremely high rates of susceptibility. Less than 5% of the population have antibodies effective against any given serotype.[2]

Add to this the remarkable robustness of the adenoviruses, which can resist heat and chemical disinfectants, while remaining viable for up to 5 weeks on surfaces.[1] We face an extremely hardy virus that can readily infect a highly susceptible population.

The Importance of Diagnosis

The fact that most adenovirus infections are self-limiting has long abetted

An article on the same subject was published in 2011. This version has been updated by the author.

complacency among physicians. In fact, there are many compelling reasons for prompt diagnosis and effective management. Long before we had treatment options, we recognized the need to break the adenovirus epidemic cycle with prompt isolation. To gain an appreciation of the importance of recognizing adenoviral infection and acting on that recognition, one has only to picture an actively infected bank teller, school teacher, checkout clerk, or ophthalmologist sharing virus with the day's stream of contacts.

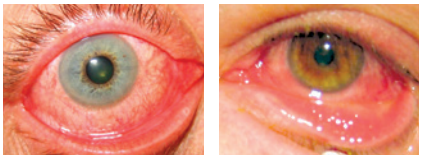

FIGURE 1 Examination alone proves unreliable in distinguishing adenovirus (left) from bacterial conjunctivitis (right).

A confident diagnosis of adenovirus infection also avoids the unnecessary use of antibiotics, which is becoming increasingly important in an age of rapidly proliferating multidrug resistance. In addition, adenoviral infections can mimic preseptal and orbital cellulitis, especially in children, and this often leads to unnecessary hospital admissions, CT scans, and intravenous antibiotics. In one study, Ruttum and coworkers found that 16% of patients with signs of preseptal or orbital infection were culture positive for adenovirus.[3] The American Academy of Ophthalmology partnered with Choosing Wisely, a health education initiative that seeks to inform patients and physicians about the overutilization of medical resources.[4] Choosing Wisely specifically advises patients and clinicians against the use of antibiotics in cases of adenoviral conjunctivitis.[4]

More Effective Treatment

Recently, we gained a new reason to welcome prompt and accurate diagnosis of adenovirus ocular infections: a promising treatment in the form of ganciclovir ophthalmic gel 0.15%. Long used in Europe for herpetic eye infections and recently FDA-approved for treatment of herpes simplex epithelial keratitis (dendritic ulcers), ganciclovir gel has shown efficacy against adenovirus conjunctivitis in early clinical use.[5] I now use it regularly in treating both herpes simplex and adenovirus ocular disease.

When matched with good diagnosis, an effective antiviral can significantly shorten adenoviral conjunctivitis and keratoconjunctivitis. It bears emphasizing that these infections, while self-limited, are not without significant morbidity, protracted courses, and vision-compromising complications. Associated subepithelial infiltrates can impair visual acuity for months and significantly exacerbate chronic dry eye disease.[6] Although such complications can be treated with topical corticosteroids, steroids have their own serious side effects. Moreover, effective treatment of even uncomplicated adenovirus conjunctivitis can alleviate and shorten what might otherwise be up to 3 weeks of significant ocular discomfort.

The Diagnostic Challenge

Though many of us would like to think otherwise, even the most skilled clinicians have never been able to reliably distinguish between viral and bacterial conjunctivitis, especially during the first week after onset (Figure 1). A classic symptom some doctors rely on to differentiate viral from bacterial infection is the presence of the eyes "stuck shut" in the morning. Rietveld and coworkers examined a cohort of 184 adults with a red eye and the presence of either an eye stuck shut in the morning or purulent or mucopurulent discharge.[7] Of the 57 patients with confirmed bacterial conjunctivitis, 53% had one eye stuck shut and 39% had two eyes stuck shut.

Among 120 patients without bacterial conjunctivitis, 62% had one eye stuck shut and 11% had two eyes stuck shut. In a study of patients in the first week of infection, Cheung and coworkers showed a misdiagnosis rate of 42% for patients with bacterial or viral conjunctivitis, while in a clinical trial to evaluate cidofovir treatment at 16 academic centers, experts showed a clinical accuracy of about 48%.[6,8]

CORE CONCEPTS

- Extreme contagiousness, prolonged discomfort, and the risk of compromised vision argue for diagnosis and treatment of adenovirus conjunctivitis.
- Rapid and affordable in-office diagnosis of ocular adenovirus is now possible.
- Dilute povidone-iodine appears effective against virus in the tears but not replicating virus in infected cells.
- Early studies and clinical experience suggest that ganciclovir ophthalmic gel shortens adenovirus conjunctivitis and reduces the risk of subepithelial infiltrates.
- Consider use of cyclosporine to reduce visual disturbance from subepithelial infiltrates.

A Culture Alternative

Historically, culture has provided the definitive diagnosis, an option seldom pursued in the clinic as it can take a week or more to get results. The late 1990s brought polymerase chain reaction (PCR) analysis, but outside of large medical centers, few clinicians have ready access to PCR; and sending patients or specimens out for testing tends to be expensive in both time and dollars. Unfortunately, the end result was that virtually all adenovirus infections were treated empirically, often with unnecessary and ineffective antibiotics.

Ten years ago, I became part of the multicenter clinical research team evaluating an experimental 10-minute in-office immunoassay for adenovirus. We compared the sensitivity, specificity, and accuracy of the rapid adenovirus detector to both viral cell culture and PCR in a group of 186 patients seen within 1 week of developing "red eye." Compared to culture, the immunoassay device

was 88% sensitive and 91% specific in diagnosing adenoviral conjunctivitis.[9]

In 2011, I participated in a second prospective, multicenter, masked, sequential, clinical trial to evaluate the efficacy of the next generation of this device. The study enrolled 128 patients presenting with a clinical diagnosis of acute viral conjunctivitis within 7 days of onset. Thirty-one patients were confirmed positive for adenovirus by viral cell culture and compared to cell culture, this device had 90% sensitivity and 96% specificity.[10] By culture, approximately 1 out 4 patients with acute conjunctivitis were confirmed to have adenoviral conjunctivitis.[10] Beyond the improved performance, the new test has several improvements to enhance usage. The second generation device is now commercially available.

A Red Eye Protocol

As part of a clinic's red eye protocol, prior to the doctor seeing the patient a technician can easily perform the test. To perform the test, tears from the palpebral conjunctiva are collected on the sterile sampling fleece located on the sample collector. The sample collector is then assembled to the test cassette, bringing the antigen in direct contact with an immunoassay strip, which is then dipped into a buffer solution to activate the test. Within 10 minutes, the results appear in a readout area (much like a pregnancy test), with a single blue control line indicating a negative result and two lines (a blue control and red result line) indicating detection of adenovirus. As the test's antigen binding involves epitopes on a conserved region of adenovirus protein, it detects all known serotypes.

After about 7 days, the disease process will typically have transitioned from primarily infectious to primarily inflammatory; nonetheless about 25% of patients remain contagious at 10 days and 5% at 2 weeks.[11] Even after a week, it is of value to test, as these patients will still test positive with the immunoassay. (And those patients whose disease by this point is purely inflammatory will test negative and can be more safely returned to school or work.)

Even in the absence of effective treatment, the rapid diagnosis of adenoviral conjunctivitis represents a significant public health achievement, as a positive result warrants patient isolation for 5 to 7 days, more thorough hygiene protocols, and treatment with refrigerated, preservative-free artificial tears to ease symptoms. Conversely, a negative result supports the empirical diagnosis of bacterial conjunctivitis (after excluding allergic and fungal conjunctivitis), allowing the clinician to prescribe an appropriate antibiotic with confidence and the patient to return to work or school after just 24 to 48 hours.

The Treatment Challenge

Because adenoviral conjunctivitis entails prolonged discomfort, lost time from work or school, and the risk of developing subepithelial infiltrates, it would be good if we could do more than just isolate patients. Adenovirus infections have long thwarted efforts to develop effective treatments. In part, the challenge has stemmed from the astonishing genetic diversity of adenovirus serotypes. Moreover, we have lacked models for basic research because the adenoviruses that infect humans do not replicate in either laboratory animals or in vitro cultures. Lastly, adenoviruses do not encode the type of nucleotide modifying enzymes that are known to activate anti-herpetic medications such as trifluridine.[12,13]

Cidofovir was among the first drugs to demonstrate activity against adenovirus, and it remains the measuring stick against which new anti-adenovirus medications are compared.[14,15] Unfortunately, systemic cidofovir has been associated with hypotony and uveitis and its ophthalmic use has been linked to punctal stenosis, eliminating cidofovir as a viable treatment for conjunctivitis.[16]

Commercially Available Options

Dilute povidone iodine (1% to 2%, five drops daily for 5 days) remains a commercially available option for treating adenoviral conjunctivitis, but one that stings and further irritates the conjunctiva. (From personal experience I can attest to both its efficacy and its ability to bring me to my knees.)

In vitro studies suggest that povidone iodine works well against free virus in the tears, but not against replicating virus inside infected conjunctival cells.[17] However, Isenberg has reported a lack of efficacy against viral conjunctivitis in a controlled trial with 459 children administered povidone iodine 1.25% ophthalmic solution four times daily for up to 2 weeks.[18]

The recent FDA approval of ganciclovir gel gives us a second commercially available, off-label option and one in a formulation that most patients find soothing to an irritated ocular surface. As mentioned, adenoviruses have long been assumed to be insensitive to antiviral drugs such as trifluridine, which require nucleotide modifying enzymes for activation. But we have evidence that ganciclovir may be an exception.

Some of the earliest indications came from the use of intravenous ganciclovir in the treatment of life-threatening systemic adenovirus disease.[19,20] Evidence of ophthalmic efficacy came with a prospective study of 18 patients with adenoviral keratoconjunctivitis.[5] The mean recovery time from symptoms of those receiving topical ganciclovir was less than half that of those who received preservative-free tears (7.7 days vs 18.5 days), and significantly fewer in the treatment group developed subepithelial opacities (2 of 9 vs 7 of 9).

In my own practice, we now regularly (off-label) use ganciclovir gel to treat adenoviral infections and are seeing associated reductions in the time that patients remain symptomatic. However, we do not yet know if ganciclovir reduces the period in which patients remain contagious, so we still recommend isolation from work or school for a full 7 days.

Treatments in the Pipeline

Pelletier and colleagues recently reported the results of a prospective, open-label, single-armed pilot study of nine patients treated with an ophthalmic suspension combining povidone

iodine 0.4% with dexamethasone 0.1% ophthalmic suspension. Adding this small amount of steroid helped relieve symptoms, but it also appeared to limit some of the antiviral activity seen with povidone-iodine alone.[21]

More forward-looking has been research into the anti-adenoviral powers of topical immunoglobulins derived from the pooled serum of thousands of serum donors.[22] In laboratory studies, such a preparation has demonstrated in vitro activity against multiple adenovirus serotypes and has shortened viral shedding in rabbits to a degree comparable to cidofovir. While fascinating, approval of topical immunoglobulin treatment will require years of further work, and even then may prove prohibitively expensive.

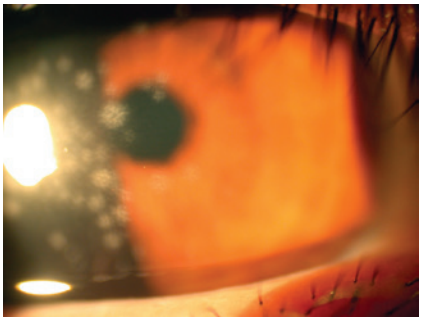

FIGURE 2 Prompt and effective treatment of adenovirus conjunctivitis reduces the likelihood of subepithelial infiltrates, which are seen here. *(Photo courtesy of Jodi Luchs, MD, FACS.)*

Managing Subsequent Keratitis

When diagnosing and treating adenoviral conjunctivitis, I warn patients that they may begin to experience decreased vision or increased light sensitivity in 7 to 14 days. As clinicians we understand that this results from the subepithelial infiltrate, or sterile keratitis, that frequently follows adenoviral conjunctivitis (Figure 2). The question is whether or not to treat this inflammation with topical steroids. One drawback is that once the steroids are withdrawn, infiltrates tend to rebound. In addition, there are the well-known risks associated with prolonged use of steroids.

I prefer the off-label use of topical cyclosporine 0.05% four times daily for 1 month followed by gradual tapering. Studies have shown it effective in resolving subepithelial infiltrates secondary to adenoviral keratoconjunctivitis while avoiding the side effects associated with ocular steroids.[23]

Summary

For the first time in history, we have effective means for the diagnosis and management of adenoviral ocular infections. My recommended protocol, when a patient presents with the signs and symptoms of acute conjunctivitis, is to test with a rapid, in-office immunoassay. If the result is positive, I prescribe ganciclovir gel five times a day for 5 to 7 days, with the addition of refrigerated, preservative-free tears as needed for further symptomatic relief. While treatment can reduce the duration of symptoms, the patient should maintain isolation for a full 7 days, as we do not yet know whether ganciclovir shortens viral shedding time. Should the patient experience problematic visual disturbance and/or light sensitivity following treatment, I recommend a month-long course of cyclosporine to resolve subepithelial infiltrates.

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 53

This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc. **DIRECTIONS:** Select the one best answer to each question in the Exam (Questions 1–10) and in the Evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. There is no fee to participate in this activity. *You can take the test online at* **http://cme.ufl.edu/ocular**.

1. Which of the following have hampered the development of anti-adenovirus drugs?
   - A. Adenoviruses that infect humans do not readily infect laboratory animals
   - B. Adenoviruses cause excessive morbidity in laboratory animals
   - C. Adenoviruses mutate too rapidly in laboratory cultures
   - D. All of the above are true

2. Antibiotic exposure interferes with subsequent ocular culture by which of the following mechanisms?
   - A. Alteration of normal flora
   - B. Inhibition of pathogen growth in vitro
   - C. Both A and B
   - D. Neither A nor B

3. Which of the following is being studied and considered for the treatment of adenovirus ocular infection?
   - A. Povidone iodine 0.4% with dexamethasone 0.1%
   - B. Immunoglobulins derived from pooled serum
   - C. Both A and B are true
   - D. Neither A nor B is true

4. When used to treat viral conjunctivitis, cidofovir has been linked to which of the following deleterious side effects:
   - A. Punctal stenosis
   - B. Subepithelial infiltrates
   - C. Corneal edema
   - D. None of the above

5. Which of the following is the most accurate?
   - A. MIC values accurately predict clinical efficacy of a topical antibiotic
   - B. MIC values are irrelevant in ophthalmologic practice
   - C. If its MIC value is in the resistant range, a topical antibiotic can't be effective
   - D. MIC values may be useful in choosing topical ophthalmic antibiotics

6. When used to treat adenovirus conjunctivitis, povidone-iodine is typically diluted to what strength?
   - A. 10%
   - B. 5%
   - C. 1% to 2%
   - D. 0.1% to 0.2%

7. Which of the following best describes a hospital antibiogram?
   - A. A patient-specific list of antibiotics given and route of administration
   - B. Annual summary of antimicrobial susceptibilities of bacterial isolates submitted to the hospital's laboratory
   - C. DNA sequence that produces a specific exotoxin
   - D. Pharmacology memo about changes to antimicrobial formulary

8. Which of the following is NOT recommended for routine bacterial conjunctival culture?
   - A. Collect with calcium alginate swab and plate on 5% sheep's blood agar
   - B. Collect with cotton swab and send to the lab within 48 hours
   - C. Collect with a transport swab and transport within 6 hours
   - D. Collect paired specimens from left and right eyes

9. Which of the following ranges best represents the rate at which adenovirus infects close contacts of an individual with active infection?
   - A. 5% to 10%
   - B. 10% to 50%
   - C. 50% to 75%
   - D. 75% to 90%

10. Which of the following is useful for rapid isolation of staphylococcal species?
    - A. Agar with mannitol salt
    - B. Sheep's blood agar
    - C. Chocolate agar
    - D. Saboraud's dextrose broth

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 53

This CME activity is jointly sponsored by the University of Florida and Candeo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Bausch + Lomb, Inc. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233. **DIRECTIONS:** Select the one best answer for each question in the exam above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11–16) to receive CME credit. CME exam expires February 29, 2016.

ANSWERS:

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
4.	A	B	C	D	**9.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

11. Extent to which the activity met the identified:
    - Objective 1: 1 2 3 4 5
    - Objective 2: 1 2 3 4 5
    - Objective 3: 1 2 3 4 5
12. Rate the overall effectiveness of how the activity:
    - Related to my practice: 1 2 3 4 5
    - Will influence how I practice: 1 2 3 4 5
    - Will help me improve patient care: 1 2 3 4 5
    - Stimulated my intellectual curiosity: 1 2 3 4 5
    - Overall quality of material: 1 2 3 4 5
    - Overall met my expectations: 1 2 3 4 5
    - Avoided commercial bias/influence: 1 2 3 4 5
13. Will the information presented cause you to make any changes in your practice? Yes No
14. If yes, please describe: _____
15. How committed are you to making these changes? 1 2 3 4 5
16. Are future activities on this topic important to you? Yes No

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records.

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