EARN 2 CE CREDITS: Don't Be Stumped by These Lumps and Bumps, *Page 70*

REVIEW® OF OPTOMETRY

April 15, 2017

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PHARMACEUTICALS REPORT

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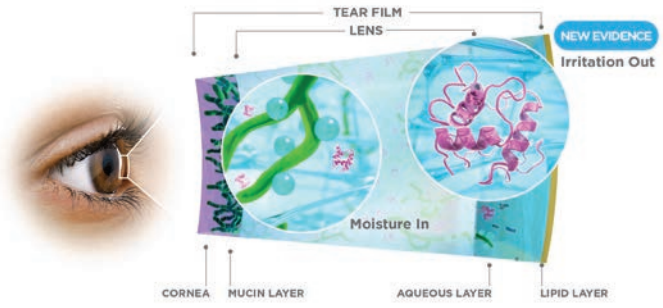

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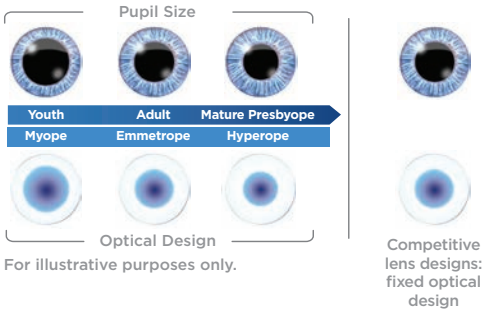

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Reference: 1. Suwala M, Glasier MA, Subbaraman LN, et al. Quantity and conformation of lysozyme deposited on conventional and silicone hydrogel contact lens materials using an in vitro model. *Eye Contact Lens.* 2007;33(3):138-143.

VOL. 154 NO. 4 ■ APRIL 15, 2017

IN THE NEWS

North Carolina Senator Danny Britt recently introduced a bill requesting $2.1 million for the creation of a **new school of optometry at the University of North Carolina at Pembroke**. With no other schools of optometry in the state (the closest being the University of Alabama at Birmingham School of Optometry), Sen. Britt believes the legislative environment is favorable for such a project, and his district would benefit from the new school, according to a press release.

Researchers recently discovered that using **SD-OCT to noninvasively measure the peripapillary retinal structure** may be a better way to measure intracranial pressure in children. SD-OCT parameters **outperformed other conventional clinical measures**, suggesting it is an effective surrogate for invasive techniques currently employed. Detecting elevated intracranial pressure in children helps ensure timely intervention and prevent neurocognitive impairment, the study said.

Swanson JW, Aleman TS, Xu W. Evaluation of optical coherence tomography to detect elevated intracranial pressure in children. JAMA Ophthalmol. February 23, 2017. [Epub].

New research suggests **larger eyes and better eyesight** in air vs. water were **key to life's transition from ocean to land**, and even consciousness, according to a recent study. Eyes tripled in size and shifted from the sides to the top of the head long before fish modified their fins into limbs, researchers found. The combination of the increase in eye size and vision through air would have conferred a one million-fold increase in the amount of space within which objects could be seen, according to the researchers.

MacIver MA, Schmitz L, Mugan U, et al. Massive increase in visual range preceded the origin of terrestrial vertebrates. PNAS. March 7, 2017. [Epub].

Stress and AMD: Recognize the Link

New research suggests ODs should be looking at more than a patient's visual acuity and ocular anatomy.

By Rebecca Hepp, Managing Editor

All clinicians know the importance of monitoring patients with age-related macular degeneration (AMD) for disease progress. What fewer think about is keeping an eye on patients' psychological status. One research team at the Ohio State University College of Optometry sought to better understand how stress levels for patients with AMD could affect their health status. But first, they had to prove the best method for monitoring patient stress in this population.

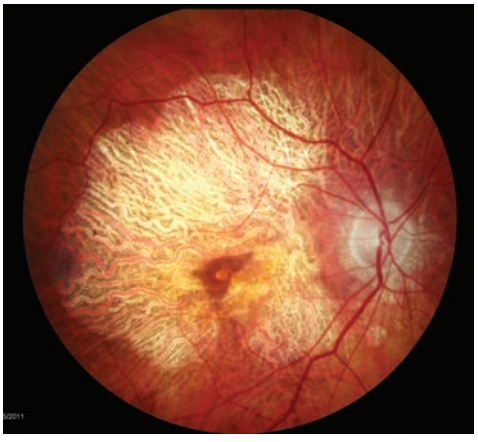

Photo: Julie Poteet, OD

AMD patients require education about influences on their ocular status, and that includes stress.

The researchers used the Perceived Stress Scale (PSS) with 137 patients with AMD and found it is a useful method of evaluating the connection between patient stress and vision loss associated with AMD. Using Rasch analysis to discover how well the PSS measured perceived stress, the study authors found nine of the 10 questions commonly used for the PSS performed well with the study participants and were able to differentiate between patients with higher vs. lower levels of perceived stress.

"Understanding a patient's level of perceived stress could help identify those who would benefit from interventions for managing stress," says Bradley E. Dougherty, OD, PhD, assistant professor at the Ohio State University College of Optometry and study author. "While it may not be commonly considered, as it's not directly related to the eye, the identification and management of perceived stress should be thought of as important to the complete care of the patient. Stress has a negative effect on patients' overall quality of life."

According to the authors, AMD patients are known for their increased rates of psychological symptoms. In addition, previous research shows PSS scores

(continued on page 9)

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Old Drug Shows Promise for Retinal Disease

The breast cancer drug tamoxifen appears to protect against photoreceptor degeneration, according scientists at the National Eye Institute (NEI).

The drug prevented immune cells from removing injured photoreceptors in an animal model of retinal injury, suggesting tamoxifen might work for treating age-related macular degeneration (AMD) and retinitis pigmentosa (RP).[1,2]

While using tamoxifen in the laboratory to activate specific genes in mouse models, researchers observed that mice treated with tamoxifen gained resistance to light-induced eye injuries and experienced little to no photoreceptor degeneration.[1]

The team then investigated the effects of tamoxifen on light-induced photoreceptor degeneration in normal mice and mice with a disease similar to RP.[2] Results showed significantly lower levels of photoreceptor degeneration compared with control mice that did not received tamoxifen. Tamoxifen-treated mice also demonstrated higher photoreceptor function, compared with controls, according to the study.[1,2]

"What's interesting is that tamoxifen, a medication linked to retinal toxicity, is now being studied as a neuroprotective drug for the retina in certain degenerative eye diseases," says Steven Ferrrucci, OD, Chief of the Optometry Department at the VA Sepulveda Ambulatory Care Center and professor at the Southern California College of Optometry at Marshall B. Ketchum University. Reported ocular toxic reactions consist of crystalline retinopathy, corneal deposits and optic neuritis, according to Dr. Ferrucci. The reported incidence of toxic reactions to tamoxifen in the literature varies between 0.9% and 12%.[3,4] "For instance, UK researchers looked prospectively at 65 women receiving the standard dose of tamoxifen, 20mg/d, finding that eight patients (12%) developed some form of ocular toxic reaction, while another study found a 3.1% rate of crystalline retinopathy in patients receiving a similar dose," says Dr. Ferrucci.[3,4]

In this case, it may be useful in certain diseases such as AMD and RP, says Dr. Ferrucci. "Certainly while exciting news, further investigation in both animal and human studies is needed before we can conclude this is a viable treatment option for such diseases."

Since the drug dosage in the animal study was equivalent to eight times the FDA-approved dose for breast cancer, the NEI scientists are currently investigating whether lower tamoxifen concentrations garner the same protective benefit.[1]

The authors say this research forms the foundation for clinical trials, which are not far off, given the established safety of the drug.[1]

1. Breast cancer drug dampens immune response, protecting light-sensing cells of the eye. National Eye Institute. http://nei.nih.gov/news/briefs/breast-cancer-drug-dampens-immune-response-protecting-light-sensing-cells-eye. Accessed March 23, 2017.
2. Wang X, Zhao L, Zhang Y. Tamoxifen provides structural and functional rescue in murine models of photoreceptor degeneration. Journal of Neuroscience. 2017;37(12):3294-310.
3. Alwitry A, Gardner I. Tamoxifen maculopathy. Arch Ophthalmol. 2002;120(10):1402.
4. Lazzaroni F, Scorolli L, Pizzoleo CF. Tamoxifen retinopathy: does it really exist? Graefes Arch Clin Exp Ophthalmol. 1998 Sep;236(9):669-73.

Legislative Update: FL and GA in Play

Optometrists in Florida are backing a bill that would expand their scope of practice to include some laser procedures. HB 1037, if passed, would allow certified optometrists in ophthalmic surgery to perform laser and non-laser ophthalmic surgery. To become a certified optometrist in ophthalmic surgery, clinicians would have to successfully complete a course and subsequent examination, approved by the board of optometry, on laser and non-laser ophthalmic surgery. The bill passed the House Health Quality Subcommittee and was under review by the Health and Human Services Committee as of March 20.

Injections in Georgia

Georgia optometrists are waging another legislative battle, this time for the right to perform injections. Senate bill 221 would allow optometrists to administer pharmaceutical agents related to the diagnosis or treatment of diseases and conditions of the eye and adnexa by injection, so long as they complete an injectables training program or are enrolled in a program and under an ophthalmologist's supervision. Despite pushback from Georgia ophthalmologists, the bill passed the Senate 34 to 17 on March 3 and is now under review in the House.

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***These statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.**

Reference: 1. Srinivasan S, Ngo W, Jones L. The relief of dry eye signs and symptoms using a combination of lubricants, lid hygiene, and ocular nutraceuticals. Poster presented at: ARVO annual meeting; April 2015; Denver, CO.

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Stem Cells: Handle with Care

A recent study reveals a new stem cell identification method that may eventually allow doctors to restore vision to patients with damaged corneas. Using a technique that involves highly sensitive atomic force microscopy, researchers put pressure on certain cells to better understand their ability to transform into mature cells.[1]

The researchers were able to differentiate limbal cells as softer and more flexible than other cells studied. Because of this, the new method shows potential as a quick identification system to find transplantable cells in a patient's own tissue. Researchers also developed a new microfluidic cell-sorting device that could speed up the existing cell sorting process.

"Studies are on track to show that this could be a very helpful procedure, but we're not there yet," says James Thimons, OD, an adjunct clinical professor at Salus University.

The Dark Side of Research

Despite these promising advances, a report recently published in the *New England Journal of Medicine* (*NEJM*) highlights the potential dangers of stem cell therapy if not handled properly. The report details three women who lost sight after undergoing stem cell treatment for macular degeneration at a Florida clinic. Clinic staff extracted stem cells from the patients' own belly fat to inject into the eyes, according to a *New York Times* article.[2]

Clinicians not associated with the Florida clinic found the patients' entering acuities ranged from 20/30 to 20/200; one year after the injections, the patients' visual acuities ranged from 20/200 to no light perception, the *NEJM* article found.[3]

To Dr. Thimons, what is most concerning about the report is that both eyes of the patients were operated on in the same day, which is atypical in clinical trials; even many routine surgical procedures are not performed bilaterally same-day.

These cases highlight the significant risk clinics touting the restorative benefits of unproven stem cell therapy pose to the population, as well as to future stem cell research. "You'd hate to see stem cells as a technology placed into a negative public view," says Dr. Thimons. "It doesn't take a great leap of faith to believe that a negative headline like this could impact the future of legitimate studies."

To prevent such issues, he stresses the importance of patient-clinician communication when a patient is looking into clinical trial options, especially those found online.

The Stem Cell Promise

Still, stem cell research appears to be heading in the right direction. The newest research that has allowed investigators to not only identify transplantable cells but also sort them quickly holds huge promise for the future—and clinicians shouldn't let negative reports of mishandled therapies stymie enthusiasm. "My hope is that we will look at this as a profession and understand the potential of stem cells, and that incidents like these are isolated," says Dr. Thimons.

1. Bongiorno T, Chojnowski JL, Lauderdale JD, Sulchek T. Cellular stiffness as a novel stemness marker in the corneal limbus. Biophysical Journal. 2016;111(8):1761-72.
2. Grady D. Patients lose sight after stem cells are injected into their eyes. NYTimes. March 15, 2017. www.nytimes.com/2017/03/15/health/eyes-stem-cells-injections.html. Accessed March 20, 2017.
3. Kuriyan AE, Albini TA, Townsend TH. Vision loss after intravitreal injection of autologous "stem cells" for AMD. N Engl J Med. 2017;376:1047-53.

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Stress & AMD

(continued from page 4)

are related to increased cortisol levels, susceptibility to infection, increased proinflammatory cytokines and slow wound healing, to name just a few negative health outcomes.

"A first step optometrists could take is using a survey such as the Perceived Stress Scale to formally evaluate perceived stress levels," Dr. Dougherty says. "From there, optometrists could familiarize themselves with local mental health providers and with other strategies that could be effective for patients to manage their own stress."

The authors also note previous research found perceived stress as measured by the PSS can be predictive of inflammation—and AMD is an inflammatory disease.

"We are investigating the relationships among stress and things such as visual acuity, change in vision with treatment and self-reported visual function," Dr. Dougherty says. "We are also interested in determining whether the increased inflammation that can result from high levels of stress may negatively affect AMD treatment results. To accomplish this, we are measuring C-reactive protein levels, which are known to be associated with AMD incidence, and investigating how those might be related to treatment outcomes."

As research digs deeper into the relationship between stress and disease progression, clinicians can treat the whole patient now, and the PSS is a good tool to start with, the study concluded. ■

Dougherty BE, Cooley SL, Davidorf FH. Measurement of perceived stress in age-related macular degeneration. Optom Vis Sci. 2017;94(3):290-6.

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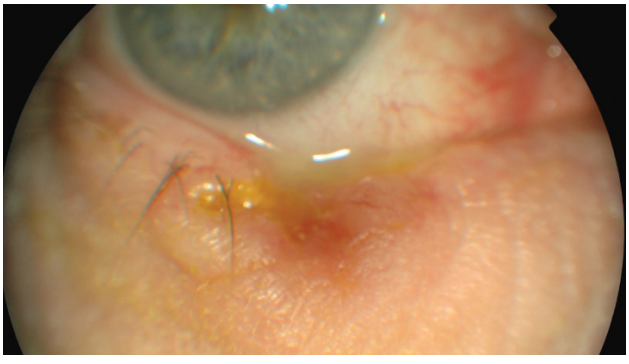

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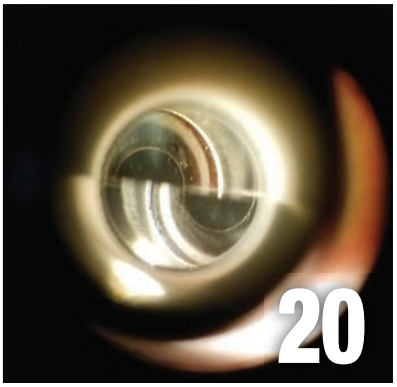

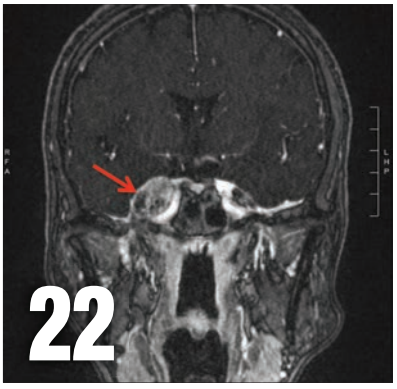

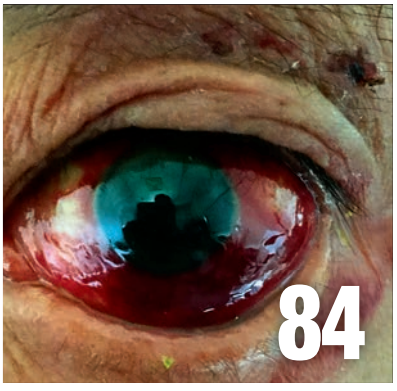

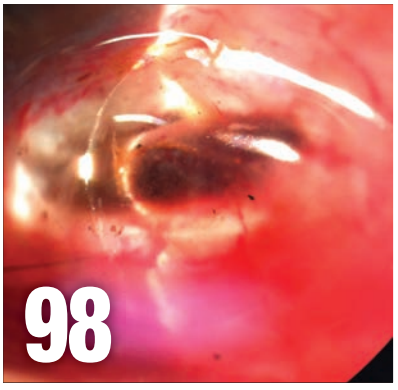

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Outlook

By Jack Persico, Editor-in-Chief

It's Like Pulling Teeth

The dental model of practice has long been touted as an inspiration for optometry. Is it finally starting to work?

"How often do I envy the dentist across the corridor?" an optometrist lamented in a prior issue of this magazine. "He has his patients trained to appear before him every six months to have their teeth examined. They come as if they were glad to come. They ought to be. But when I send notices to my patients that they should come to me for an annual examination of their eyes, they ignore the notices and I may not see them for another year. Yet their eyes are getting older every day."

It's a familiar refrain, and you've likely felt it too. What's striking about this quote isn't the message, it's the vintage. That article appeared in 1930. Yes, optometry has been swooning over the much-vaunted dental model of practice at least since Herbert Hoover was president.

Our depression-era author was quick to stress that he wasn't motivated by self-interest. "Keep in mind, please, that I am not complaining of lack of practice on my own account," he wrote. "I am commenting on the common heedlessness of the public in regard to its eyes, the most useful and the most blessed part of the human anatomy."

In other words, the template for today's Think About Your Eyes public education campaign was written on a Remington typewriter while Louis Armstrong played on the radio.

I was thinking about the long history of this sentiment during a press briefing from Essilor at Vision Expo. The company's execs mentioned that "giving vision a louder voice" in the public discourse will be a top priority as they integrate with Luxottica and become the biggest conduit to the consumer in eye care. Essilor and others have long been supporters of Think About Your Eyes. Alcon recently pledged to give $5 to the program for every annual supply of its daily or monthly contact lenses purchased, to encourage healthy wear schedules and support the campaign's public advocacy goals.

Sure, these corporate efforts benefit the bottom lines of manufacturers, but they also help people modify their lifestyles in ways that promote health and wellness—a too-rare confluence of capitalism and altruism.

But it's been a long road. "The public acts in some ways as if it doesn't care a continental about its eyesight," our 1930 author wrote. (If you're unfamiliar with old slang, *care a continental* = give a damn.) After literally decades of frustration, we're finally seeing results. The Vision Council says Think About Your Eyes generated 1.15 million eye exams in 2016, a 38% increase over 2015. Even better: exam cycles shortened from 24 to 14 months. That's solid progress. But there's more work to do if your practice is still less popular than one where someone puts a drill in the patient's mouth.

At each visit and in your marketing, stress that routine care allows disease prevention, makes early treatment possible, and helps people feel and see better. With industry support reaching mass audiences and ODs personalizing the message in their communities, public attitudes *can* change for the better. Even if it sometimes feels like pulling teeth. ■

By Paul M. Karpecki, OD, Chief Clinical Editor

Dollars and Sense

We need to recognize that our responsibility to patients doesn't end at the Rx pad.

Studies show that, beginning this year and increasing for the foreseeable future, the supply of ophthalmologists is no longer sufficient to meet the demand for cataract removal and other surgical procedures. The number of new ophthalmology graduates has remained stagnant for some time, while demand for eye care is soaring. This leaves an incredible void and an opportunity we are wise to embrace: medical eye care.

Our profession has risen to the challenge admirably. Optometric colleges have been training new grads in medical therapeutics and clinical procedures since before we had the laws to perform them, and our legislative advocates have been tireless in pushing for the freedom to put those skills to use for the public.

Industry has stepped up and supported us, too. When I entered practice in the 1990s, it was still somewhat controversial for pharmaceutical companies to detail ODs and advertise their products to us in journals like this one. Not any more. Drug manufacturers (and forward-thinking ophthalmologists as well) have since realized that the enormous need for eye care services simply requires that optometrists provide most routine eye care so that ophthalmologists can concentrate on surgery.

Unfortunately, all this evolution and cooperation can be undone by one inescapable problem: even the best medication—prescribed with care and attention by a well-trained OD—is useless if patients can't afford to get it. That "last mile" of getting the drop into their hands is often the toughest slog.

Restrictive insurance formularies shouldn't undo all the care and attention you've given your patient in the exam room. Although generics are sometimes an option, they can still be expensive in many cases. For example, various generic steroids cost more than $100 to patients paying out of pocket.

Drug companies are seeking to ensure their pharmaceuticals are financially obtainable for a broad swath of patients. Most provide assistance to those in need. Here are some key programs we can take advantage of to help our patients:

• Bausch + Lomb offers an option whereby patients in need pay no more than $35 for their portfolio of medications, including Bepreve for allergic conjunctivitis at $10. The caveat: it won't apply to patients who are enrolled in Medicare, and patients must fill their prescriptions at Walgreens or a participating independent pharmacy.

• Allergan has found that patients are paying high deductibles in the first few months of the year. In response, it has created a program that allows patients to pay next to nothing for their first three-month supply of Restasis.

• Shire has been able to place Xiidra on over 80% of commercial insurance plans within a year of its approval, which is relatively quick. The company also offers a free 60-vial tray to patients with their first prescription.

• Sun Pharmaceutical offers a program that essentially provides BromSite free to most first-time users.

• Alcon has a program for Pazeo for allergic conjunctivitis where qualifying patients pay no more than $10. This wouldn't apply to patients enrolled in Medicare Part D, Medicaid or other government-sponsored healthcare programs with a pharmacy benefit.

• Akorn has an RxAssist program to help patients afford their antibiotic and glaucoma medications. Allergan, Alcon, Shire, B+L/Valeant and Sun also have patient assistance programs that allow indigent patients to access drugs at reduced cost or, in some cases, no charge.

Until healthcare costs are controlled in an all-encompassing way—and none of us should hold our breath waiting for that—it will fall to us to "work the system" on behalf of our patients. ■

Relevant financial disclosures: Akorn, Aerie Pharmaceutical, Alcon, Allergan, Bausch + Lomb, Shire, Sun Pharmaceuticals.

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Haters Gonna Hate

It's a complex emotion reserved for rare occasions—you know, no shows, online glasses sales and patients presenting with a complaint. **By Montgomery Vickers, OD**

Hate is such a damaging word, isn't it? Webster's defines it as "intense hostility." Do you have intense hostility toward something? Could it be the election … for chairman of deacons at the church? Perhaps free eye examination advertising? No shows? People who serve white wine with beef bourguignon? (OK, that's one I understand.)

"Intense hostility" turns out to be the least important part of the definition. Webster's goes on to say *why* hate occurs: because of "fear, anger and sense of injury."

Fear

Fear produces a rush of adrenaline causing our heart rate to increase and our brain to get ready for fight or flight, or maybe explain why we charge extra for a contact lens fitting. Sometimes fear is immediate, like when a patient says, "Doctor, I have a complaint." Sometimes it is subtle, slow and debilitating, like when your wife says, "Let's talk about planning a trip tonight." Or your son keeps asking for his Rx to buy glasses online.

But remember, the body's response to fear is identical to its response to elation. It's your choice how to handle it. For me, moping around the office all day seems to help. It means I am very, very happy, obviously.

Anger

Does getting angry work? Sure it does! Whoever you are angry with will no doubt get angry right back; and since the other person is angry at you now, you will feel vindicated for being angry in the first place. It's a win-win.

I guess cussing out a no show will, nearly 100% of the time, solve the problem. They will never, ever schedule an appointment again, so you no longer have to fret they will no show. Problem solved.

Anger certainly has some advantages. If you get a dry eye patient mad enough, their eyes will water and they won't need punctal occlusion. Raise enough Cain and your receptionist will stop chewing gum all day, or at least swallow it when you appear. I could go on and on. Get angry and watch your problems melt away. Maybe.

Sense of Injury

Hate doesn't come from *actual* injury, but from *sense of injury*. If you put peroxide-based contact lens cleaning solution in a patient's eye, it will cause actual injury. Pain, not hate, is the final outcome. There will be plenty of hate later when their eye isn't killing them. By the way, I would not advise putting peroxide in anyone's eye except in very rare cases of someone who totally deserves it, like a diabetic who is three months late for their yearly examination, for example.

Sense of injury means you probably see it coming in the first place, so you can clear it up ahead of time by turning them over to collections, for example (to prevent your hate) or giving them an official office t-shirt (to prevent their hate). Find a way to smell injury in the air *before* the actual injury occurs. That's why we teach contact lens insertion and removal, check IOPs and ask about their vision plans before they show up all crazy and cocksure.

Hate is never really appropriate, although there are certainly exceptions. Why else would it be in Webster's? OK, it can get confusing. I hate when that happens. ■

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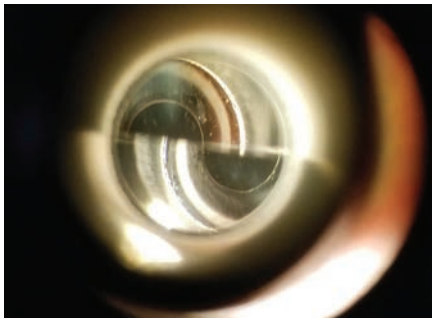
Tonometry: To Dye For?

Even fundamental techniques deserve skepticism and reinvention.

Edited by Paul C. Ajamian, OD

Q I would like to streamline my exam in every way possible and heard from a colleague that they don't use fluorescein to obtain Goldmann pressures. What's your take on this?

A Sam Quintero, OD, adjunct associate professor at University of Houston College of Optometry, says he hasn't used fluorescein in years and experiences excellent results when performing tonometry—and forgoing it saves him a step in the process. He encourages students to aperform Goldmann tonometry without it. He notes that "students don't challenge the modalities as taught," but he encourages them to question long-standing practices. "For instance, the sole purpose of the dye in Goldmann tonometry is to enhance the observation of the tear film," which can be accomplished without dye, with practice, he says.



The mires are crystal clear without fluorescein, as seen in this photo.

Overcoming Assumptions

When Dr. Quintero presents the concept of going without fluorescein to students, he tells them I don't use fluorescein when I measure IOP with the Goldmann tonometer, and I will have the students look through the teaching tube and emphasize that they look for the tear layer. "I like to seek out new ways to arrive at the same answer in a more efficient manner," says Dr. Quintero. "I am an efficiency fanatic and spend as little time arriving at the correct answer as possible."

Here is the typical with-dye scenario, according to Dr. Quintero:

"Some students take too long to measure IOP in the first eye; by the time they get to the second eye, you guessed it, they now have to instill the fluorescein again and, as a consequence, it can take as much as seven to eight extra minutes to complete this procedure—one that should have lasted approximately one minute total," says Dr. Quintero. Another problem he sees with students: On occasion, they spill a drop on the patient's clothing. "And now you have an unhappy patient, no matter what you say or how much you reassure them" that the dye won't permanently stain

Nevertheless, Dr. Quintero tells his students to be aware of the expectations from other attending ODs and not to engage in quarrels. However, he also cautions them to "do as the National Board requires and perform tonometry as described on the skills assessments for this technique—one must use the dye or else you fail this skill on Part III."

Flush the Fluress

Dr. Quintero suggests Fluress (fluorescein sodium and benoxinate hydrochloride ophthalmic solution, USP, 0.25%/0.4%, Akorn) contains too much fluorescein to be of value in tonometry. "Invariably, the mires are huge and distorted, requiring a delay for the solution to dissipate and the mires to thin, rendering it ineffective and a big waste of time."

Recent research reveals IOP is lower—a mean difference of 1.4mm Hg—when tonometry is used without fluorescein.[1] Older literature shows much greater differences—up to 7mm Hg—than anecdotal data.[2]

Andrea Knouff, OD, founder of Eyeclectic Vision Source in Atlanta, hasn't used fluorescein in clinical practice for a number of years either. "I find a high correlation between results with and without dye, and so have chosen to do without it," eliminating a step and saving valuable chair time, says Dr. Knouff. "If I ever have a question, or the mires are too faint, I can always put a dry strip in the eye and light up the mires a bit," she says. Forgoing fluorescein also preserves the patient's contact lenses when they are reinserted at exam's end.

Dr. Knouff advises ODs rely on our other tried-and-true methods and tests of detecting glaucoma. "Use careful stereoscopic nerve evaluations, pachymetry, fields and OCTs for glaucoma diagnosis, instead of putting too much emphasis on IOP readings alone." ■

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Find the Nerve to Fight Diplopia

When a patient's double vision is caused by a cranial nerve palsy, ODs must act quickly. **By Cecelia Koetting, OD, and Richard Mangan, OD**

Double vision is a complaint that can bring a dull, sick feeling to an optometrist's stomach. Diplopia can develop from a host of pathologies including dry eye, cranial nerve (CN) palsies and retinal issues.[1] We know these patients require a thorough case history and some quality chair time to diagnose properly and get to the cause of the problem. When patients present with a CN palsy causing double vision, optometrists are tasked with isolating which nerve or nerves are involved and, ultimately, the underlying cause.

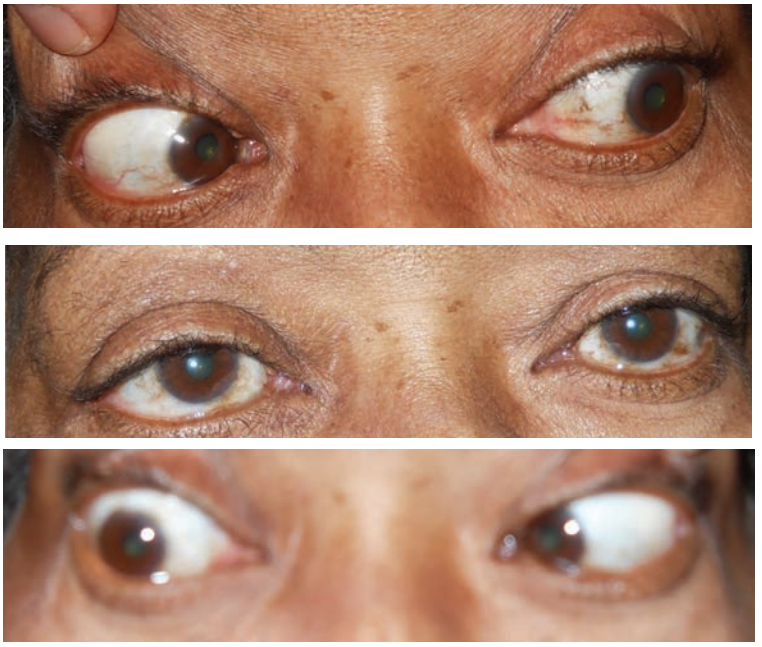

Fig. 1. Note the normal movement of the eyes gazing to the left and straight in the top two photos. The bottom photo shows the patient's eyes in right gaze and her inability to fully abduct the right eye.

The Patient

A 63-year-old woman presented to our office for examination with a chief complaint of new-onset diplopia starting approximately two months earlier. She described it as "side-by-side images" and even occasional "triple vision." She also reported an increase in headaches for and that her overall vision had decreased. Also of note, the patient was established with a neurologist and was last seen two months earlier, at which point magnetic resonance imaging (MRI) was done that the patient self reports was normal.

The patient had no prior history of strabismus or any ocular surgery, but did have a history of lung cancer in 2005 and relapse in 2014. When asked in clinic if her double vision improves with one eye covered, the patient stated that it goes away when her right eye is covered.

A former smoker, she had quit approximately 12 years earlier. She also had hypertension and hyperlipidemia, which she was controlling medically. She was not diabetic or borderline diabetic. Best-corrected visual acuity was 20/20 OU through her current glasses. Red desaturation and color vision were normal and no afferent pupillary defect was noted at the exam. Versions and ductions reveal a complete loss of abduction in the right eye and full range of motion in the left (*Figure 1*). In primary gaze, prism measurement showed a 40PD esotropia, OD. External examination was normal in each eye, and dilated fundus exam revealed no abnormalities.

How We Handled It

We performed a forced duction test on the right eye, which was negative. The patient's blood pressure was checked in office and found to be 140/80 using her right arm.

Based on her presentation, we determined it was most likely a VI CN palsy. The most common cause of VI CN palsy is ischemia due to either diabetes or hypertension. The next most common are tumor or increased intracranial pressure. If the medical history supports uncontrolled hypertension or diabetes, imaging at the initial presentation may not be necessary. In this case, the medical history does

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[1]ASCRS Clinical Survey 2015. Global Trends in Ophthalmology and the American Society of Cataract and Refractive Surgery.

not support an ischemic cause, so we recommended imaging. That same day, the patient underwent MRI and magnetic resonance venography (MRV) of the head and orbit with and without contrast.

Blood work including erythrocyte sedimentation rate, C-reactive protein, and a complete blood count with A1c was also ordered.

The results of her blood work were normal, but the MRI and MRV both had significant findings. Compared with her MRI two months prior, a sizable (2.1x1.6x2.4cm) peri-sphenoid lesion abutting the right cavernous sinus and involving right Meckel's cave was detected (*Figure 2*).

Additionally, two smaller enhancing brain nodules were found in the left parafalcine occipital lobe and in the left frontal lobe. All were considered suspicious for lung cancer metastases.

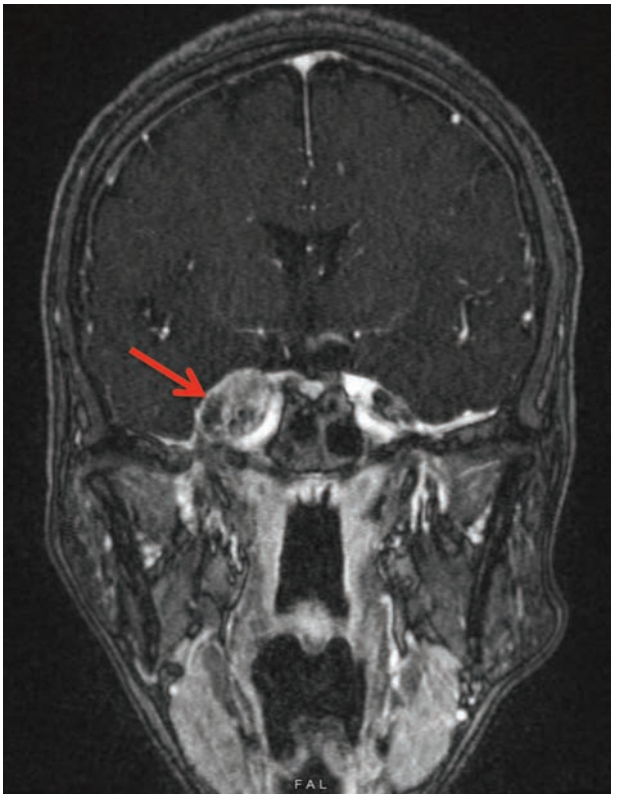

Fig. 2. This is our patient's FLAIR MRI with contrast of the head. The red arrow is pointing to the 2.1x1.6x2.4cm peri-sphenoid lesion abutting the right cavernous sinus and involving right Meckel's cave

Follow-up

With the cause identified, it was time for our patient's neurologist and neurosurgeon to take charge in treatment. But our roles as optometrists were not over. Working closely with neurology during treatment is vital to showing improvement in the lesion and its effects.

The patient underwent five rounds of radiation and came in every four weeks for versions/duction testing and visual fields. While all cases may not need to be seen this frequently, all CN palsies should be monitored for improvement.

Anatomy

Cranial nerves III, IV and VI control our extraocular muscles and each plays a specific role in the movement of our eyes. CN IV controls our superior oblique muscles, which control intorsion, depression and abduction.[2,3] Loss of this muscle's function causes an upward deviation of the affected eye with a cyclotorsion that causes the patient to tilt their head away from the lesion.[2,3] This is the most common cause of acquired vertical diplopia that is worse on downgaze.[4] CN VI controls our lateral rectus muscle, which controls abduction.[5] With loss of innervation to this muscle, we are unable to turn the eye away from the midline and patients will often turn their head to avoid double vision.

This leaves CN III to control all the other extraocular muscles and, when affected, tends to be the most dramatic, leaving the eye in a "down and out" position.[5] CN III also controls the innervation of the levator muscle, which, if paralyzed, may also result in ptosis.[5] The parasympathetic pupillary constricting fibers travel along the external portion of the CN III, which may be affected during a compressive lesion or aneurysm.[3] An APD can be a sign of an aneurysm, which is emergent.[3]

When any one of these three cranial nerves is palsied it can result in diplopia, and the nerve experiencing the palsy should be identified.[2-4,6] With CN III palsy, it is extremely important to monitor for pupillary involvement at the time of the exam and in the coming weeks thereafter.

Causes

Studies show that the most prevalent ocular CN palsy is that of CN VI, followed by CN III and then CN IV.[7-11] The most common cause of acquired palsy in all three is ischemic changes from vascular diseases including diabetes, hypertension and atherosclerosis.[2,12]

Mass lesions both in the orbit and in the brain are likely causes as well for CN III, IV and VI palsies. Depending on the location, a lesion or aneurysm on CN III can cause pupillary involvement.

Trauma is the third most com-

mon cause of these ocular palsies, with a higher occurrence of CN IV palsies related to the long distance it covers inside the cranial vault.[5,9-11]

Although not common, research shows a CN VI palsy can occur with giant cell arteritis (GCA).[13]

Treatment

In CN palsy cases involving the III, IV or VI nerve where the likely cause is ischemia, the patient should be monitored for improvement approximately a month after onset to make sure it is resolving. It may take three to six months before it is completely resolved. However, if a patient is appropriately making changes in blood sugar or blood pressure with their primary care doctor and not showing improvement in muscle movement recovery, it may indicate another pathology and warrant imaging. If the cause is indeterminate at the time of diagnosis, or a CN III palsy presents with an afferent pupillary defect, an MRI and MRV of head and orbit with and without contrast should be ordered. Be sure to order blood work to rule out undiagnosed hypercholesteremia or diabetes. In patients older than 50 years who have a CN VI and GCA is suspect, blood work including erythrocyte sedimentation rate and CRP must be ordered on a STAT basis.

Working hard to determine a source of diplopia in your patient caused by a CN palsy is more than just good care. It can be lifesaving. ■

Dr. Koetting practices at Virginia Eye Clinic, where she leads the externship program.

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Caring for the Chronic Patient

The changing care model is making these patients more challenging than ever.

By John Rumpakis, OD, MBA, Clinical Coding Editor

Many, if not most, of the ocular conditions for which we prescribe medications are chronic in nature. In addition, certain medications often create or exacerbate a disease state. For example, ocular surface disease can be caused by chronic use of certain glaucoma medications.[1]

To manage these patients, clinicians need time to not only examine the patient but also test to establish disease progression. But it's not as simple as it sounds.

Outcome-based care—for which you need to see the patient less, do less testing and still get measurable results—is the reality of our health care system today. To many, this mandate creates the paradox of the ages for patients who need more specialized care. So, how does this impact your practice as you learn to "re-manage" these disease states?

Efficiency is Important, But Effectiveness More So

Managing these chronic diseases efficiently and effectively is not difficult, just different from what you are doing, or were taught in school.

First, you must become familiar with the American Optometric Association's Clinical Practice Guidelines and the American Academy of Ophthalmology's Preferred Practice Patterns for the diseases you are managing.[2,3] These guidelines provide a protocol of evidence-based medicine. You might be surprised to learn that many of the tests you order don't necessarily deliver optimal outcomes. Follow-up visits also may be less frequent than you expect. However, you should always provide the specific care that is medically necessary for the individual patient, even if it is in conflict with the respective guidelines.

Outcome-based Coding

Let's say two ODs are managing their respective patients who have the same ICD-10 diagnosis: primary open-angle glaucoma, bilateral, moderate stage, H40.1132.

Optometrist #1, Dr. Smith, is not familiar with either the AOA or AAO guidelines or practice patterns, and has incorporated a lot of new technology into his practice within the last few years. He has visual evoked potential (VEP), electroretinography (ERG), optical coherence tomography (OCT), autofluorescence (AF) imaging and corneal hysteresis, in addition to fundus imaging and visual fields (VF). He sees this patient four to five times each year and performs VEP and ERG at least twice annually, OCT at least three times, AF once and corneal hysteresis once. He is able to manage the patient successfully and achieves a 15% drop in intraocular pressure (IOP) and maintains that IOP level.

In contrast, optometrist #2, Dr. Jones, is familiar with the guidelines and is more effective and efficient in delivering care. She also has purchased much of the same technology as Dr. Smith, but employs it only when the clinical evidence demonstrates the need for it. She sees her patient every six months and performs one VF and one OCT. She also achieves a 15% drop in IOP and maintains that IOP level.

Which physician is going to be attractive to health insurance carriers? You may think Dr. Smith is doing a better job by covering all of the bases, but this testing—translated into coding patterns when combined with H40.1132—would suggest just the opposite. He is less effective and efficient in getting the same outcome as Dr. Jones. Most likely, he will not be as attractive to carriers and may be dropped from the panel, paid less by the carrier or not even asked to participate at all.

This is the reality and potential impact of outcome-based care. Insurance carriers will grade each physician and it's entirely plausible that practitioners in the same practice may have different patient groups for whom they are able to provide care.

Caring for patients with chronic conditions is a cornerstone of optometric practice. We must practice at the highest level while simultaneously evaluating our effectiveness and efficiency. Diligence is crucial to maintaining our position as primary eye care providers. ■

Send questions and comments to rocodingconnection@gmail.com.

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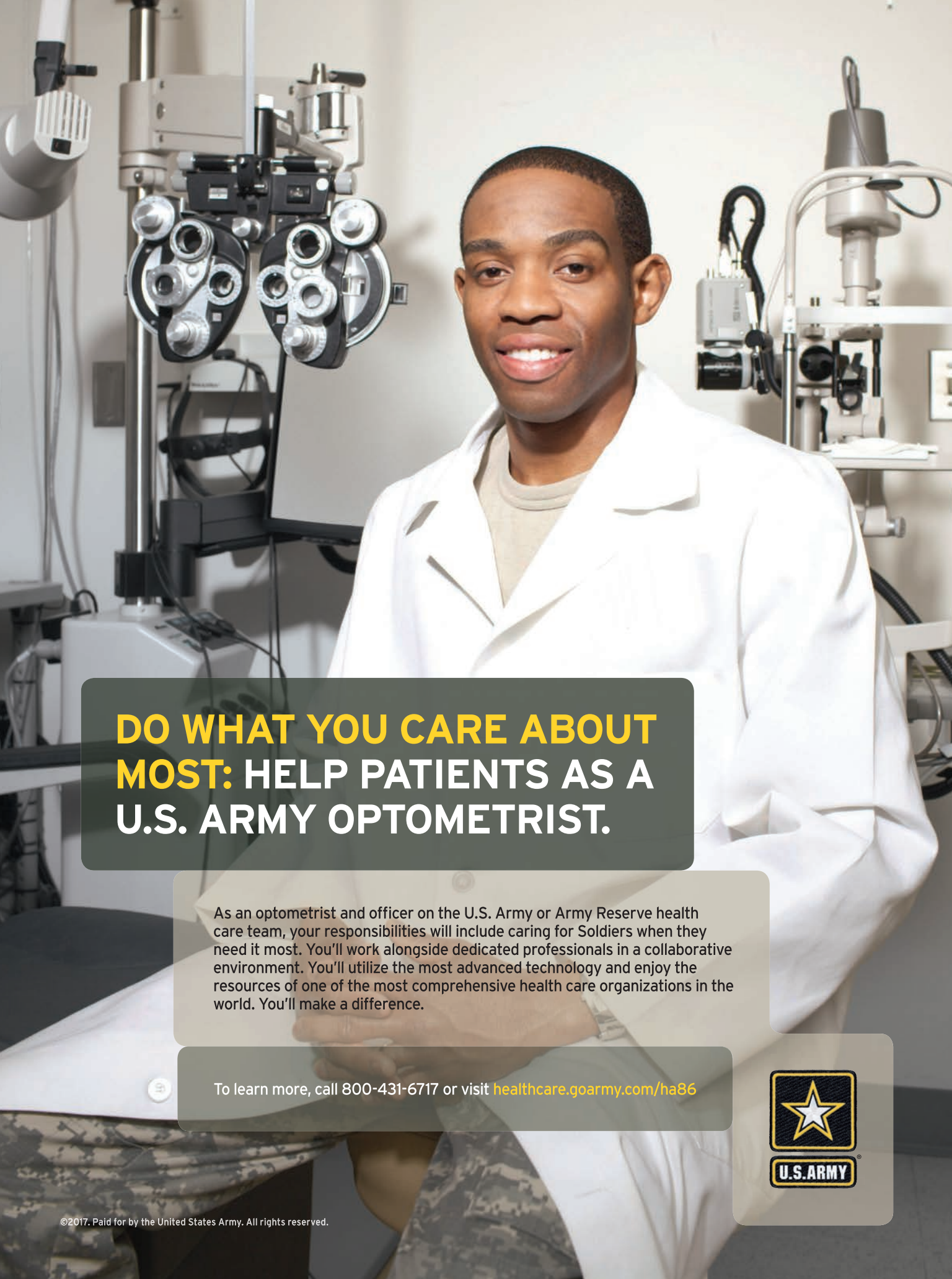

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How Antibiotics Work—and Why They Sometimes Don't

Before reaching for the Rx pad, know the drug, the patient and the disease.

By Bruce Onofrey, OD, RPh

Since their introduction, antibiotics have revolutionized our approach to treating, controlling and preventing human and animal infectious diseases. The modern antibiotic era has markedly improved survival rates and longevity, as catastrophic disease outbreaks were controlled and previously fatal infections became clinically manageable. Overall, these changes greatly improved the quality of human life.

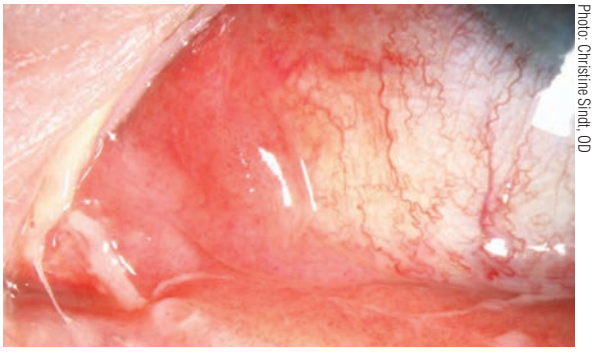

Photo: Christine Sindt, OD

Fig. 1. This patient presented with dacryocystitis.

However, the emergence and spread of antibiotic resistance has become a major problem. This global phenomenon has raised the alarming possibility of subsequent generations returning to the pre-antibiotic era, when common infections were often fatal due to the lack of effective treatments. Medical history and research shows that the prevalence of resistance genes and resistant bacteria increases in response to the selective pressure created by antibiotic use. Evidence is mounting that much of the problem is rooted in the inappropriate and excessive use of these life-saving therapeutics, and that one of the most effective countermeasures is to dole out antibiotics in a prudent and judicious manner.[1]

In light of the evidence, we will cover strategies and information to empower clinicians with the resources and information they need to make sound decisions pertaining to antibiotic use.

First, Know Thine Enemy

In adults, several well-recognized gram-positive microbes comprise the list of the most common pathogens—including several staphylococcal species. They range from the opportunistic pathogen *Staphylococcus epidermidis*, an organism that commonly colonizes the ocular adnexa as a normal part of the ocular flora, up to the true pathogen *Staphylococcus aureus*, which produces exotoxins that allow it to produce significant tissue damage and threaten sight. Regarding resistance, the most problematic member of the staphylococcal family of pathogens is MRSA—methicillin-resistant *S. aureus*.[3]

Other gram-positive organisms include several *Streptococcus* species. For example, *Streptococcus pneumonia* can be particularly virulent. It produces enzymes including streptokinase and hyaluronidase

that allow it to penetrate tissue, potentially leading to corneal perforation or orbital cellulitis.[3]

Common gram-negative pathogens include *Haemophilus* species, *Pseudomonas* and *Neisseria*. See *Table 1* for the full list of the common ocular pathogens.

Betting the Farm

The worldwide animal industry is estimated to use more tons of antibiotics than does all of human medicine, a practice that elevates the risk of treatment failure for us all.[4] For the growing antibiotic resistance problem to be effectively contained or reversed, responsible antibiotic use in the human medical community must be accompanied by a corresponding effort among veterinarians, farmers and others in the food animal and companion animal industries.

The overuse of potent antibiotics for non-bacterial disease is a major reason for resistance.[4] Physicians are pressured by patients to prescribe them in spite of evidence of non-bacterial signs and symptoms. Patients start treatment and then stop prematurely when their symptoms subside, allowing the less susceptible bacteria to survive, thus producing a strain resistant to traditionally effective treatments. Furthermore, overuse and misuse can allow bacteria of different species and even different genus to transfer resistance genes. For instance, research shows antibiotic resistance, once acquired, disseminates throughout *Enterococci*, via horizontal transfer of mobile genetic elements, and confers vancomycin resistance from *Enterococci* to MRSA.[5]

In the case of eye disease, optometrists often reach for the latest and greatest antibiotic for non-sight-threatening conditions when an older antibiotic would have better efficacy. This overuse of current-generation antibiotics for minor infections exposes common pathogens to new antibiotics and can hasten the development of resistant strains. Even worse, many clinicians prescribe antibiotics for prophylaxis when in many cases no real need exists. This not only leads to an increase in resistance among common ocular flora, but also toxicity from the use of an unnecessary therapeutic agent.

Bugs and Drugs

The World Health Organization, the Food and Drug Administration and the Centers for Disease Control and Prevention all monitor antibiotic resistance trends among bacterial pathogens. The organisms that produce ocular disease are rarely targets of these investigations. It wasn't until 2008 that results were available from the first multicenter, nationwide antibiotic resistance surveillance program specific to ocular pathogens.[6] The first of these, the Ocular Tracking Resistance in the US Today (Ocular TRUST) study, annually evaluates, *in vitro*, the susceptibility of three bacterial species—*Staphylococcus aureus*, *S. pneumonia* and *H. influenza*—to several antibiotics: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, penicillin, azithromycin, tobramycin, trimethoprim and polymyxin B in national samples of ocular isolates.[6]

The study reported antibiotic resistance among ocular isolates of the test organisms collected between 2005 and 2006 from 35 institutions across the United States. The study found that 16.8% of *S. aureus* isolates were methicillin resistant (MR), with many isolates concurrently resistant to other antibiotic classes. A significant proportion of pneumococcal isolates had intermediate resistance to penicillin (18.3%), azithromycin (22.4%) and trimethoprim (22.4%), whereas no notable resistance was reported for *H. influenza* isolates. Results of the second and third years of the Ocular TRUST study (TRUST 2 and TRUST 3) showed methicillin resistance among *S. aureus* isolates increased to nearly 50% in 2008 and methicillin resistance among coagulase-negative *Staphylococci* (CoNS) was as high as 62.0%. Results for *S. pneumonia* and *H. influenza* appeared unchanged.[6]

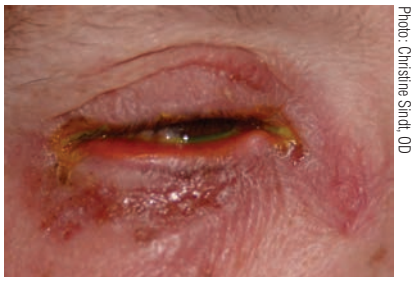

Photo: Christine Sindt, OD

Fig. 2. This patient presented with an instance of cellulitis.

The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study was initiated in 2009 to survey antibiotic resistance among *S. aureus*, CoNS, *S. pneumonia*, *H. influenza* and *Pseudomonas aeruginosa* isolates from ocular infections.[7] As in the Ocular TRUST study, ARMOR was a multicenter, nationwide prospective surveillance study and provided resistance data to extend the information gleaned from Ocular TRUST.[7] It presents antibiotic resistance profiles and trends for more than 3,000 ocular isolates collected during the first five years of the ARMOR study. The isolates, which included 1,169 *S. aureus*, 992 CoNS, 330 S. pneumoniae, 357 *H. influenza* and 389 *P. aeruginosa*, were collected from 72 eye

Table 1. Common Ocular Pathogens[3]

I. Gram-positive Organisms
- A. Staphylococci
  - 1. *S. aureus*
  - 2. *S. epidermidis*
- B. Streptococci
  - 1. alpha-*Hemolytic streptococcus*
  - 2. beta-*Hemolytic streptococcus*
  - 3. *Streptococcus pneumoniae*
- C. Bacilli (rods)
  - 1. Bacillus
    - a. *B. anthracis*
    - b. *B. cereus*
    - c. *B. subtilis*
  - 2. Cornybacterium
    - a. *C. diphtheria*
    - b. *C. xerosis*
  - 3. Listeria
  - 4. Nocardia
  - 5. Mycobacterium

II. Gram-negative Organisms
- A. Neisseria
  - 1. *N. gonorrhea*
  - 2. *N. meningitidis*
- B. Bacilli
  - 1. Enterobacteriaceae
    - a. *E. coli*
    - b. Shigella
    - c. Klebsiella
    - d. Serratia
    - e. Proteus
  - 2. Moraxella
  - 3. Haemophilus
    - a. *H. Influenza*
    - b. *H. aegyptius*
  - 4. Brucella
  - 5. Pseudomonas
    - a. *P. aeruginosa*
    - b. *P. cepacia*

care centers, community hospitals and university hospitals across 36 states.[7] Gram-positive isolates such as *Staphylococcus* and *Streptococcus* species came primarily from adults and, as would be expected, *H. influenza* was primarily isolated from children younger than 10 years.[7] *H. influenza* represents the most common ocular pathogen in the pediatric population. In ARMOR, pseudomonal isolates were most common in patients between 10 to 29 years old.[7]

As with the TRUST study, *Staphylococcus* species were found to be the most antibiotic resistant. Both methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible *S. aureus* (MSSA) as well as CoNS demonstrated the highest levels of general antibiotic resistance.[7]

Of the 1,169 *S. aureus* isolates, 465 (39.8%) and 743 (63.6%) were resistant to ciprofloxacin and azithromycin, respectively. In addition, 227 isolates (19.4%) were resistant to tobramycin. All *S. aureus* isolates were susceptible to vancomycin, and only a small proportion were resistant to trimethoprim (4.7%) and chloramphenicol (0.4%).[7]

Regarding *Streptococcus* species, only azithromycin has a significant rate of failure. The resistance was found to be 34%, much higher than all other drugs tested.[7] The gram-negative *H. influenza* species in children was found to be susceptible to all test drugs.[7] More information that can be derived from the Ocular TRUST and ARMOR studies can be found in *Table 2*.

Of greatest importance: the rise of resistant among the most common adult pathogens—coagulase negative and positive *Staphylococcus* species—the high failure rate of fluoroquinolones and the efficacy of older drugs like trimethoprim and tobramycin.[7]

Disease Factors

Selecting an antibiotic therapy is highly dependent on the risk to the patient. We don't want to undertreat—or overtreat, as low-risk infections can often be treated empirically with a host of topical broad-spectrum agents. However, in the case of higher risk infections, which include bacterial keratitis, postoperative refractive surgery infections, periocular infections and prophylaxis prior to procedures, specific protocols are required to ensure we meet the standard of care. Preseptal cellulitis, dacryoadenitis, dacryocystitis, internal hordeola and chlamydial infections may require both systemic and topical therapy *(Figures 1, 2 and 3)*.

A significant risk factor for ocular infectious disease is contact lens use. Despite the development of new materials and lens care systems, ODs must deal with the unpredictable human factor. Poor hygiene, dirty, dusty work environments, smoking, overwear of contact lenses and failure to replace lenses according to recommended schedules are all risk factors for developing potentially serious corneal infections.

Most non-sight-threatening ocular disease is treated empirically. If the condition is serious enough to threaten visual function, it's imperative to determine the identity and susceptibility of the organism. For instance, sight-threatening keratitis may require the compounding of specific antibiotics for their appropriate therapy *(Figure 4)*.[3] These include the compounded forms of vancomycin, amikacin and azithromycin *(Table 3)*.

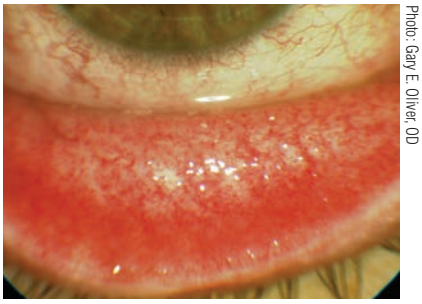

Photo: Gary E. Oliver, OD

Fig. 3. This patient's chlamydial conjunctivitis will likely require topical therapy.

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Indications and Usage

BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

  It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.
- BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.
- The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see brief summary of full Prescribing Information on the adjacent page.

NSAID=nonsteroidal anti-inflammatory drug.

References: 1. BromSite [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139. **4.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed July 18, 2016. **5.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66.

SUN-OPH-BRO-014 09/2016

SUN OPHTHALMICS

BromSite™ (bromfenac ophthalmic solution) 0.075% Brief Summary

INDICATIONS AND USAGE
BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of BromSite should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Use with Other Topical Ophthalmic Medications
BromSite should be administered at least 5 minutes after instillation of other topical medications.

Dosage Forms and Strengths
Topical ophthalmic solution: bromfenac 0.075%.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear
BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS
Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS
Pregnancy

Risk Summary
There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite during late pregnancy should be avoided.

Data
Animal Data
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 18 years have not been established.

Geriatric Use
There is no evidence that the efficacy or safety profiles for BromSite differ in patients 65 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, advise patients to administer BromSite at least 5 minutes after instillation of other topical medications.

Concomitant Use of Contact Lenses
Advise patients not to wear contact lenses during administration of BromSite. The preservative in this product, benzalkonium chloride, may be absorbed by soft contact lenses.

Sterility of Dropper Tip/Product Use
Advise patients to replace the bottle cap after use and do not touch the dropper tip to any surface as this may contaminate the contents.

Advise patients to thoroughly wash hands prior to using BromSite.

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SUN OPHTHALMICS

Topical vs. Systemic Therapy

Ocular infections can be unique in that, in many cases, topical therapy is preferred over systemic. Topical therapy allows for a highly concentrated dose of medication to be applied directly to the site of infection. The benefits are obvious: minimal systemic absorption, reduction in systemic toxicity and direct delivery of high drug concentration to avascular tissues (i.e., the cornea). Systemic medications are necessary when infections involve deeper, vascularized structures such as the lids, periorbital area and lacrimal apparatus.

The choice of drug depends on the pathogen and the patient's history, which includes allergies, preexisting medical conditions and the patient's current medications. Another major consideration for using systemic medications is pregnancy. Doctors must select an effective medication that does not pose a risk to the fetus. The FDA's classification system can help clinicians review the risk of medications in pregnant patients *(Table 4)*. High-risk diseases warrant high-risk treatments and discussions with the patient, family doctor and OB/GYN. Otherwise, clinicians should avoid high-risk treatments in low-benefit situations.

The Drugs

A host of new and old agents are currently available to help us combat infectious disease. Many have become obsolete while others that had fallen out of favor have been resurrected as useful therapies.

Aminoglycosides. These drugs are bactericidal and their efficacy is concentration dependent, both desirable characteristics of a topical anti-infective.[8] They inhibit bacterial ribosomes, the workhorses of cellular protein synthesis.

Table 2. Resistance in MRSA and *Pseudomonas*[7]

***S. aureus* – MRSA**	**% Resisitant**
Ofloxacin	76%
Ciprofloxacin	76%
Levofloxacin	72%
Gatifloxacin	68%
Moxifloxacin	57%
Besifloxacin	NA
Azithromycin	93%
Chloramphenicol	0.7%
Tobramycin	41%
Trimethoprim	7%
Vancomycin	0%
Pseudomonas	
Ofloxacin	6%
Ciprofloxacin	5%
Levofloxacin	4%
Gatifloxacin	NA
Moxifloxacin	NA
Besifloxacin	NA
Tobramycin	3%
Polymyxin B	3%

Tobramycin is the most commonly prescribed aminoglycoside, a category which also includes two topical drugs—neomycin and gentamicin—and the newest aminoglycoside, amikacin (no ophthalmic form is currently available).[3] Amikacin is generally compounded to treat tobramycin-resistant *Pseudomonas*. Topical neomycin is highly sensitizing, and gentamicin has significant corneal toxicity.[9] Tobramycin is mostly popular for its anti-pseudomonal activity.[3] The ophthalmic form is available as a 0.3% solution (3mg/cc), but can be compounded in a concentration as high as 13.5mg/cc for use in suspected gram-negative corneal infections.

Its use is also limited by its corneal toxicity—it's now been replaced by topical fluoroquinolone agents, which are effective against most gram-negative bacteria, including *Pseudomonas*, without the toxicity issues and the need to be compounded. Overall, we don't see many indications for tobramycin today. Trimethoprim, however, shows high efficacy against MRSA and is less toxic for management of non-sight threatening conjunctivitis.[6] Vancomycin is the drug of choice for sight-threatening resistant *Staphylococcus* species.

Trimethoprim is a synthetic anti-infective agent. Like the sulfonamides, it is a folic acid inhibitor, but mediates its effects slightly differently; it's also safe for sulfonamide-sensitive patients.[10]

Its activity is limited to gram-positive bacteria.[3] Therefore, it is usually combined with a drug that has gram-negative activity like polymyxin B. This combination has broad-spectrum activity and low toxicity, and it is a good option to empirically treat bacterial conjunctivitis in all age groups. It is bacteriostatic, not bactericidal, and is a time-dependent antibiotic. This means the concentration in tissues must remain above the organism's MIC_{90} level (the minimum concentration needed to inhibit growth of 90% of the isolates present) for a specific period of time for it to be effective. Trimethoprim has recently made a comeback for managing non-sight-threatening MRSA conjunctivitis.[7] It exhibits low toxicity, high efficacy against gram-positive bacteria—specifically MRSA—and is inexpensive.

Polymyxin B is a topical peptide antibiotic and a bactericidal cell wall inhibitor effective against *Pseudomonas*, *Escherichia coli*, *Enterobacter* and *Klebsiella*.[3] The more effective fluoroquinolone agents have supplanted its use in cases of serious sight-threatening gram-negative infection.

Bacitracin, once a popular bactericidal topical antibiotic, is rarely used today for several reasons. First, it is a narrow-spectrum drug with efficacy only for gram-positive organisms such as *Staphylococcus* and *Streptococcus* species.[3] Second, it frequently produces contact dermatitis reactions.[3] Finally, it is only available as an ointment, which most patients dislike due to greasiness and blurred vision.[3]

Erythromycin and azithromycin. These are both available in topical and oral dosage forms. These drugs represent the macrolide protein synthesis class of antibiotics. Topical use of erythromycin was once quite common. It had good gram-positive activity and was effective against *Chlamydia trachomatis*. It also has very low corneal toxicity. Unfortunately, it is only available in ointment form for topical use. And, its ineffectiveness against *H. influenza* and propensity to irritate the GI tract has caused it to fall out of favor.

Erythromycin is bacteriostatic, with limited efficacy against pediatric *Haemophilus*.[11] Oral erythromycin interferes with the hepatic metabolism of drugs metabolized by the cytochrome P-450 system, whereas azithromycin does not.[12] Erythromycin is notorious for producing GI irritation, while once-daily azithromycin rarely does.[12] Because of its marked ability to quickly treat chlamydial infections (a single dose of 1,000mg in adults), long half-life, lack of hepatic drug interactions and efficacy against *Haemophilus*, azithromycin has become one of the most popular oral antibiotics for treating ocular disease.[11] Furthermore, it can be used safely in both pregnant patients and those allergic to penicillins.[3]

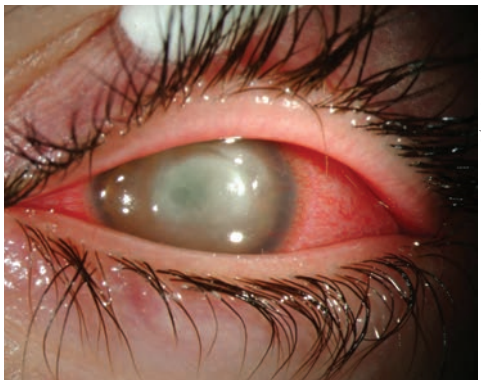

Photo: Christine Sindt, OD

Fig. 4. Keratitis, seen here, requires aggressive therapy to stave off vision loss.

Note that azithromycin is not effective in treating MRSA infections because of a greater than 90% resistance seen in the ARMOR study.[13] It is commonly used to treat marginal blepharitis due to reported anti-inflammatory properties.[3]

Fluoroquinolones (FQ). This drug class functions by inhibiting the enzyme DNA gyrase in both gram-positive and gram-negative organisms, an enzyme necessary during microbial replication.[3]

The topical formulations of these agents revolutionized the topical management of ocular infectious disease. They possessed the ideal characteristics of an anti-infective agent. They are bactericidal, concentration-dependent, rarely produce sensitization or toxicity and are broad-spectrum agents. Of course, due to these favorable characteristics, they were—and are still—widely overprescribed. Furthermore, the majority of the fluoroquinolones used are for prophylaxis in agricultural animals.[14] Broad exposures of the drugs to the biosphere and the food chain has resulted in a significant reduction in their efficacy. This is particularly problematic because resistance has primarily developed in gram-positive *Staph*. species.[7]

In an effort to combat resistance, new generations of FQs have been developed.

The first drugs approved to treat bacterial keratitis were ciprofloxacin and ofloxacin. Improvements in third-generation FQs included a purified version of ofloxacin, a 50/50 mixture of left- and right-handed stereoisomers, though only the left-handed isomer was biologically active. By producing a purified left-handed isomer, levofloxacin, they greatly lowered the required MIC_{90}.

The fourth-generation fluoroquinolones adds a methoxy functional group to the fluoroquinolone structure, making it more effective against resistant gram-positive organisms, and decreasing resistance. The fourth-generation drugs include moxifloxacin 0.5% and gatifloxacin 0.3% and 0.5%. Both drugs are available in oral formulations, but they are rarely used systemically to treat eye disease.

Besifloxacin represents an improved version of the FQ drug class. In addition to fluorine attached to the quinolone ring, an

Table 3. Antibiotic Selection for Sight-threatening Pathogens

Vancomycin	50mg/cc	MRSA
Gatifloxacin or Moxifloxacin	0.5mg/cc	*Pseudomonas*
Tobramycin	13.5mg/cc	*Pseudomonas*
Amikacin	50mg/cc	*Pseudomonas*

Solomon R, Donnenfeld ED, Holland EJ, et al. Microbial keratitis trends following refractive surgery: results of the ASCRS infectious keratitis survey and comparisons with prior ASCRS surveys of infectious keratitis following keratorefractive procedures. J Cataract Refract Surg. 2011;37(7):1343-50.

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atom of chlorine is attached as well. Furthermore, this drug is not used orally or in agriculture. Current studies of efficacy are limited, but have demonstrated reduced resistance in FQ-resistant bacteria.[15]

Vancomycin. This is a bactericidal cell wall inhibitor with specificity for gram-positive bacteria.[12] It is compounded as a 25mg to 50mg/mL topical form or an intraocular injection to treat MRSA endophthalmitis and is the principal drug used to treat serious ocular MRSA infections.[13,16] The ARMOR study showed it was 100% effective against ocular MRSA isolates; however, vancomycin-resistant strains of MRSA have surfaced.

Chloramphenicol. This is an extremely potent inhibitor of bacterial ribosomal protein synthesis. It is a bacteriostatic, broad-spectrum antibiotic.[3] Its spectrum of activity is impressive. It is effective against gram-positive and gram-negative bacteria, anerobic and aerobic organisms, tick-borne rikettsiae and MRSA.[3] It is highly lipid soluble and therefore has excellent tissue penetration when used topically, and can pass through the blood-brain barrier and blood-eye barrier when it is used systemically.[3]

Chloramphenicol is widely used to topically treat eye disease in many parts of the world due to its high efficacy and low cost.[17] Its use in the United States for eye disease is limited due to its systemic toxicity in both systemic and topical dosage forms. It has the potential to produce fatal aplastic anemia at a rate of one case in 24,000 of treatment courses.[18]

Amoxicillin-clavulanate (Augmentin). This is a combination of the broad-spectrum aminopenicillin amoxicillin and clavulanate, a non-anti-infective compound that binds to the enzyme beta-lactamase.

Table 4. FDA Pregnancy Category of Risk of Selected Antibiotics[3]

Tobramycin (topical)	B
Fluoroquinolones (topical)	C
Trimethoprim/polymyxin B (topical)	C
Cephalosporins	B
Azithromycin	B
Amoxicillin-Clavulanate	B
Chloramphenicol (topical)	C

Clavulanate's ability to inhibit beta-lactamase improves efficacy against organisms traditionally resistant to penicillin therapy. This includes beta-lactamase producing *Staphylcoccus*, *Streptococcus* and *Haemophilus* bacteria.[3] It is not effective against MRSA strains. The drug is a bactericidal, cell wall-inhibiting antibiotic. It is well tolerated and safe in pregnancy.[19] The major issue with it and other penicillins is the significant number of individuals allergic to this class of therapeutic agent.[19]

Cephalosporins. This group of oral agents is very similar to the aminopenicillins. They inhibit cell walls and are bactericidal.[3] Compared to the penicillins, they exhibit improved resistance to beta lactamase, but are not as effective as clavulanate-protected amoxicillin.[19] Given an approximate 3% incidence of cross-sensitivity with penicillins, cephalosporin use in penicillin-sensitive patients should be limited.[3]

Over time, researchers have developed several generations of cephalosporins. The most commonly prescribed first-generation drug, cephalexin, is primarily effective against gram-bacteria in adults.[20] When treating children younger than 10 years of age who tend to colonize *Haemophilus*, clinicians should use a second-generation cephalosporin.[21]

Disinfectants

These compounds have the ability to kill bacteria, virus, fungi and protozoa. Their use is limited primarily by their toxicity.[22]

Povidone-iodine, a 21-iodine-based disinfectant, has become quite popular for disinfection of the eye and adnexa prior to surgical procedures.[22] It has also been used in its 5% ophthalmic dosage form to treat adenoviral conjunctivitis.[23] A povidone-based product is currently in clinical trials for the treatment of both viral and bacterial eye disease. The drug contains a combination of povidone-iodine 0.4% and dexamethasone 0.1%.[24]

Non-ophthalmic Topicals

Mupirocin, a combination of pseudomonal acids sold as Bactroban (GlaxoSmithKline), is available as a topical ointment and cream. It is profoundly effective against gram-positive bacteria, most importantly MRSA. It is the topical drug of choice for impetigo and MRSA skin infections and is administered nasally in MRSA carriers to reduce their contagion potential.[25] It is not approved for ophthalmic use, but certainly could be used off-label on lids and periocular infected skin.

When *Star Trek*'s producers were asked how the ship's transporter works, they responded without pausing, "Very well, thank you." Unfortunately, clinicians responsible for selecting an antibiotic agent don't have the luxury of such a breezy dismissal of the rigors of science. The treating doctor must choose an agent that's both safe and effective for their patient, ideally one with minimal impact on individual and global resistance patterns. This is accomplished by being familiar with the pharmacology of all the anti-infective agents we use.

This includes their indications, contraindications, side effects, adverse effects, dosages and forms. Most are prescribed empirically, without identifying the pathogen, then fine-tuned based on staining, culturing and sensitivity testing in sight-threatening disease. We also must give special consideration to issues such as drug allergy, pregnancy, reduced renal or hepatic function and special dosing in children.

In short: In an age of flourishing bacterial resistance to antibiotics, know the patient, know the drug and know the disease before treating any infection. ■

Dr. Onofrey is a clinical professor at the University of Houston College of Optometry and is an author of The Ocular Therapeutics Handbook.

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Anti-inflammatories:

Sort Out Your Many Steroids and NSAIDs

With so many medications out there, treatment can get complicated. Here is a rundown of your options and when to use them. **By Laine Higa, OD**

Ongoing advances in topical ocular therapeutics have given the eye care provider more options in the treatment of ocular inflammation than ever. In this article, we review the various topical corticosteroid and nonsteroidal anti-inflammatory drug (NSAID) options available. A closer look at when and how to implement these medications into your treatment regimen will help you care for all of your patients who present with ocular inflammation. Additionally, a succinct review of immunomodulators for the dry eye patient will hone in on this common cause of inflammation.

The Inflammatory Pathway

The successful treatment of ocular inflammation requires a solid foundation and understanding of the inflammatory pathway (*Figure 1*). Inflammation is the body's response to repair tissue to normal structure and physiologic function. In the presence of tissue damage or an offending agent, neutrophils and monocytes recruit macrophages to remove the offending stimulus.[1] This recruitment initiates the healing process and manifests the cardinal signs of inflammation: redness, swelling, heat and pain.[1]

Tissue injury causes degradation and lysis of the cell membrane via the phospholipase A_2 (PLA_2) enzyme, resulting in arachidonic acid (AA) formation. AA mediates the inflammatory cascade and is metabolized by 5-lipoxygenase (LOX) and cyclooxygenase isoenzymes (COX-1/COX-2).[1] When AA is metabolized via LOX, the generated leukotrienes recruit white blood cells to the damaged area.[1]

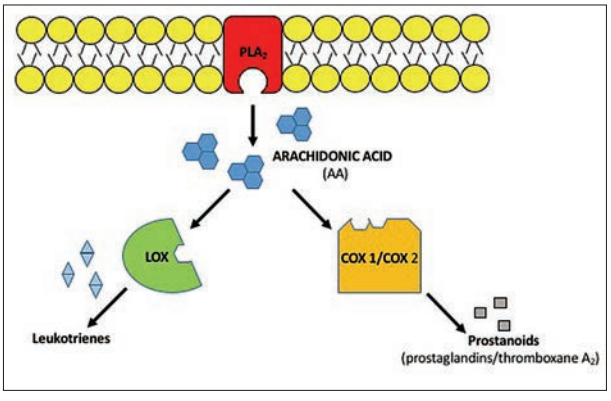


Fig. 1. This illustration demonstrates the inflammatory pathway of the innate immune system: PLA_2, LOX and COX-1/COX-2.

Similarly, when AA is metabolized via the COX-1/COX-2 isoenzymes, prostanoids (prostaglandins and thromboxane A_2) are produced.[1] Prostanoid formation increases arterial dilation and vascular permeability, which account for the redness, edema and pain associated with inflammation.[1]

The two major classes of anti-inflammatories—corticosteroids and NSAIDs—each cause different pathway inhibition (*Figure 2*).

Corticosteroids

The anti-inflammatory properties of corticosteroids are mediated at the genomic level.[2] When corticosteroids bind to receptors in the cytoplasm, the bound complex migrates into the nucleus and upregulates the expression of anti-inflammatory proteins and downregulates the expression of proinflammatory proteins.[2] More specifically, lipocortins, which are produced after corticosteroid cellular modulation, inhibit PLA_2 and histamine synthesis in mast cells.[3] Corticosteroids also have non-genomic

modulating effects mediated by the corticosteroid-receptor binding, which include inhibition of vasodilation, vascular permeability, decrease in scar formation and the stabilization of intracellular and extracellular membranes.[3] Because corticosteroids inhibit the inflammatory cascade earlier than NSAIDs, corticosteroids are more effective anti-inflammatory agents.[4]

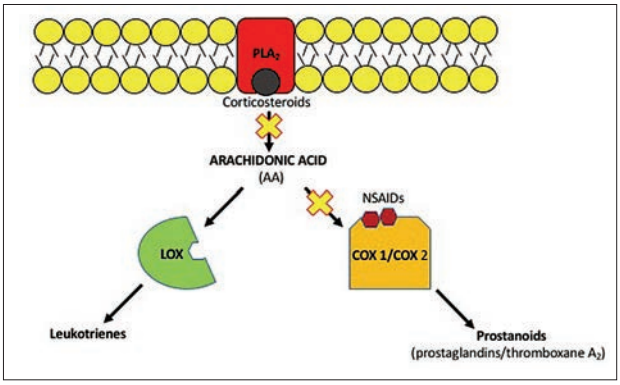


Fig. 2. The two classes of anti-inflammatory drugs each inhibit the inflammatory pathway differently.

In my personal clinical experience, employing topical corticosteroids for many inflammatory (i.e. uveitic, ocular surface, atopic) conditions has yielded positive results. Although the condition may not be completely resolved at the first follow up, I usually see a dramatic decrease in symptoms.

If there is no improvement in patient symptoms or clinical signs, an astute clinician should investigate medication compliance and instillation. As many of the corticosteroid options are in suspension form, failing to shake the bottle prior to instillation tends to be the culprit of delayed resolution. Additionally, the varying strengths of topical corticosteroids allow clinicians the option to increase the medication strength when little improvement is observed.

Indications and Contraindications

Many of the adnexal and anterior segment inflammatory conditions can be successfully treated with topical steroid therapy. Additionally, first-line therapy for post-op retinal cystoid macular edema (CME) is topical corticosteroids and NSAIDs.[5] Indicated conditions for corticosteroid use include steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe.[6]

Corticosteroids inhibit the resident immune system to employ its anti-inflammatory properties. This decrease in the immune system increases the risk for opportunistic infections. When you have concern for infectious etiologies, be cautious to initiate isolated corticosteroid therapy.

As red eye presentations can often be difficult cases, consider the following before initiating therapy:

- Take a thorough case history that may preclude corticosteroid use, at least initially
- Instill vital dyes that may reveal an epithelial herpetic etiology

Initiating Therapy

New drug designs have increased corticosteroid potency and metabolism with decreased side effects.[7-10] Before initiating corticosteroid therapy, clinicians should consider the following baseline factors:

- Presence of an anterior chamber reaction (cell/flare)
- Significance of hyperemia/injection
- Symptomatology (photophobia, pain, irritation) level
- Targeted location of treatment
- Presumed diagnosis

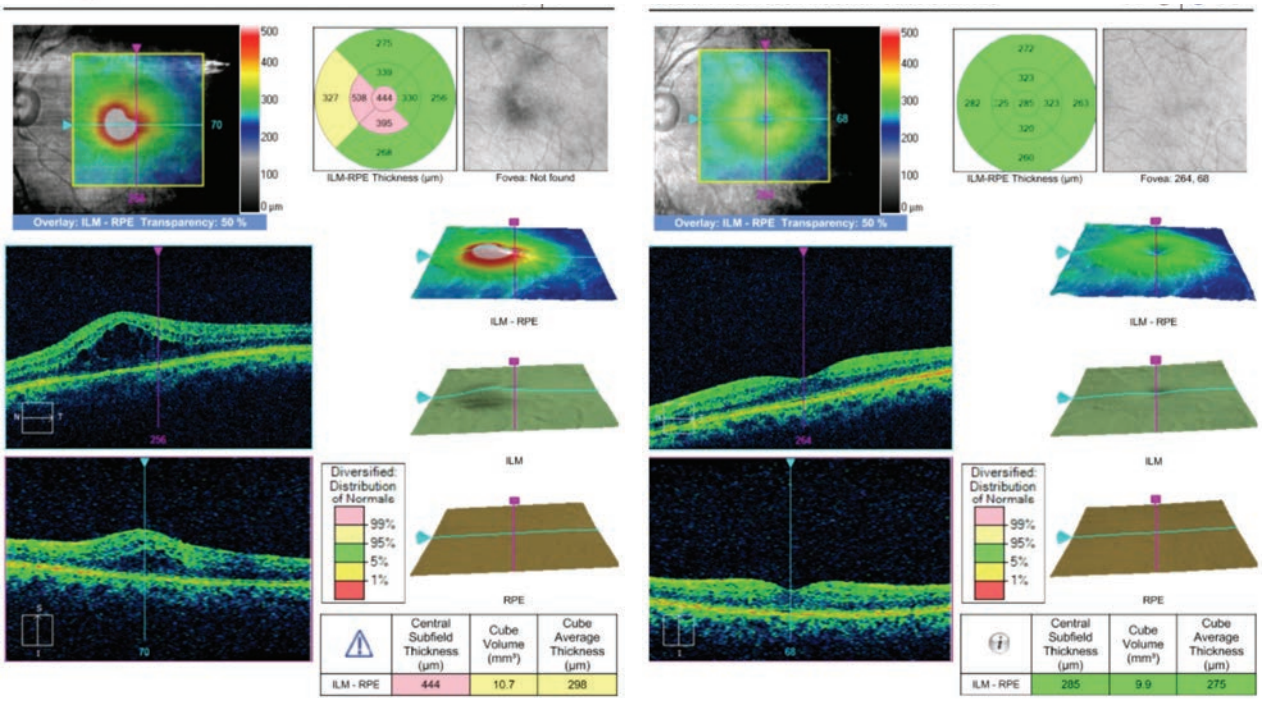
Intraocular inflammation should be treated with maximal efficacy topical corticosteroids, which are formulated to increase penetration into the eye for more targeted anti-inflammatory action.[4] Dermatologic, surface and corneal diagnoses, however, would benefit from lesser-strength corticosteroid options.[4]

Location-specific therapy decreases the risk of side effects and corticosteroid-related sequelae. Ocular hypertension and a hastening of posterior subcapsular cataract formation are well documented in the literature with prolonged corticosteroid use.[2-4,8,9,11,12] Research suggests roughly 33% of the adult population are moderate responders—IOP increases by 6mm Hg to 15mm Hg.[3] Alternatively, 4% to 6% of the general population are high responders—IOP elevates above 15mm Hg with therapy.[3] Family history of glaucoma, diabetes, myopia and younger age are all risk factors that preclude responders to elevations in IOP.[11,12]

However, more often than not, the benefits of corticosteroid treatment outweigh the potential side effects. Additionally, visual acuity, IOP assessment and ophthalmoscopic evaluation of the optic nerve head at subsequent visits will ensure clinicians catch any possible side effects before they become vision threatening.

Intraocular Inflammation

Intraocular inflammatory conditions require aggressive corticosteroid therapy to prevent vision-threatening complications and sequelae.[4,7] An appropriate corticosteroid penetrates the ocular surface to inhibit inflammation at its source. Durezol (difluprednate 0.05%, Alcon) and Pred Forte (prednisolone acetate ophthalmic suspension 1%, Allergan) are corticosteroid options for



The OCT on the left shows a patient with CME. This was successfully resolved with Durezol BID OS and Ilevro QD OS over a nine-week period, as seen in the right OCT.

endogenous inflammations of the eye.[4]

Approved by the FDA in 2008, Durezol—a synthetic difluorinated prednisolone derivative—is the most recent corticosteroid addition to the list of drugs approved for the treatment of postoperative inflammation and pain.[7] In addition to difluorination and augmentation with butyrate, Durezol has increased corneal penetration due to the substitution of a hydroxyl group with acetate.[7] This translates into topical dosing that is half of what is needed with Pred Forte, which may help improve patient compliance. A study that investigated Durezol dosed QID compared with prednisolone acetate 1% dosed at eight times a day found Durezol to be noninferior in a multicenter randomized double-masked trial.[7] Additionally, Durezol is formulated as an emulsion, which does not require shaking prior to instillation. In one study, researchers found Durezol had superior dose uniformity compared with Pred Forte and its generic counterpart because of its emulsion formulation.[13]

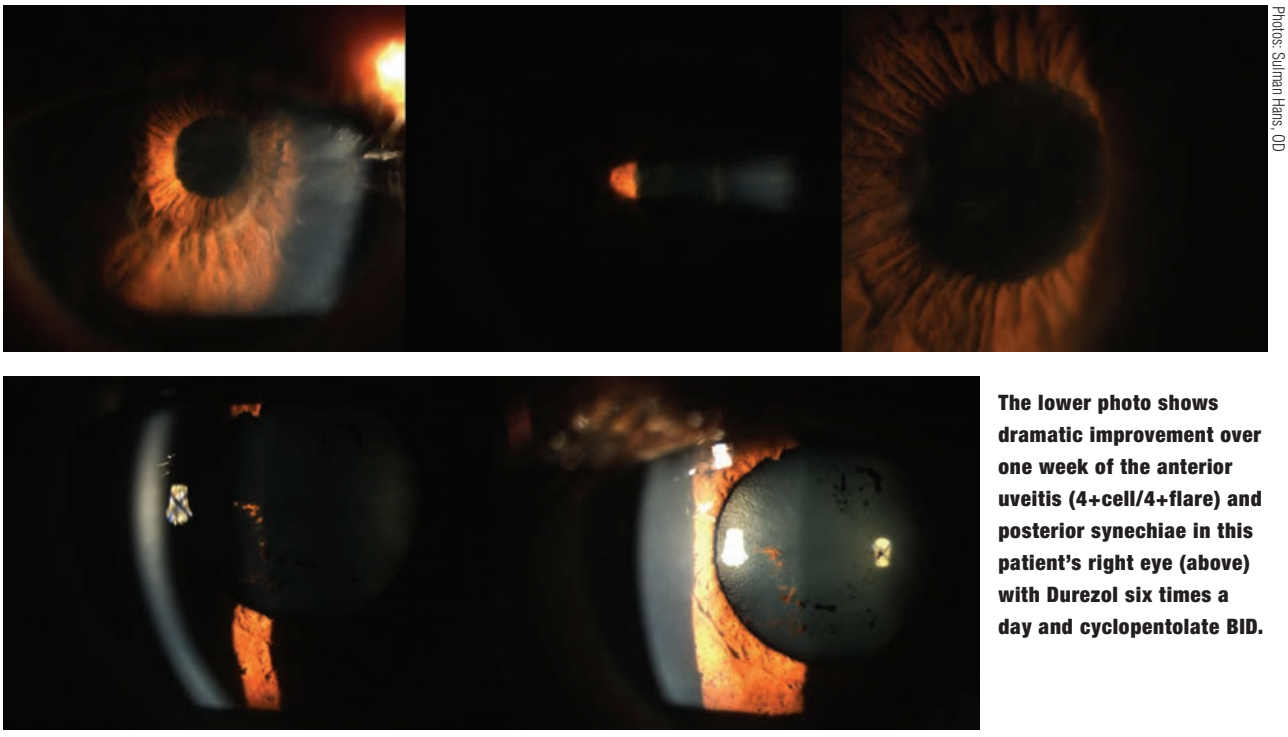
Historically, Pred Forte has been the main option for intraocular inflammation treatment.[7] Research shows Pred Forte has varying anti-inflammatory benefits compared with the generic formulation. In a comparative analysis of prednisolone acetate suspensions, one study found that Pred Forte exhibited greater homogeneity and bioavailability of the drug between doses compared with EconoPred (Alcon) and generic prednisolone acetate.[14] Pred Forte and its generic counterparts are formulated in a suspension and require vigorous shaking before instillation.

Other maximally effective corticosteroids for treating intraocular inflammation include Vexol (rimexolone 1%, Alcon) and prednisolone phosophate sodium 1%.

Available in generic formulations, Vexol and prednisolone phosphate sodium provide for cost-conscientious prescribing. Additionally, research found Vexol had equal efficacy in the treatment of anterior uveitis with a decreased chance of increasing IOP compared with Pred Forte.[15] This may be a good alternative for known steroid responders or glaucoma patients.

Ocular Surface

Retrometabolic drugs are currently used in the treatment of many systemic conditions.[8] Such agents convert the inactive drug metabolite into a structurally modified analogue. After eliciting therapeutic benefit, the analog undergoes rapid degradation and metabolism, thereby decreasing the opportunity for adverse drug reactions.[9] Because these synthetic analogs possess the same therapeutic benefit with decreased adverse drug reactions, they are known as soft drugs.[8,9]



Photos: Sulman Hans, OD

The lower photo shows dramatic improvement over one week of the anterior uveitis (4+cell/4+flare) and posterior synechiae in this patient's right eye (above) with Durezol six times a day and cyclopentolate BID.

Loteprednol etabonate, for example, is a cortienic acid-based derivative that exhibits highly lipophilic properties, reported to be 10 times greater than dexamethasone, allowing increased penetration into cell membranes.[9,10,16] Researchers found C-labelled loteprednol etabonate 0.5% metabolites in highest concentration in the cornea of rabbit eyes and lower metabolite concentrations in the iris/ciliary body and aqueous humor, respectively, indicating a majority of loteprednol etabonate metabolism occurs in the cornea.[17,18] Additionally, researchers increased penetration of loteprednol etabonate in the cornea and conjunctiva compared with the aqueous humor levels due to rapid hydrolysis.[19]

Lotemax (loteprednol etabonate 0.5%, Bausch + Lomb)—available as a gel or ointment—is a useful anti-inflammatory option to have in your arsenal. A 0.2% suspension formulation of loteprednol etabonate is available under the name Alrex, and a combination of loteprednol etabonate 0.5% and tobramycin 0.3% is branded as Zylet.

Both Lotemax 0.5% gel and ointment are FDA-approved for the treatment of postoperative inflammation and pain.[20] Alrex is FDA-approved for the treatment of seasonal allergic conjunctivitis.[21] Though the literature is divided on its efficacy in treating anterior uveitis compared with prednisolone, there is increased safety with loteprednol etabonate use, evidenced with a lower frequency of IOP elevation.[3]

Other conditions that respond well to lesser-strength (compared with Pred Forte and Durezol) corticosteroids include keratoconjunctivitis sicca, corneal-involving viral conjunctivitis, allergic and vernal conjunctivitis and to prevent scarring of the cornea.[4]

Alternative options for the treatment of ocular surface inflammation include FML (fluorometholone ophthalmic suspension 0.25%, 0.1%, Allergan) or prednisolone acetate 0.12%. These alternatives are available in generic formulations and are lower in cost compared with their branded counterparts.

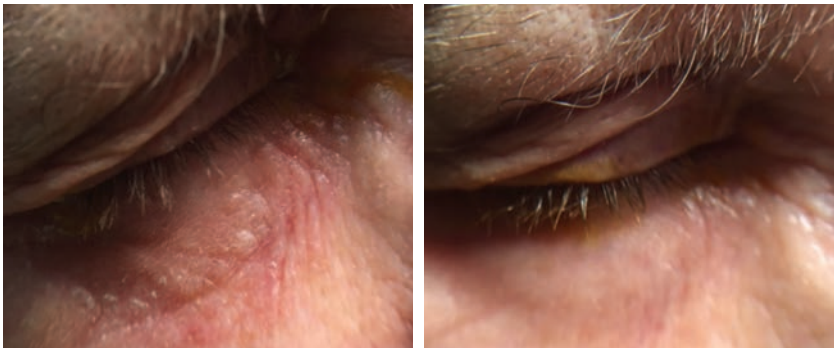
Dermatological Inflammation of the Eyelids/Adnexa

Inflammation of the eyelids and adnexa are common presentations, and a detailed history and thorough ophthalmoscopic evaluation should yield whether it is allergic in nature or of infectious etiology. In cases of moderate to significant dermatologic inflammation, topical corticosteroids are warranted.

Dermatologic presentations can be treated with ointment formulations (an off-label use), such as Lotemax 0.5% and FML 0.1%, as they allow for increased contact time at the site of inflammation.[4]

If the inflammation is secondary to infectious etiologies, clinicians can use a combination corticosteroid/antibiotic ointment such as Tobra-

Dex (tobramycin 0.3%/dexamethasone 0.1%, Alcon), TobraDex ST (tobramycin 0.3%/dexamethasone 0.05%, Alcon), Maxitrol (neomycin 0.35%/dexamethasone 0.1%, Alcon) or Blephamide (sulfacetamide 10%/prednisolone acetate 0.2%, Allergan), to name a few. These provide good gram-positive coverage for the normal flora of the eyelids/skin. Additionally, consider sulfa allergies prior to prescribing some of these alternatives.



This patient's neomycin ointment hypersensitivity of the right eyelid (left) was resolved (right) with topical FML 0.1% ointment applied BID OU for four weeks.

Ending Treatment

All corticosteroid therapy should be tapered to prevent any bouts of repeat inflammation. Unfortunately, tapering schedules are more of an art than a science. There is no universally accepted tapering regimen in the literature other than defined improvement by the Standard Uveitic Nomenclature (SUN) group.[22] With improvement, and thereby response to the steroid regimen, the taper can be initiated. Ultimately, the clinician is responsible for changing dosing schedules and the start of the taper based on clinical improvement and intuition. When a clinician inevitability encounters a reoccurrence of inflammation because a steroid is tapered too quickly, initial dosing schedule of the steroid is required.

NSAIDs

Topical nonsteroidal anti-inflammatory therapy is used sparingly in the primary care setting, mostly to prevent and treat postoperative inflammation. A vast majority of the NSAID options are FDA-approved for the treatment of pain and inflammation associated with cataract surgery.[4]

Additionally, NSAID therapy can be used to maintain mydriasis during cataract surgery and decrease pain in photorefractive keratectomy patients.[18]

Indications

In addition to the synergistic effects NSAID and corticosteroids have on postoperative CME formation and treatment, NSAID use primarily ameliorates pain on the ocular surface. Anecdotally, research suggests NSAIDs can be used temporarily to treat pain and irritation related to mechanical or surgical irritation of the conjunctiva and cornea, pre-post 5% betadine wash for viral epidemic keratoconjunctivitis or in combination with a strong corticosteroid for recalcitrant cases of uveitis.[4] Most indications for NSAID use are off-label therapy options.

Generally, topical NSAIDs will be used in combination with maximal efficacy corticosteroids in the treatment of postoperative CME, typically in concert with the cataract surgeon.

Today's NSAID options are dosed anywhere from QID to QD. Clinicians should follow the recommended dosing to limit risk for side effects related to prolonged NSAID use. As with corticosteroid use, duration of use should be limited (roughly one month). Chronic use retards corneal epithelial healing and corneal melting and perforation, although extremely rare, are reported in the literature.[23]

Newest to the topical NSAID drug market are Ilevro (nepafenac 0.3%, Alcon) and Prolensa (bromfenac 0.07%, Bausch + Lomb). Both Ilevro and Prolensa are dosed QD and are FDA-approved for postoperative inflammation and pain.[24,25] Ilevro, a prodrug, is highly permeable to the cornea and is rapidly hydrolyzed to amfenac in the aqueous.[26,27] Amfenac is a potent inhibitor of COX-1/COX-2 isoenzymes.[27] Once-a-day dosing is possible due to the increased nepafenac concentration from 0.1% to 0.3%. Almost structurally identical to amfenac, Prolensa contains a bromine atom that makes Prolensa highly lipophilic, increasing corneal penetration and duration of action.[27] As NSAIDs are intrinsically acidic, Prolensa has been buffered to a pH of 8.3 for additional comfort with instillation.[27]

An NSAID's formulation is key to ensuring the patient is obtaining a therapeutic concentration of drug with each instillation. NSAID formulations in suspension require shaking to increase the drug's bioavailability.

Other NSAID options available include: Acular LS and Acuvail (ketorolac tromethamine, Allergan), Bromsite (bromfenac ophthalmic solution, Sun Pharmaceuticals) and Voltaren (diclofenac sodium, Endo Pharmaceuticals). These options may be dictated by the patient's insurance coverage or budget. They range in

dosing from BID to QID and may sacrifice medication compliance, given the increase in dosing compared to their QD counterparts.

Advancement in drug delivery systems and drug formulations continue to equip eye care providers for successful treatment of many inflammatory conditions. The ever-changing field promises future advancements to help patients heal quicker and decrease vision-threatening conditions. With proper selection, evaluation and education, eye care providers have a large repertoire of treatment regimens for the successful treatment of their patients. ■

Dr. Higa graduated in 2014 from the Illinois College of Optometry and completed a one-year postgraduate residency in primary care at The Eye Institute. He currently is an instructor at Salus University-PCO where he works with interns and residents. He has a special interest in ocular surface disease and anterior segment inflammation. Dr. Higa has received honoraria from Allergan but has no direct financial disclosures for the products mentioned.

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Dry Eye Disease

Topical anti-inflammatory drugs provide eye care providers a long-term treatment strategy for dry eye disease (DED) with almost no risk of systemic ADR when dosed as approved.[28,29] Both Restasis (cyclosporin A 0.05% emulsion, Allergan) and Xiidra (lifitegrast 5% solution, Shire) act on T-cells in the tear film, conjunctiva and cornea to decrease tissue destruction and further inflammation related to DED.[30-33]

Restasis was FDA-approved in 2003 to increase the eye's ability to produce tears in patients with inflammation related to keratoconjunctivitis sicca.[34] Dosed BID, Restasis is a calcineurin inhibitor that prevents interlukin-2 (IL-2) formulation.[30] IL-2 is secreted by T-helper cells and stimulates the proliferation of cytotoxic T-cells and additional T-helper cells. Restasis halts the propagation of additional T-cells, decreasing further damage to the ocular surface. Clinically, the effects of Restasis will not manifest immediately because of activated T-cells on the ocular surface prior to its use. To combat this, clinicians should consider using topical corticosteroids in conjunction with Restasis for a few weeks.[32] The corticosteroid will help target the inflammation, while Restasis will maintain long-term anti-inflammatory effects.

Xiidra, FDA-approved in 2016 to treat the signs and symptoms of dry eye, is the second and newest addition to topical immunomodulatory drugs for the treatment of dry eye.[35] Xiidra also inhibits the T-cell mediated inflammatory pathway by preventing the recruitment and activation of T-cells to the ocular surface. Xiidra does this by blocking the adhesion of lymphocyte function-associated antigen-1 (LFA-1) to intracellular adhesion molecule-1 (ICAM-1).[31] By blocking this interaction, T-cells do not migrate out of the blood vessel and decrease the interaction with antigen presenting cells.[31] Furthermore, there is a decrease in cytokine release at inflammation sites. Formulated in a solution, Xiidra is dosed BID and is preservative-free. Future studies of this new agent will help to educate doctors on its clinical performance and role in the treatment regimen. A topical soft steroid such as Lotemax may also be considered at initiation of Xiidra, given the pre-existing inflammation likely present on the ocular surface.

Having two therapeutic options available provides perceptive practitioners an alternative drug choice if a patient has failed on prior therapies, thus increasing the likelihood of success in the management of this complicated disease process.

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Glaucoma Therapy:
Finding the Right Combination

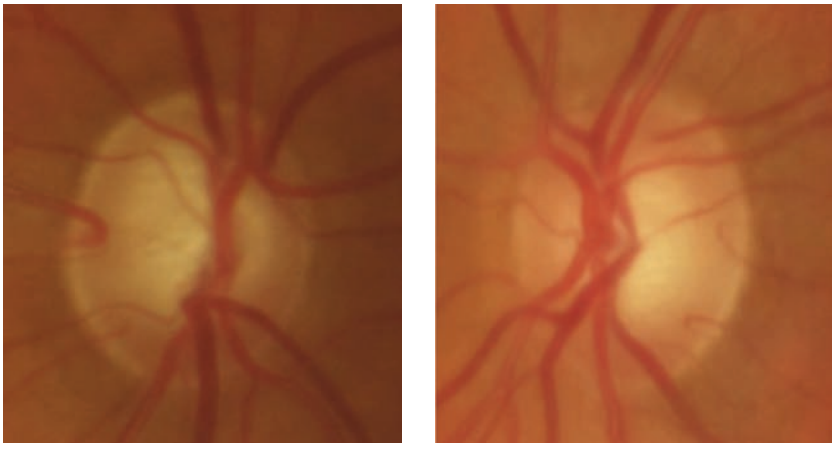
Understanding the basic pharmacology for each glaucoma medication can help you sort out which ones work well together for combination treatment.

By Susan Yee, OD

As a progressive eye disease, glaucoma is on every optometrist's radar, especially primary open-angle glaucoma (POAG), the most common form.[1-10] Research estimates it will affect around 80 million people worldwide by the year 2020.[6,7,11] The main therapeutic goal for patients diagnosed with POAG is slowing disease progression and the rate of visual field loss—accomplished by reduction of intraocular pressure (IOP) with medical therapy.[1,3,6,8,10-13]

These days, however, medical therapy isn't as simple as prescribing eye drops and sending patients on their way. Clinicians mainly prescribe from one of four classes of IOP-lowering medications: beta blockers (B-blockers), carbonic anhydrase inhibitors (CAIs), prostaglandin analogs (PGAs) and alpha 2-adrenergic agonists.[2,7,9,14]

Each class can cause local and systemic adverse reactions, and clinicians must take all of them into consideration when choosing the right therapy for each patient (*Table 1*).[4,8,9,15,16] And when patients don't see the IOP lowering effects they need with one class of drug, clinicians can add a second or even a third drug, which further complicates the treatment plan. This article discusses the many IOP-lowering medication options and factors that can influence treatment choices.



This 69-year-old white male has no family history of glaucoma. His initial IOP was 42mm Hg in the right eye and 36mm Hg in the left. With brimonidine BID, dorzolamide BID and latanoprost QHS, his IOP is now 15mm Hg in both eyes.

Physiology and Mechanism of Action

Aqueous humor, produced at the ciliary processes, is regulated by neuro inputs from both the sympathetic and parasympathetic systems and by vascular contractile-dilation in the ciliary body. Aqueous is produced by diffusion, ultrafiltration and active secretion, involving the active transport of Na+, Cl- and HCO_3-. Aqueous production occurs in the posterior chamber and passes out of the anterior chamber through the trabecular meshwork. Most resistance to aqueous outflow is located in the extracellular matrix (ECM) of the trabecular meshwork. Glycosaminoglycans within the ECM influence the hydration of the trabecular meshwork, and the parasympathetic

cholinergic innervation of the iris and the ciliary muscle all influence aqueous humor outflow.

Aqueous outflow is also assisted by an unconventional route through the uveal meshwork and the ciliary muscle called the uveoscleral pathway. Prostaglandin F2α within the ciliary muscle decreases the flow resistance of its interstitial space, thereby increasing aqueous outflow through the uveoscleral pathway. B-blockers and alpha agonists reduce aqueous production by their effects on the B2 adrenergic and presynaptic α2 receptors, respectively. Alpha agonists also can increase trabecular meshwork outflow. CAIs inhibit the activities of carbonic anhydrase responsible for HCO_3- secretion, thus reducing the production and active secretion of aqueous humor from the ciliary body. Prostaglandin analogs increase uveoscleral outflow by activating prostaglandin F2α receptors, leading to ECM remodeling in the ciliary muscle, in turn reducing hydraulic resistance and increasing uveoscleral outflow.[9,16]

Where to Begin

PGAs are often first-line treatment for IOP reduction in POAG and ocular hypertension (a condition with elevated IOP but no detectable glaucoma damage) and are recommended by both the American Academy of Ophthalmology Preferred Practice Patterns and the UK-based National Institute for Health and Care Excellence guidelines.[1,9,12,17-19]

For some, PGA monotherapy is enough to achieve and maintain adequate IOP control. For many, however, more than one medication is required to achieve desirable IOP reduction, and clinicians must consider adding a B-blocker, a CAI and/or an alpha agonist to an existing PGA.[3,13,20]

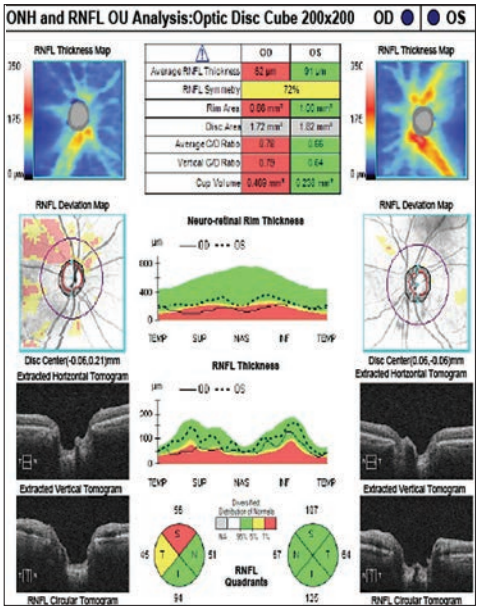
Two is Better than One

Research has yet to outline which adjunctive agents are most effective in achieving IOP control. Some monotherapy clinical trials suggest that B-blockers and alpha agonists are more effective than CAIs in IOP control. However, a systemic review and meta-analysis revealed similar mean diurnal IOP-lowering efficacy when a B-blocker, an alpha agonist or a CAI agent was combined with a PGA.[21] One study found adding a CAI to a PGA lowered nocturnal IOP more than with either a B-blocker or alpha agonist.[21]

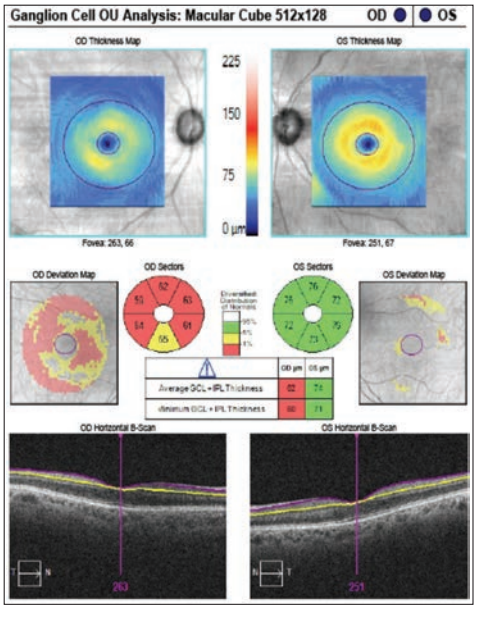
In lieu of better clinical data, clinicians must take factors such as efficacy, frequency of dosing schedule, ocular side effects and tolerability into consideration when prescribing an additional medication.[8,21] Research suggests incidence of eye pain and burning sensation is higher with alpha agonists and CAIs compared with B-blockers, which can affect patient compliance.[21] Another major advantage of using a B-blocker as adjunctive therapy is its FDA-approved once-daily dosing of timolol 0.5% gel forming solution, although generally FDA-approved dosing for B-blockers is BID.

Aqueous production drops at night, which may explain why B-blockers are ineffective in nocturnal IOP reduction. Most research indicates timolol has the greatest IOP-lowering efficacy in the morning, while PGAs are most effective in the evening. Clinicians may prescribe a concomitant therapy of timolol 0.5% gel daily in the morning and PGA at night for optimal IOP reduction—limiting the dosing frequency to only twice a day. Also, one study found timolol causes less severe ocular side effects with higher tolerability, which may increase patient compliance with medication adherence.

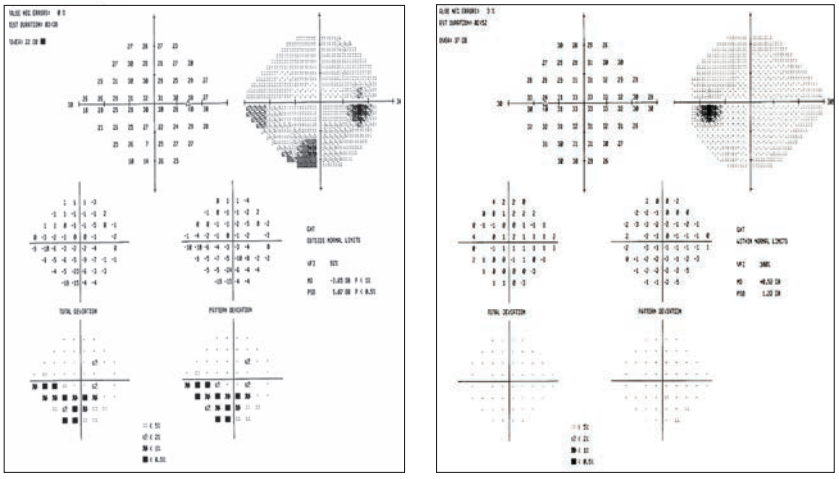
CAIs are good alternative agents



The patient's RNFL scan shows superior and temporal rim thinning in the right eye.



The patient's GCA correlates with rim thinning in the right eye and a normal left eye.



Visual fields show the inferior arcuate in the right eye that correlates with RNFL and GCA. The fields are clean in the left eye.

to add to PGAs for patients who are contraindicated to B-blockers or if the IOP-lowering effects are not satisfactory. Topical CAI agents are FDA-approved for TID dosing, but are often used BID in clinical practice, especially as adjunctive therapy. Another option for therapy with PGAs is an alpha agonist. Like CAIs, alpha agonists are also FDA-approved for TID dosing, but are often used BID. Some studies have suggested the alpha agonist brimonidine in particular provides a neuroprotective role, which may slow down the progressive loss of retinal ganglion cells in glaucoma.[3,5,9,13,21]

Contraindications

All IOP-lowering medications possess some degree of local and systemic side effect. Some, however, are contraindicated for patients with specific systemic conditions. Patients with asthma, chronic obstructive pulmonary disease, bradycardia, heart block, congestive heart failure or those taking an oral beta blocker should not be treated with a topical B-blocker.[4,8,9] PGAs should be avoided by those who are pregnant or have an ophthalmic inflammatory condition. Alpha agonists are contraindicated in neonates, children younger than two and those who are taking monoamine oxidase inhibitors.[15,16]

Third Time's the Charm

Unfortunately, some patients still do not achieve adequate IOP control with two adjunctive medications. In these cases, treatment becomes more complicated when a third topical hypotensive agent is added.

Some of the challenges with multiple drug therapy include an increase in dosing frequency, risk of drug washout, ocular side effects and exposure to preservatives, the latter causing an increase in ocular surface disease and discomfort. These factors can potentially interfere with medication adherence and decrease overall efficacy.[14,22,23] When patients are placed on multiple concomitant hypotensive agents, clinicians should consider fixed-combination medications as an alternative to traditional concomitant therapy.[10,19]

Combinations, Simplified

Most fixed-combination medications contain a B-blocker with a CAI, an alpha agonist or a PGA—only one combines a CAI with an alpha agonist. In the United States, only three fixed-combinations are FDA-approved: Cosopt (dorzolamide/timolol, Akorn) BID, Combigan (brimonidine/timolol, Allergan) BID and Simbrinza (brinzolamide/brimonidine, Alcon) TID.[13,24]

One of the main advantages of fixed-combination is dosing frequency. Concomitant treatment involving a B-blocker (BID) and a CAI (BID or TID) or an alpha agonist (BID or TID) requires patients instill two separate medications in the morning and in the evening for a total of four drops per day, five minutes between drops—which can be troublesome and time consuming. Fixed-combination therapy can reduce dosing frequency to two or three drops (when already on a PGA) per day. Less daily dosing simplifies a patient's treatment plan, avoids medication washout, decreases preservative exposure and, in many cases, decreases ocular effects without affecting IOP-lowering efficacy.[3,10,13,20,25]

Here is a closer look at the combined mechanisms of action for the available fixed-combination medications (*Table 2*):

B-blocker/CAIs work synergistically to reduce overall aqueous production.[3]

B-blocker/alpha agonists also work synergistically as an aqueous suppressant. Alpha agonists can also enhance outflow through the uveoscleral pathway—perhaps further reducing IOP.[3]

CAI/alpha agonists decrease aqueous production and increase uveoscleral outflow. It is often a good alternative treatment for those who cannot take B-blockers or wish to avoid PGAs due to ocular effects of hyperemia, eyelash growth, iris or periorbital hyperpigmentation, especially with monocular treatments.[13]

B-blockers/PGA lower IOP by decreasing aqueous production and increasing outflow.[3,10,20]

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Table 1. Glaucoma Drug Options[4,7,8,12,15,16]

Class	Names	Mechanism of Action: Reduce IOP	Ocular Effects	Systemic Effects
Beta-blocker	• Timolol • Betagan (levobunolol, Allergan) • Ocupress (carteolol, Novartis) • Betoptic (betaxolol, Alcon) • Optipranolol (metipranolol, Valeant Pharmaceuticals)	• Decrease aqueous production	• Conjunctival allergy • Hyperemia • Corneal epithelial disorders • Reduced corneal sensitivity • Blurry vision	• Decrease blood pressure/pulse • Bradycardia • Worsen asthma/COPD • Depression • Impotence • Lethargy
Carbonic anhydrase inhibitor	• Trusopt (dorzolamide, Merck) • Azopt (brinzolamide, Alcon) • Diamox (acetazolamide oral capsule, Teva Pharmaceuticals) • Neptazane (methazolamide oral capsule, Perrigo)	• Decrease aqueous production	• *Same as B-blockers* • Ocular irritation • Foreign body sensation	*Topical use:* • Bitter taste • Fatigue • Diuresis • Gastrointestinal upset *Oral use:* • Nausea • Unpleasant taste • Dysesthesia of fingers/lips • Anorexia • Metabolic acidosis
Prostaglandin analog	• Xalatan (latanoprost, Pfizer) • Travatan (travoprost, Alcon) • Rescula (unoprostone isopropyl, Sucampo) • Zioptan (tafluprost, Akorn) --- • Lumigan (bimatoprost, Allergan)	• Increase uveoscleral outflow --- • Increase uveoscleral and trabecular meshwork outflow	• *Same as B-blockers* • Eyelash growth • Iris/eyelid pigment • Deepening of upper eyelid sulcus • Recurrence of herpes • Macular edema post cataract surgery	• Rarely, upper respiratory infection • Rarely, myalgia
Alpha 2-adrenergic agonist	• Alphagan (brimonidine, Allergan) • Iopidine (apraclonidine, Alcon)	• Decrease aqueous production • Increase uveoscleral outflow	• Allergic conjunctivitis • Hyperemia • Mydriasis • Dry eye	• Affects blood pressure/pulse • Drowsiness • Dizziness • Dry mouth • Dysarthria
Parasympathomimetic /cholinergic agonist	• Pilocar (pilocarpine, FDC Limited)	• Increase trabecular meshwork outflow	• Miosis • Visual field constriction • Night vision loss • Myopia • Red eye • Brow ache • Retinal detachment • Cataract	*Direct-acting:* • Rare systemic reactions *Indirect-acting:* • Sweating • Tearing • Nausea/vomiting • Diarrhea • Bradycardia • Stomach ache

Treatments on the Horizon

Because glaucoma is the second leading cause of blindness worldwide, researchers are continually on the hunt for better therapeutic options.[1,3,7,8,12,14] These new meds are designed to simplify treatment with a once-daily dosing schedule:

Vyzulta (latanoprostene bunod 0.024%, Bausch + Lomb) is a compound of latanoprost and a nitric oxide (NO) donor that reduces IOP by increasing aqueous outflow through both the trabecular meshwork/Schlemm's canal and uveoscleral pathways. In phase III trials, once-daily use of this drug performed better than both twice-daily timolol and once-daily latanoprost. Mild punctate keratitis and ocular hyperemia are the most common ocular side effects.[2,4,9,14,26-28]

Rhopressa (netarsudil 0.02%, Aerie Pharmaceuticals) is both a RHO-associated protein kinase inhibitor and norepinephrine transporter inhibitor. It has two mechanisms of action aimed at IOP reduction: increasing trabecular meshwork outflow and decreasing aqueous production. Rho-kinase inhibitors destabilize filamentous actin, leading to more empty space

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in trabecular meshwork and improving outflow. Norepinephrine transporter inhibitors result in reduced aqueous production. It has a once-daily dosing schedule, and the most common ocular side effect is mild hyperemia.[2,4,9,11,14,28] A phase III clinical trial was completed in 2016.

Roclatan (Aerie Pharmaceuticals), currently in phase III clinical trials, is a combination of netarsudil 0.02% and latanoprost 0.005%. It is administered once daily to act on both the trabecular meshwork and the uveoscleral outflow pathways to reduce fluid production.[9,14,24,28]

Trabodenoson (Inotek Pharmaceuticals) is an adenosine analog that targets A1 receptors, resulting in the removal of proteins from the trabecular meshwork, lowering outflow resistance and IOP.[9,14,29] Researchers are working to combine trabodenoson with latanoprost and brimonidine for glaucoma treatment.[2,4,9,14,28] In January 2017, Inotek announced the results of phase III clinical trials, which did not achieve superiority to placebo at all 12 time points.[30]

Because the only way to manage glaucoma is to reduce the primary risk factor—elevated IOP—clinicians must be prepared to prescribe any number of IOP-lowering drugs, as monotherapy or in combination. PGAs have emerged as the gold standard initial monotherapy treatment for POAG; but when monotherapy cannot achieve desirable IOP reduction, additional medications, whether through concomitant therapy or fixed-combination medications, can help adequately control a patient's IOP. In the future, newer treatment modalities may lower IOP and slow glaucoma progression with even better dosing regimens. ■

Dr. Yee is a staff optometrist in the Salisbury VA Health Care System, Salisbury, NC.

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Table 2. Fixed-combination Medications[3,4,8,13,24]

	Effects on aqueous humor (AH)	Market availability
Cosopt (dorzolamide/ timolol, Akorn)	Decrease AH/decrease AH	USA/other countries
Combigan (brimonidine/ timolol, Allergan)	Decrease AH, increase outflow/ decrease AH	USA/other countries
Simbrinza (brinzolamide/ brimonidine, Alcon)	Decrease AH/decrease AH, increase outflow	USA/other countries
Brinzolamide/timolol	Decrease AH/decrease AH	Other countries
DuoTrav (travoprost/ timolol, Alcon)	Increase outflow/decrease AH	Canada/other countries
Latanoprost/timolol	Increase outflow/decrease AH	China/other countries
Bimatoprost/timolol	Increase outflow (uveoscleral and TM)/decrease AH	China/countries worldwide
PGA/alpha agonist/ B-blocker	Increase outflow/decrease AH	Mexico

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DRY EYE: Master the Science Beneath the Surface

Learn how inflammatory mediators govern the disease course—and provide an avenue to treatment. **By Michelle Hessen, OD**

Inflammation plays a significant role in the etiopathogenesis of dry eye.[1] It promotes ocular surface disruption and symptoms of irritation. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[1,2] Once investigators identified inflammation's role in dry eye development, research could target treatment using anti-inflammatory agents that inhibit the expression of inflammatory mediators on the ocular surface. By doing so, these agents help restore a healthy tear film and reduce signs and symptoms of afflicted patients.

This article reviews the inflammatory process, how different anti-inflammatory drugs can disrupt that process and how to appropriately apply that knowledge in your clinic.

Pathophysiology

Growing evidence shows dry eye-related ocular surface inflammation is mediated by lymphocytes.[3] Based on earlier immunohistopathological evaluations, patients with both Sjögren's syndrome (SS) related and non-SS dry eye have identical conjunctival inflammation manifested by T-cell infiltrates and upregulation of CD3, CD4 and CD8, as well as lymphocyte activation markers CD11a and HLA-DR.[4] These results suggested that clinical symptoms and signs of dry eye may be dependent on T-cell activation and resultant autoimmune inflammation. Multiple other studies demonstrated the role of proinflammatory cytokines and matrix metalloproteinases (MMPs) in the pathogenesis of dry eye.[5-6]

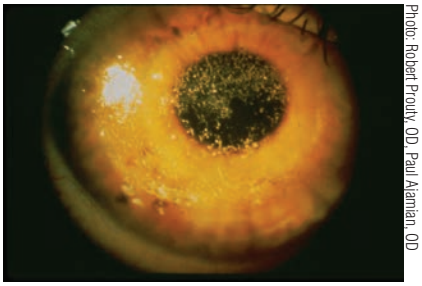

Photo: Robert Prouty, OD, Paul Ajamian, OD

This patient has severe dry eye due to Sjögren's syndrome. Identifying the cause of a patient's dry eye is key to targeting treatment.

Interleukin (IL)-1 is one of the most widely studied cytokines accompanying dry eye. Researchers point to an increase in the proinflammatory forms of IL-1 (IL-1α and mature IL-1β) and a decrease in the biologically inactive precursor IL-1β found in the tear film of dry eye patients.[5] Investigators recognize that IL-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α also play a significant role in SS-related dry eye as compared with healthy eyes.[6] This explains why treatments in development today specifically target inflammatory cytokines.

The response of cells to extracellular stimuli, such as ocular surface stress due to changes in the tear film composition, hyperosmolarity or ultraviolet (UV) light exposure, is partially mediated by a number of intracellular kinase and phosphatase enzymes.[7]

According to one study, "mitogen-activated protein (MAP) kinases are integral components of parallel MAP kinase cascades activated in response to a number of cellular stresses including inflammatory cytokines (e.g., Il-1 and TNF-α), heat shock, bacterial endotoxin and ischemia."[7] Researchers have identified these stress-activated protein kinases in the tear film of patients with dry eye and documented that activation of the stress pathways

The leading cause of ocular discomfort and contact lens dropout is dryness.

Meibomian Gland Function, the foundation of a healthy tear film.

Gland structure captured with Dynamic Meibomian Imaging (DMI).

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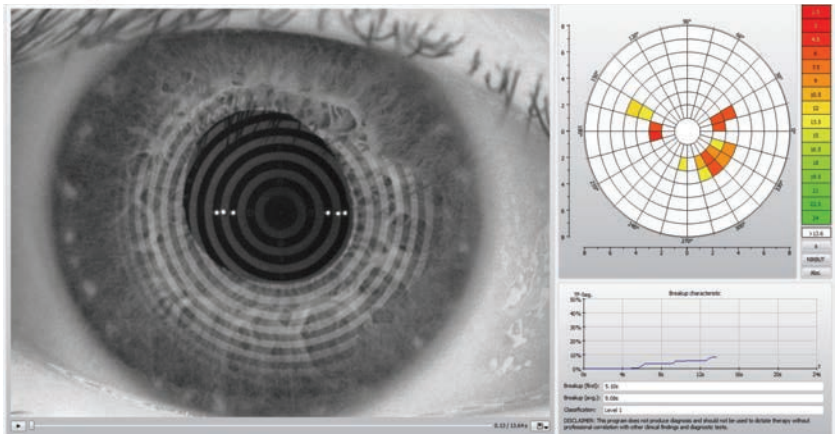

Photo: Dan Fuller, OD

This Keratograph 5M (Oculus) image shows an assessment of a patient's noninvasive tear break-up time.

results in the transcription of stress-related genes, including MMPs, mainly MMP-9.[8]

Another study shows that MAP kinases stimulate the production of inflammatory cytokines—including IL-β, TNF-α and MMP-9—causing ocular surface damage.[9]

Lymphocyte function-associated antigen-1 (LFA-1), with its cognate ligand intercellular adhesion molecule-1 (ICAM-1), plays an important role in the cell-mediated immune response and inflammation associated with dry eye.[10] LFA-1 is expressed on the cell surface of leukocytes and binds with high affinity to ICAM-1 and with lower affinity to ICAM-2 and ICAM-3.[11,12] ICAM-1 is expressed on the cell surface of leukocytes, endothelial cells, keratinocytes and epithelial cells.[13] LFA-1 binding to ICAM-1 is involved in dendritic cell migration to regional lymph nodes in the afferent arm of the dry eye inflammatory pathway.[14,15] LFA-1 and ICAM-1 may be involved in the dry eye immunoinflammatory efferent pathway as well.[14-16]

Naïve T-cells are primed in the lymph nodes through interaction with dendritic cells and differentiate to T_H1 and T_H17 effector cells.[14-16]

These activated CD4+ effector T-cells migrate from the lymph nodes to the ocular surface and lacrimal glands, where they exert inflammatory effects. Researchers suggest that LFA-1/ICAM-1 may play a role in reactivation of CD4+ cells at the ocular surface to further promote release of proinflammatory cytokines from either the T-cells or antigen presenting cells.[17]

Finally, research shows that inhibition of ICAM-1 and LFA-1 in mice reduces the number of inflammatory infiltrates in the lacrimal gland.[18] Ultimately, it is possible that LFA-1/ICAM-1 may possibly recruit and retain LFA-1 expressing T-cells to the epithelium and conjunctiva, thus inducing proinflammatory cytokine release.

All these inflammatory mediators and pathways relate to the pathogenesis of dry eye and play a role in targeting treatment strategies.

First-line Therapies

When treating dry eye, over-the-counter lubricants (e.g., artificial tears, gels, ointments) may be common but, for patients who need multiple doses per day or who have a punctal occlusion, your aim will be to reduce the cytotoxic effects often associated with those products, as they contain benzalkonium chloride (BAK). Instead, opt for preservative-free agents for these patients.

Before any other treatment, examine the patient for blepharitis. If present, the first step is to differentiate between bacterial and *Demodex* infections. In bacterial cases, it may be necessary to prescribe topical antibiotic or an antibiotic/steroid combination. If *Demodex* is at the root of the infection, turn to a product that contains 4-Terpineol, such as Cliradex (Biotissue) or Cliradex Light.

Corticosteroids

Topical steroids, through several mechanisms, help reduce ocular inflammation. Corticosteroids function via suppression of cellular infiltration, capillary dilation, proliferation of fibroblasts and collagen deposition.[19] They stabilize intracellular and extracellular membranes.[19]

Corticosteroids increase the synthesis of lipocortins that block phospholipase A_2 and inhibit histamine synthesis in the mast cells.[19] Inhibition of phospholipase A_2, an essential step in the inflammatory cascade, prevents the conversion of phospholipids to arachidonic acid. Corticosteroids also interfere with transcription factor NF-kB, which regulates synthesis of a number of proinflammatory molecules, thereby stimulating lymphocyte apoptosis.

Corticosteroids mediate their anti-inflammatory effects primarily through the modulation of the cytosolic glucocorticoid receptor at the genomic level.[20,21] After corticosteroids bind to the glucocorticoid receptor in the cytoplasm, the activated corticosteroid-glucocorticoid receptor complex migrates to the nucleus, where it upregulates the expression of anti-inflammatory

proteins and represses the expression of proinflammatory proteins.[20,21] However, recent work suggests the activated corticosteroid-glucocorticoid receptor complex also elicits nongenomic effects, such as inhibition of vasodilation, vascular permeability and migration of leukocytes.[20,22]

Several clinical studies demonstrate the effectiveness of topical steroids in treating dry eye.[23-25] In a retrospective clinical series, topical administration of a 1% solution of nonpreserved methylprednisolone, given TID or QID for several weeks to patients with SS-related dry eye, provided moderate to complete relief of symptoms in all patients.[23] In addition, a decrease in corneal fluorescein staining score (2.6 ± 0.5 on a 12-point scale) and complete resolution of filamentary keratitis were seen.[23] This therapy was effective even for patients suffering from severe dry eye who had no improvement from maximum aqueous tear enhancement/replacement therapies.[23]

One pilot study looked at 64 patients to evaluate the efficacy of Lotemax (loteprednol etabonate 0.5%, Bausch + Lomb) ophthalmic suspension QID vs. placebo to treat the inflammatory component of dry eye associated with aqueous tear deficiency and delayed tear clearance.[24] After two weeks of therapy, Lotemax-treated patients with moderate to severe clinical inflammation showed a significant decrease in central corneal staining, nasal bulbar conjunctival hyperemia and lid margin injection, compared with the placebo group.[24] No patients experienced clinically significant increase in intraocular pressure following one month of therapy.[24]

Patients treated with topical corticosteroids should be monitored closely for known risks of cataract formation, glaucoma, corneal thinning and infectious keratitis.[25]

NSAIDs

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are used to manage allergic conjunctivitis, postoperative ocular pain, cystoid macular edema after cataract surgery and several other conditions in addition to dry eye. NSAIDs treat inflammation by inhibiting the production of prostaglandins via the cyclooxygenase enzyme.[26] However, research shows NSAIDs—specifically diclofenac—can reduce corneal sensitivity, too.[27] This may cause insult to the disrupted epithelium in dry eye patients.[28-34] The literature shows several cases of corneal melt associated with use of topical NSAIDs, including diclofenac, ketorolac, nepafenac and bromfenac.[28-34] In all of these cases, preexisting epitheliopathy was identified.[28-34] Although the exact relationship between corneal melt and topical NSAID use is still not clear, various suggested mechanisms include activation of matrix metalloproteinases, impairment of wound healing and neurotrophic effect resulting from the analgesic action of these drugs.[28-34]

Short-term use of NSAIDs can be useful in ameliorating symptoms of ocular discomfort in dry eye. However, they should be used with caution and under close monitoring, and the treatment should be preferably discontinued if the corneal epithelium becomes damaged.

Cyclosporin A

The immunomodulating effects of cyclosporin A are achieved through binding with cyclophilins. Cyclophilin A, which is found in the cytosol, and the cyclosporin-cyclophilin A complex inhibits a calcium/calmodulin-dependent phosphatase, calcineurin, the inhibi-

tion of which is thought to halt the production of the transcription of T-cell activation by inhibiting IL-2.[35]

Cyclophilin D is located in the matrix of mitochondria. Cyclosporin A-cyclophilin D complex modulates the mitochondrial permeability transition pore, thereby inducing a mitochondrial dysfunction and cell death.[36] The reduction in inflammation, via inhibition of T-cell activation and downregulation of inflammatory cytokines in the conjunctiva and lacrimal gland, allows enhanced tear production.[37-41] Topical cyclosporine also increases goblet cell density and decreases epithelial cell apoptosis.[42] Commercially available Restasis (topical cyclosporine 0.05%, Allergan) or a 1% compounded preparation is frequently used to treat various inflammatory ocular surface disorders.[43]

Dosing topical cyclosporine at a frequency greater than twice a day may be more effective for patients who do not demonstrate improvement of severe dry eye disease with the twice-daily regimen.[44,45]

Lifitegrast

This formulation blocks the binding of the surface proteins LFA-1 and ICAM-1, thereby reducing inflammation in dry eye.[46] The recommended dosing of the commercially available Xiidra (lifitegrast 5%, Shire) is twice daily.[47] Researchers recently completed a one-year multicenter, randomized, placebo-controlled study of the safety of lifitegrast ophthalmic solution 5.0% in 331 participants (220 lifitegrast, 111 placebo) with dry eye.[47] There were no serious treatment-emergent adverse events (TEAEs). Overall, 53.6% of participants receiving lifitegrast experienced ≥1 ocular TEAEs vs. 34.2% in the placebo group.[47] Most TEAEs were mild-moderate in severity. Rates of discontinuation because of TEAEs were 12.3% (lifitegrast) vs. 9.0% (placebo).[47] The most common (>5%) TEAEs occurring in either treatment group were instillation site irritation (burning), instillation site reaction, reduced visual acuity, dry eye and dysgeusia (change in taste).[47] There was no indication of systemic toxicity or localized infectious complications secondary to chronic immunosuppression.

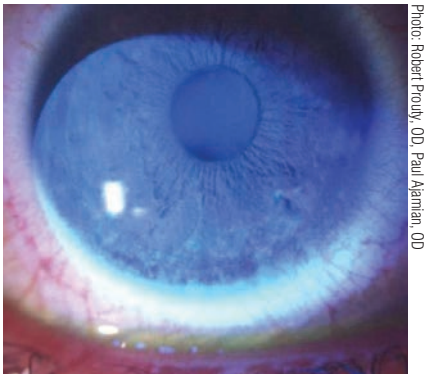

Photo: Robert Prouty, OD; Paul Ajamian, OD

Superficial punctate keratitis in a Sjögren's patient on Restasis therapy.

Tacrolimus

This topical anti-inflammatory agent (previously known as FK506) is a macrolide antibiotic.[48] Although the mechanism of tacrolimus is similar to cyclosporin A, research shows the potency *in vitro* has been shown to be significantly greater.[49] Only when bound to immunophilin does it become biologically active, thus effectively inhibiting calcineurin, and inhibiting T- and B-lymphocyte activation via reduction in IL-2 synthesis.[48,50,51] Tacrolimus suppresses the immune response by inhibiting the release of other inflammatory cytokines as well, such as IL-4 and IL-8.[50,52,53]

Systemic tacrolimus has been reported to be effective for improving dry eye associated with graft vs. host disease (GVHD). However, there are potential adverse reactions to be aware of when administering long-term systemic therapy.[54] Topical tacrolimus is available in 0.03% and 0.1% concentrations as an ointment (typically applied externally to eyelids) as well as compounded eye drops. It is a promising off-label treatment of dry eye in the setting of chronic GVHD and SS.[55-57]

Tetracycline Derivatives

Oral tetracycline derivatives possess antibacterial as well as anti-inflammatory properties. Doxycycline has been shown to inhibit c-Jun N-terminal kinase and extracellular signal-related kinase mitogen-activated protein kinase signaling in epithelial cells of the ocular surface exposed to hyperosmolar stress, downregulating the expression of CXCL8 and proinflammatory cytokines IL-1β and TNF.[58] Doxycycline inhibits MMP-9 activity and supports ocular surface integrity.[59,60]

Additionally studies demonstrated that minocycline inhibits expression of cell-associated proinflammatory molecules, including major histocompatibility complex class II.[61] Doxycycline has been reported to be effective in patients with ocular rosacea by reducing irritation symptoms, improving tear film stability and decreasing the severity of ocular surface disease.[62-64] In addition, doxycycline has been useful in the treatment of corneal erosions.[65,66]

Azithromycin

This broad-spectrum macrolide antibiotic has been shown to have good tissue penetration to the eyelid and favorable pharmacokinetics for daily dosing. Azasite (topical azithromycin, Akorn) is FDA approved to treat bacterial conjunctivitis, but may be used as off-label therapy for clinical control or relief of symptoms and signs of meibo-

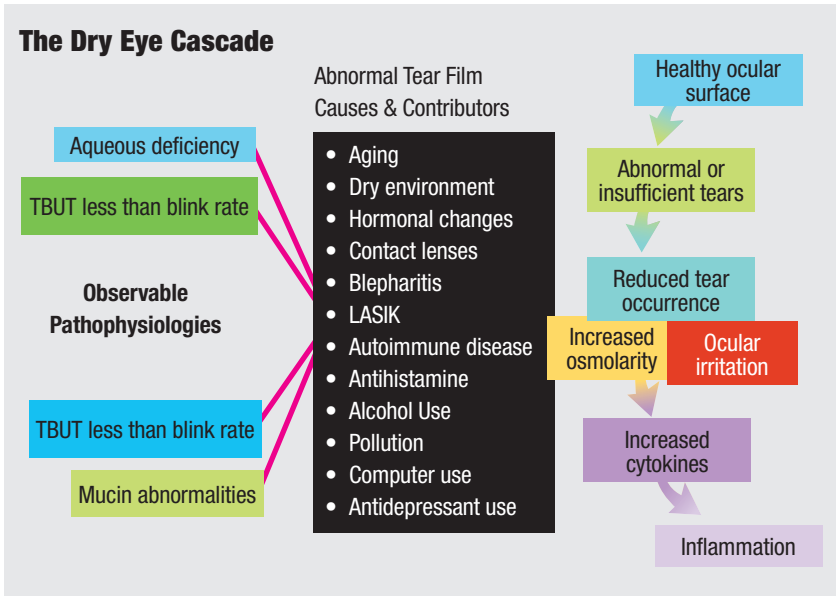

Diagram: Bruce Onofrey, OD, RPh

The increased prevalence of dry eye disease can be attributed to a number of factors. Understanding the mechanism of action behind therapeutic options can help you best target your patients' treatments.

mian gland dysfunction, as well as improvement in lipid behaviors of meibomian gland secretion.[67] It has also been noted that topical azithromycin management could lead to improvement in meibomian gland orifice plugging.[68] A single oral dose of 1g has been shown to provide prolonged high levels after 14 days in drug-targeted ocular tissues, to decrease inflammatory cytokines and suppress production of proinflammatory mediators.[69-72] Good intracellular penetration and long half-life of azithromycin can provide an effective antimicrobial and favorable immunomodulatory effect without compliance issues of long-term tetracycline use.[70,72] Research shows the drug could block activation of NF-kB, leading to decreased inflammatory cytokine levels such as IL-6 and IL-8.[73] Besides, azithromycin has been shown to suppress the production of proinflammatory mediators by inhibiting cultured human corneal epithelial cells.[74]

Autologous serum

Serum contains several anti-inflammatory factors that have the capability to inhibit soluble mediators of the ocular surface inflammatory cascade of dry eye. These include inhibitors of inflammatory cytokines (e.g., IL-1 RA and soluble TNF-receptors) and MMP inhibitors (e.g., tissue inhibitors of metalloproteinases).[75-77] Clinical trials show autologous serum drops improve ocular irritation symptoms and conjunctival and corneal dye staining in dry eye that occurs in the setting of SS.[78-80] Conversely, there is greater risk of microbial growth as autologous serum drops, in addition to antimicrobial agents, contain high protein content and are generally nonpreserved.[81]

Recent studies have investigated cord serum drops (prepared from donor umbilical cord serum) as well as allogenic serum drops (from a relative donor).[82-84] A clinical trial of 17 patients with GVHD and 13

patients with SS-associated dry eye treated them for one month with cord blood serum. Patients received cord blood once a day (containing 0.15ng epithelial growth factor per drop). Patients reported a decrease in discomfort symptoms as measured with the Ocular Surface Disease Index score (OSDI) (22.3 ± 10.3 vs. 39.3 ± 16.9). Also, clinical findings such as impression cytology score (3.8 ± 1.2 vs. 6.6 ± 2.1), tear osmolarity (312.5 ± 7 vs. 322 ± 9.1mOsm/L), and corneal sensation (measured with Cochet-Bonnet esthesiometers) (48.2 ± 2.1 vs. 49.7 ± 2.1 nylon/mm/length) improved significantly.[82]

Another study, this one involving 12 patients with chronic GVHD-associated severe dry eye treated with cord blood serum for six months, reported statistically significant improvement ($p<0.01$) in symptom score (on a scale of 0-4, 3.83+/-0.38 vs. 0.83+/-0.57), corneal sensitivity (52.08+/-6.06mm to 57.50+/-3.00mm), tear film BUT (from 2.50+/-0.91 sec. to 5.71+/-1.04 sec., $P<0.01$) and corneal fluorescein staining (7.42+/-2.02 to 1.29+/-0.46).[83]

Allogenic serum drops are prepared using blood from a family member rather than the patient's own. In one study, allogeneic serum tears were used for the treatment of dry eye in 16 patients with GVHD. After four weeks of continuous use the symptom scores (32.5-8.9 OSDI score), tear osmolarity (311.1 to 285.1mOsmL), and corneal staining (2.5 to 1.8) improved as well as increased goblet cell density (90.6 to 122.6 cell/mm^2), and tear break-up time (2.9 to 4.4 sec.).[84]

Dry eye therapy should target the inflammatory cascade, given its significant role in etiopathogenesis. When selecting an appropriate treatment plan, it is important to consider severity of the condition based on clinical exam including osmolarity, Schirmer, tear break-up time and ocular surface staining. It is also necessary to identify concurrent ocular disease as well as possible systemic conditions that may be contributing factors. The treatment goal is to improve patient symptoms, restore a healthy tear film, prevent further destruction of the ocular surface and ultimately reestablish an intact epithelium. ■

Dr. Hessen is a clinical instructor at the Wilmer Eye Institute's Ocular Surface Diseases and Dry Eye Clinic at Johns Hopkins School of Medicine, where she specializes in ocular surface disease, including autoimmune disorders.

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Resist the Itch: Managing Allergic Conjunctivitis

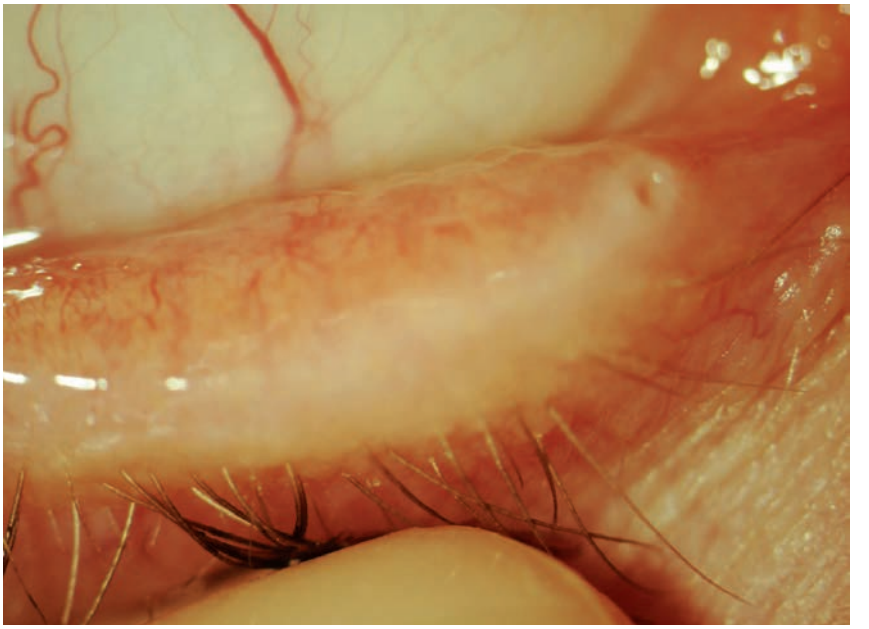
Flowers may be blooming, but this season leaves many ODs seeing red.

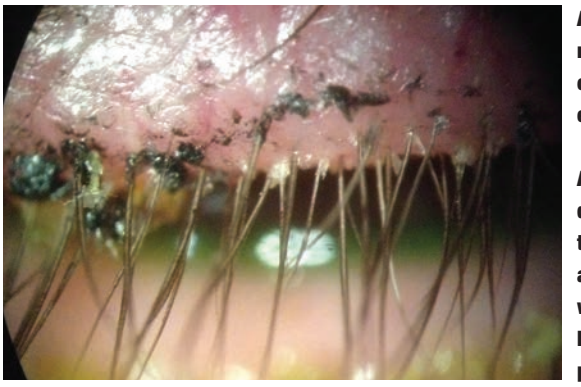
By Charissa Young, OD

While some enjoy the blooming flora and warm sun of spring, others only see elevated pollen levels and a rise in temperature as the dreaded start of allergy season. Their noses will stuff, their throats will itch and their eyes will become itchy and red. Sadly, many patients mismanage ocular allergy by employing over-the-counter (OTC) red eye solutions that neither address the problem nor relieve the symptoms. When it becomes too much, many of these patients will land in our offices seeking relief.

The good news is that allergy medication is more targeted than ever, and with the right background optometrists can bring patients the relief they're seeking. Gone are the days when ODs simply threw a combination antihistamine and mast-cell stabilizer drop at anything that itches.

Over the last decade, an explosion of research has focused on the ocular surface, increasing our understanding of how our environment, and





Above, this patient displays nasal inferior papillary conjunctivitis in the right eye.

At left, if a patient describes the itch as being toward the eyelid, there's a chance they're dealing with a *Demodex* infection, like the patient in this photograph.

its offending allergens, impacts the anterior segment.

This article provides an update on the state of ocular allergy therapies and how optometrists can use that knowledge to bolster their roles in treatment.

Comorbidities

Before delving into ocular allergy management, get familiar with your comorbidities. In many cases, managing them can reduce the need for directly treating the allergic reaction. Some of my most successful cases have started with first managing the coexisting conditions that were exacerbating the allergy.

Demodex: Ask if the patient's itch is directed toward the conjunctiva or the eyelid. If it's the former, it's likely the result of an allergy; if it's the latter, you should suspect *Demodex*.[1] Look closely at the base of the lash follicles for protruding tails. If you're still unsure, try using forceps to gently twirl a lash within its follicle to draw out the mite.[2] Patients with *Demodex* blepharitis alone will find no relief from topical allergy medications, so eradicating the mites via mechanical debridement and chemical eradication (e.g., ophthalmic-grade tea tree oil or hypocholorous acid 0.01%) is necessary to relieve itchy eyelids.[3]

Both patients suffering from allergy and *Demodex* should be advised to wash their linens weekly and to replace makeup containers to reduce exposure to offending agents. If patients are compliant with your *Demodex* treatment regimen and a papillary reaction is still present after several weeks (the life cycle of *Demodex* mites is approximately 14 days) adjunctive topical allergy medications are indicated.[4]

Dry eye disease. If *Demodex* is ruled out, consider whether the patient has exacerbated allergies due to a poor tear film—due to either meibomian gland dysfunction or aqueous deficiency.

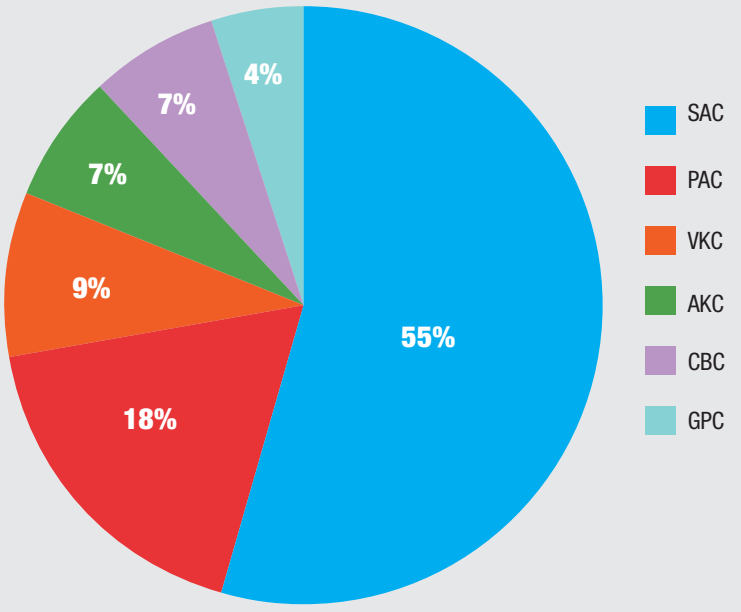
Is their ocular itch directed toward the caruncle, where stagnant tears—loaded with allergens and allergic mediators—have collected?[5] A 2016 study in China shows an alarmingly high incidence of dry eye (98%) in young children with allergic conjunctivitis.[6] More times than not, if I have a patient with both signs of dry eye disease and allergy and I lead with dry eye treatment, it reduces or, in some cases, eliminates the need for allergy treatment. With new dry eye treatments rapidly being made available, one common principle persists: if you decrease inflammation on the ocular surface and improve meibomian gland function, the tear production of most dry eye patients will improve.[7] More tears means less concentration of allergens and allergic mediators on the eye, often serving as an effective treatment for the ocular allergy, which is the exact reason OTC artificial tears provide relief as well. However, they only provide temporary relief and should be used as adjunctive, not primary, treatment.

Avoid punctal plugs in patients with a history of allergy, to allow blinking to naturally flush irritants away through the punctum.

Getting a History

During the patient's workup, investigate what symptoms related to allergies the patient has. Do they have both ocular and systemic symptoms? Patients may inadvertently take OTC allergy medications for allergy-related ocular itch, not realizing that they can actually worsen

OCULAR ALLERGY DIAGNOSIS



Percentage of patients with a specific ocular allergy diagnosis: Seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), contact blepharoconjunctivitis (CBC) and giant papillary conjunctivitis (GPC).[3]

Prevalence and Characteristics of Ocular Allergy

In the United States, ocular allergies affect up to 40% of the population. While itching is reported in 90% of cases, the other most common symptoms—hyperemia (84.6%) and tearing (76.5%)—are also shared complaints in dry eye and other anterior segment conditions and should be differentiated. Of allergic conjunctivitis cases, 73% are largely environmental, 55% are diagnosed as seasonal allergic conjunctivitis (SAC) and 18% are perennial allergic conjunctivitis (PAC). Allergy testing for these patients is a cornerstone for treatment, as patients can be educated to develop ways to minimize their exposure and receive specific allergen immunotherapy for long-term management. The remaining 27% of ocular allergy sufferers tend to have more severe ocular reactions, from enlargened papillae to lid edema, requiring specific treatment strategies and more likely necessitate adjunctive topical steroids.

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the situation. Oral antihistamines reduce aqueous and mucus production due to their anticholinergic activity, which decreases the eye's ability to dilute allergens on the ocular surface.[8] Counsel those patients about the differences and switch to a targeted ocular-allergy approach. If the patient experiences allergy-related rhinitis and other systemic symptoms, recommend OTC allergy orals, emphasizing the benefits of second-generation histamine H1 antagonists over their more ocular surface-drying first-generation counterparts.

Allergen Identification

The first rule of allergic conjunctivitis management is to identify and avoid the allergen whenever possible. While some patients know their specific triggers, the majority do not. Some clinics reported up to 80% of their allergic conjunctivitis patients had never had an allergy test before.[4] In-office testing for tear osmolarity, adenovirus and MMP-9 inflammatory biomarkers have been invaluable in our viral conjunctivitis and dry eye management, as their instant results to guide our treatments. Now, there's in-office testing to add to your ocular allergy evaluation. The Doctor's Rx Allergy Formula (Bausch + Lomb) takes three minutes to prepare and collect patient samples without use of a needle. In less than 15 minutes, practitioners will receive the patient's sensitivity results against 58 common allergens. In addition to these, there is also one positive and one negative control.[5] If patients test negative across all allergens tested or do not show minimal response to the histamine control, they are unlikely to benefit from antihistamines or mast-cell stabilizers that inhibit histamine release.[4] These patients may warrant referral to an allergist for longer-term management.

Contact Lenses

Before we discuss therapeutics, minimizing allergen exposure on the eye needs to go one step further. Fitting patients in daily disposable contact lenses is a foundation of our practice, not only due to the improved lens wear experience and convenience, but also decrease in contact lens-related complications. Of our patients fit in soft contact lenses, 90% are currently wearing a daily disposable modality. The thinking is that wearing a new lens daily will minimize allergen buildup, whereas a biweekly or monthly lens leads to buildup of allergens and irritants over time. When switching to a daily disposable is not an option due to the patient's prescription, switching to a hydrogen peroxide cleaner in conjunction with manual cleaning (none of that "no-rub solution" business for allergy sufferers) optimizes the modality.

Allergy Therapeutics

While our arsenal of topical allergy medications has remained unchanged since extra-strength Pazeo (olopatadine 0.07%, Alcon) was released three years ago, our management of allergic conjunctivitis can continue to become more nuanced with each passing season. I recommend prescription medications in place of OTC options, as many patients seem to have already tried OTC ketotifen without relief (hence, why they are in your chair in the first place). In fact, when given both ketotifen 0.025% and olopatadine 0.1% to try on a twice-daily dose schedule, 81% preferred olopatadine, citing improved comfort and more reduction in allergy symptoms.[7]

The mainstays of allergic conjunctivitis therapy are topical combination antihistamine and mast-cell stabilizer eye drops. This dual mechanism provides both short- and long-term relief for its effect on decreasing histamine release. The two primary once-daily dosing topical allergy medications are Lastacaft (alcaftadine, Allergan) and Pazeo, Pataday and Patanol (olopatadine, Alcon). In a head-to-head alcaftadine 0.25% vs. olopatadine 0.2% study of 284 subjects, both topical solutions decreased itching severity within three minutes of instillation and continued to provide itch relief at 16 hours. When comparing the two, alcaftadine provided more relief.[6] That said, due to olopata-

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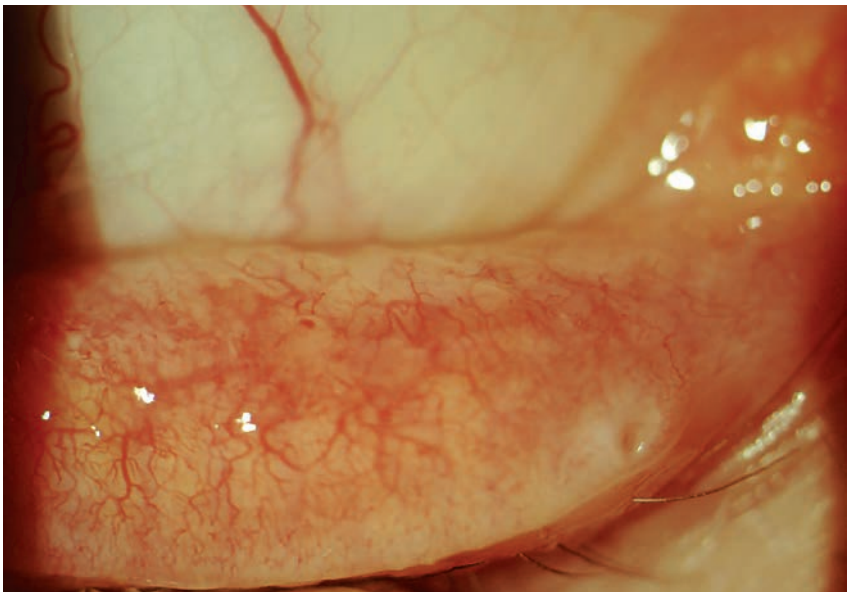
dine's different available concentrations, you can customize your treatment regimen to the condition severity. Start at lower concentrations and discuss with the patient that, if more frequent dosing provides relief, the stronger formulation may be warranted.

Unfortunately, all the major ocular allergy formulations contain benzalkonium chloride (BAK) as the preservative. If you've ever had a patient in your chair with a laundry list of allergies, it's not uncommon for them to be sensitive or even allergic to BAK.[8] The last thing you want is for your patient to develop allergic conjunctivitis secondary to their topical allergy medication, compounding their problem. Palliative ocular allergy therapy includes allergen avoidance, cool compresses, regular linen cleaning, preservative-free artificial tears and, if warranted, short-term fluorometholone 1% ointment (non-BAK preserved).

Systemic Options

Depending on your state, prescribing systemic medications such as fluticasone nasal spray and oral loratadine for allergy may be additional treatment options. For patients who can't tolerate oral antihistamines, montelukasts—while less effective—can also provide relief.[9] When topical treatment alone is insufficient, consider fluticasone nasal spray or oral loratadine, but proceed with caution. While oral medications can benefit both systemic and ocular allergy, beware of increased ocular dryness due to the anticholinergic effects. If considering a steroid nasal spray, educate the patient and monitor them more often, as ocular side effects include potential increased intraocular pressure and higher risk of central serous retinopathy.[10]



When patients suffer from ocular inflammation due to allergy, as seen here, education about avoidance of triggers is a vital aspect of treatment.

However, if a patient's ocular allergy is so severe that you're considering those therapies or they're experiencing severe systemic symptoms, comanaging with an allergist can help provide the best outcome.

Don't Wait, Educate

Because we often only see patients once a year for their annual comprehensive eye exam (and often not during allergy season), take the opportunity during this visit to ask patients if they have a history of allergy. Begin educating patients about preventative measures and the importance of not rubbing their eyes, which further exacerbates the condition due to mast-cell degranulation and increased histamine release.[11]

Starting this dialogue early with patients can not only build your medical practice, but also build patient satisfaction as you preemptively take their eye care beyond the exam chair. Manage co-existing conditions, prescribe when indicated, and most importantly, identify the allergen whenever possible so patients can minimize their exposure. ■

Dr. Young specializes in dry eye and contact lenses at Specialty Eyecare Group in Seattle.

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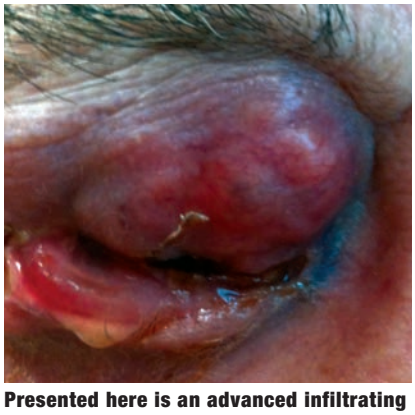
Don't Be STUMPED by These LUMPS and BUMPS

Most eyelid lesions are benign, but some can lead to severe clinical outcomes if not caught early. **By Rodney Bendure, OD, and Jackie Burress, OD**

The vast majority of eyelid lesions encountered in the typical optometry practice are benign.[1] However, it is important clinicians are able to identify lesions capable of infiltration, tissue destruction and metastasis. To start, clinicians must appreciate the basic anatomy of the eyelid. At only 0.7mm to 0.8mm, the eyelid is the thinnest skin on the human body.[2] Yet, it contains all the components of skin on other areas except a layer of subcutaneous fat. Beginning externally and working posteriorly, we first encounter the epidermis, which contains several layers of cells including keratinocytes, melanocytes, Langerhans cells and Merkel cells. Commencing at the melanin-containing basal cell layer, epithelial cells differentiate and migrate toward the skin surface, eventually losing their melanin granules, flattening and producing keratin. The underlying dermis is comprised of connective tissue, nerves, blood vessels and lymphatics. Deeper, you will find the orbicularis muscle and tarsal plate. Finally, the palpebral conjunctiva covers the posterior surface of the eyelid, abutting the globe. Adnexal structures, including glands and hair follicles, are located in the dermis and tarsal plate.[1]



Presented here is an advanced infiltrating eyelid malignancy.

Physical Characteristics

Specialists use a number of terms to describe the presentation of a particular lesion. Knowing these terms will help clinicians better clas-

Release Date: April 2017
Expiration Date: April 15, 2020
Goal Statement: Although the majority of lesions present on the eyelids are benign, the identification and diagnosis of lesions that are cause for concern are imperative to avoid adverse clinical outcomes. This course provides a comprehensive overview of the identification of eyelid lesions and the treatment options for each.
Faculty/Editorial Board: Rodney Bendure, OD, and Jackie Burress, OD

Credit Statement: This course is COPE approved for 2 hours of CE credit. Course ID is **53200-AS**. Check with your local state licensing board to see if this counts toward your CE requirement for relicensure.
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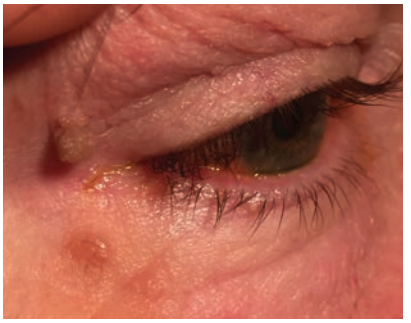
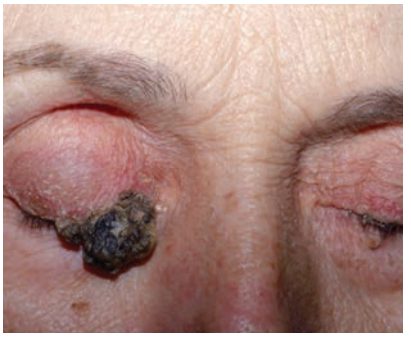


This superior lesion is a typical squamous papilloma. The inferior lesion is a junctional nevus.

sify and more accurately convey lesion characteristics to the pathologist. First, the term *tumor* does not necessarily describe a cancer. Rather, it is a general term for an area of swollen tissue. *Neoplasia*, likewise, is a general term describing the abnormal growth of tissue, be it benign (noninvasive) or malignant (likely to spread aggressively and metastasize).[3] *Ulceration* refers to a loss of epithelial tissue. *Hyperkeratosis* indicates the increased production of keratin, often noted clinically as scaling. *Induration* is seen as redness and swelling of a lesion. *Crusting* is dried exudate on the skin surface.[1]

At the microscopic level, the pathologist may describe *atypia*, or an abnormality of an individual cell, whereas *dysplasia* denotes a change in the size, shape and organization of the cellular structure of a tissue.[1]



An example of advanced seborrheic keratosis.

Learn the Lingo

With all the terms used to describe neoplasms, it's not surprising that a lot of clinicians get lost in the milieu. Brush up on these terms:

Neoplasm: A new growth. Essentially, this term grossly defines a mass of tissue that has outgrown the surrounding tissues.

Tumor: A general medical term historically used to describe any area of swollen tissue, including those caused by inflammation, hemorrhage or edema. This term is often used interchangeably with neoplasm, though its connotation may be worse.

Benign: Neoplasms that have been deemed relatively innocent by clinical and microscopic evaluation, and are unlikely to spread to other sites. These can be excised and carry a good prognosis, although they can cause local tissue destruction if left untreated.

Malignant: All malignancies are cancers. All cancers are malignancies. However, all tumors and neoplasms are not cancers or malignancies. To use the term malignant or cancer means that the lesion has tendency to spread to and undermine neighboring tissues as well as to metastasize (spread to distant sites). Therefore, malignant tumors carry the potential for early mortality.

Cancer: A malignant neoplasm.

Adenoma: Benign epithelial neoplasm derived from a gland.

Papilloma: Benign epithelial neoplasm which produces finger-like fronds.

Carcinoma: Malignant neoplasm derived from epithelial cells (any epithelial cell, not just skin).

Squamous cell carcinoma: A carcinoma (malignant neoplasm), derived from stratified squamous epithelium.

Adenocarcinoma: A malignant lesion comprised of epithelial cells (carcinoma), which grow in a glandular pattern (adeno).

Hamartoma: A mass of disorganized tissue comprised of cells native to the host organ. An example would be an iris Lisch nodule composed of melanocytes.

Choristoma: A congenital, benign mass of normal tissue located in non-native tissue. An example would be a limbal dermoid containing fat, connective tissue and epidermal appendages.

Clinically, a number of additional terms are used to describe the shape and consistency of a lesion to help differentiate the etiology. A *cyst* is a nodule lined with epithelial tissue and filled with a material that is fluid to near solid in consistency. *Bullae* are large, fluid-filled cysts. *Pustules* are smaller cysts less than a centimeter in size. *Vesicles* are even smaller fluid-filled cysts, generally less than half a centimeter in diameter.[1]

Macule refers to an area of flat epidermal tissue, usually less than a centimeter across, with color change only. Examples are freckles and vitiligo. *Plaques* are similar, but larger (2cm or more) and slightly elevated. A *papule* is a solid lump less than a centimeter in size. *Nodules* are essentially just larger papules.[1]

Examination

A thorough lesion exam always begins with a detailed history. The patient should be queried regarding UV exposure, smoking, immunosuppression and history of cancer and radiation therapy. Lesion-specific questions such as the length of symptoms, rate of growth, bleeding, ulceration, color changes and alteration of tissue such as loss of lashes should be addressed.

During the exam, clinicians should document a detailed description of each lesion's characteristics.

ABCs of Skin Lesions

While no hard and fast rules exist, certain characteristics provide clinicians with clues as to the nature of skin neoplasms. These rules, easily remembered using the mnemonic ABCDE are described in detail here:

Asymmetry: If you draw a line through a benign lesion, both halves are typically symmetrical.

Borders: Benign lesions have regular borders.

Color: Variations in color in a single lesion raise suspicion of malignancy.

Diameter: Lesions larger than 6mm diameter are suspicious of malignancy.

Evolution: Growth, bleeding, crusting, loss of lashes or changes in color increase suspicion of malignancy.

In particular, record lesion size, location, pigmentation, ulceration, loss of normal eyelid architecture and consistency—whether fleshy or firm, freely mobile or affixed to underlying tissues. Take time to palpate the lesion to assess these characteristics. In addition, photographs are an important part of your documentation. External photography can be accomplished using a slit lamp camera, fundus camera with anterior segment features or even a smart device. It is especially helpful to have a metric ruler near the lesion for reference. A photography tip—don't use excessive illumination, as it can wash out the lesion.

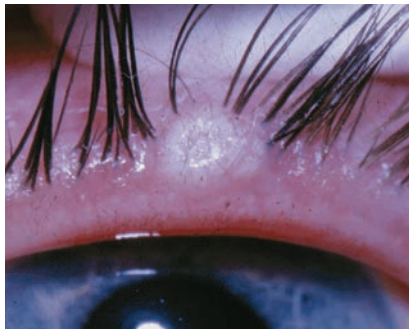


Photo: Cogan Collection, NEI/NIH

This is a typical lesion seen with molluscum contagiosum.

Tumor Classification

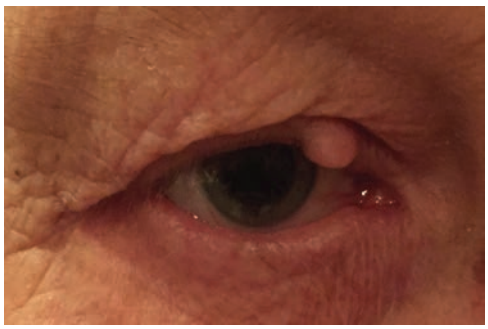
Eyelid tumors, like neoplasms in other areas of the body, are classified by their cell origin. Many clinicians find it useful to categorize eyelid lesions as either inflammatory (e.g., chalazion), infectious (e.g., hordeolum) or neoplastic. Neoplasms can further be described by their oncogenic potential, whether benign, premalignant or malignant.

Benign Tumors

Benign lid lesions are by far the most prevalent form of neoplasms seen in eye care, accounting for more than 80% of lid lesions.[8] Epithelial tumors are the most common type of eyelid neoplasms; these include papillomas, seborrheic keratoses, inclusion cysts and many more.[9] A thorough history and examination of the lid lesion can often result in accurate diagnosis.

Squamous papilloma. Far and away the most common benign epithelial eyelid tumor, this arises as an excessive growth of the squamous epithelium. It is characterized as either a sessile (flat) or pedunculated (skin tag) growth with an oft-keratinized surface. This slow-growing tumor is common in middle-aged and elderly patients and often presents as multiple lesions. Squamous papilloma is treated by simple excision at the lesion base, cryotherapy, or laser or chemical ablation. Prognosis is excellent, though patients often develop additional papillomas with age.[1,10]

Seborrheic keratosis. This is another very common slow-growing, benign epithelial tumor. It is typically described as having a greasy, "stuck-on" appearance.



Shown here is an epidermal inclusion cyst.

Affecting middle-aged and elderly individuals, these benign lesions are well-demarcated, elevated plaques with variable levels of pigmentation. They tend to enlarge and darken gradually over time. Excision with electrocautery or cryotherapy will generally eliminate recurrence. Prognosis is excellent.[1,10] However, a sudden increase in the size or number of lesions can occur in individuals with occult malignancies and should therefore raise suspicion.[11]

Cutaneous horns. These are somewhat non-specific hyperkeratotic lesions, which may be associated with a variety of both benign and malignant eyelid lesions, including seborrheic keratosis, verruca vulgaris, basal cell carcinoma (BCC) or squamous cell carcinoma (SCC). Thus, this is a clinically descriptive term and not a specific lesion type. Treatment is excision requiring pathologic evaluation.[10] Because the horn is an extension of an undetermined underlying tumor, biopsy requires excision of epidermal tissue beneath the lesion as well.[11]

Epidermal inclusion cysts. These arise from entrapment (usually traumatic) of epidermal tissue within the dermis. They appear as discrete white or light yellow, firm, solid, slow-growing cysts. Treatment is by excision, though the entire cyst wall must be removed to prevent recurrence. Prognosis is excellent.[10,11]

Molluscum contagiosum. A

Excisional Biopsy Protocols

Lesions with clearly benign characteristics (e.g., squamous papilloma, seborrheic keratosis, verruca vulgaris) can be excised in office and should be sent for pathologic confirmation. Benign lesions are characterized by even coloration, well-defined regular borders, lack of ulceration, no induration, a history of slow growth and a maintenance of normal skin structures such as lashes and glands.[1] Minor surgical procedures to remove such lesions can be performed by optometrists in Oklahoma, Kentucky, Louisiana and Tennessee.[4-7] Here's how to perform an excisional lesion removal:

Benign lesion removal. To excise a benign lesion, you'll need a 3mL syringe with a one-half inch 27- or 30-gauge needle to inject a small amount of 1% to 2% lidocaine with epinephrine 1:100,000 at the base of the lesion; we often find patients tolerate simple excision without anesthesia, especially for pedunculated masses. Just prior to anesthetizing the base, the area should be sterilized with an ophthalmic betadine swab.

Once the area is numb, the mass is grasped with toothed forceps, pulled slightly away from its base and snipped free. Light pressure for a few minutes with a small gauze pad usually stops any bleeding, but a disposable thermal cautery unit comes in handy in case bleeding continues. Place the specimen in a formalin container suitable for transport to the laboratory for histologic evaluation. Prior to releasing the patient, apply a prophylactic antibiotic ointment such as erythromycin or Polysporin and advise the patient to keep the area clean and dry and to apply the ointment three times daily for three days.

Place the specimen in formalin to transport to the laboratory.

Malignant lesion removal. Lesions suspicious for malignancy should be promptly referred to an oculoplastics specialist for evaluation, biopsy and reconstruction if needed. Patients may be apprehensive as to what they can expect when referred for lesion removal. It is incumbent upon the referring practitioner to be familiar with the possible treatment techniques to allay any fears the patient may have. A number of alternative methods may be employed for the removal or destruction of eyelid tumors, including chemotherapy, radiation or photodynamic therapy.[1,10] However, in our experience complete excisional biopsy is far and away the most common treatment method used by our oculoplastics specialists.

For large or aggressive lesions, the preferred method for removal is under frozen section, namely Mohs micrographic surgery.[19,26,27] This procedure is particularly useful in periocular cutaneous tumor removal because it causes the least collateral tissue damage while ensuring complete tumor excision.[19,26-28] In addition, Mohs procedure has a nearly 100% success rate (97.5% overall, 99.4% for primary lesions and 92.4% for recurrent lesions).[19,29,30] Mohs surgery works especially well with basal cell carcinoma and squamous cell carcinoma because these types of tumors have a continuous growth pattern as opposed to tumor types with "skip areas" such as sebaceous adenocarcinomas.[19]

Eyelid repair and reconstruction. Repair of the involved eyelid requires special techniques. If less than one-third of the full thickness of the eyelid is removed, a simple direct closure may be performed. For larger defects, more elaborate lid reconstruction procedures using tissues harvested from adjacent areas may be needed.[1]

poxvirus infection, this is characterized by small, typically 1mm to 2mm, flesh-colored papules with an often-umbilicated center. These are more common in the very young and the immunocompromised. Lid margin lesions can cause a follicular conjunctivitis. These lesions are spread by skin-to-skin contact and regress spontaneously except in the immunocompromised, where they can develop into disfiguring lesions. Molluscum contagiosum can be removed if desired by excision, curettage, electrodesiccation or cryotherapy. The prognosis is good in healthy people, and the risk of transmission is low.[1,10]

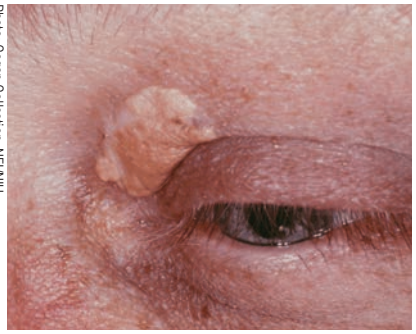


Photo: Cogan Collection, NEI/NIH

Shown here is an example of an xanthelasma.

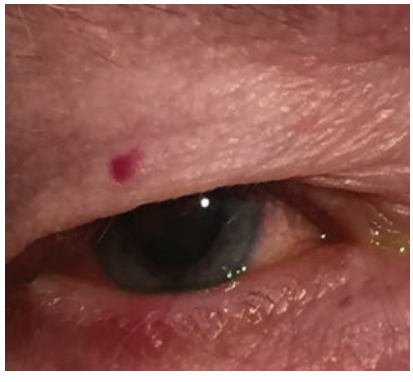
Verruca vulgaris. Also known as a viral wart, this is an epidermal growth caused by the human papilloma virus, typically types VI or XI. Two forms exist: filiform, which are also called digitate because they project in a finger-like fashion from their base, and plana, which are flat. Beginning as small papules slightly lighter than the surrounding skin, they tend to darken and become hyperkeratotic with time. While benign, eyelid margin warts can cause punctate keratitis or even corneal pannus.[12] Observation is often adequate, as these lesions tend to eventually outgrow their blood

supply and spontaneously involute, but may be removed by excision, cryotherapy or chemical cautery if eye irritation ensues or for cosmetic reasons.[13]

Xanthelasma. This usually presents on the eyelids as yellow plaques filled with lipid-laden macrophages. These arise after the age of 50 and should prompt suspicion of a lipoprotein disorder when present in patients younger than this.[1,10] Excision, electrodissection, laser treatment and application of trichloroacetic acid all may be employed with excellent results. However, the lesions tend to recur about 50% of the time.[1,10]

Syringoma. This benign adnexal tumor appears in multiple, discrete, skin-colored lesions measuring from 1mm to 2mm on the lower eyelids and cheeks of some females beginning in puberty. Heredity appears to play some role in the development of this condition. These lesions are benign adenomas of eccrine ducts. Prognosis is good, although numerous excisions or electrocautery sessions may be required due to the number of lesions; recurrence is common.[1,10]

Eccrine hydrocystomas. Also known as sudoriferous cysts, these arise from sweat glands along the eyelid margin. These fluid-filled cysts appear translucent, though thicker-skinned lesions may appear bluish. They may be treated by cyst drainage, but sometimes require removal of the entire cyst wall if recurrent.[10,11]



A hemangioma is present on the upper eyelid.

Apocrine hydrocystomas. Commonly called cystoadenomas, these resemble sudoriferous cysts except their contents are creamy white. Treatment is by excision.[11]

Pilomatricoma. This arises from the germinal matrix of a hair bulb and is thus another adnexal tumor. This benign tumor is more common in young females.[1] It presents as a hard, indurated nodule. The body reacts in granulomatous fashion due to calcium deposition. Excision is the treatment of choice.[1]

Trichoepithelioma. This is noteworthy because its appearance is sometimes confused with basal cell carcinoma. These lesions are more common in males, usually arising during puberty.[10,14,15] These small skin-colored tumors are benign skin appendage growths. Treatment is by excision. Since these cannot be clinically differentiated from basal cell carcinoma by physical examination alone, pathologic and immunohistochemical evaluation is warranted.[10,14,15]

Freckles or ***ephelis.*** These are small, flat brown skin lesions appearing most commonly on sun-exposed skin, including the eyelids. These are merely a hyperpigmentation of the basal cell layer, with no further penetration into the epidermis or dermis. These may lighten in the absence of sun exposure and darken upon re-exposure. The prognosis with these lesions is very good.[1,9] No treatment is necessary, although avoidance of ultraviolet light and use of sunscreen can reduce pigmentation.[11]

Nevi. These are small macules of hyperpigmented melanocytic cells located in the deep epidermis or dermis. These acquired lesions arise in childhood and reach full size by adulthood, darken upon ultraviolet light exposure and tend to involute by the sixth decade.[1,10] In adults, they tend to be asymptomatic and stable in appearance. These lesions tend to be one of three main types:[1,10]

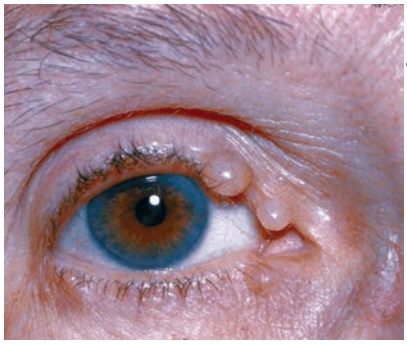


Photo: Cogan Collection, NEI/NIH

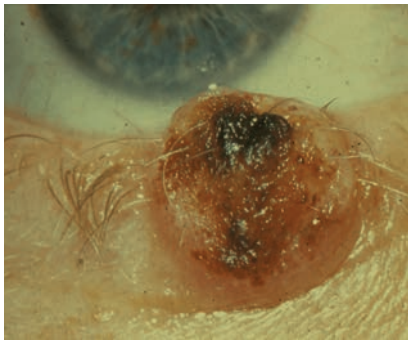
Seen here are hydrocystomas.

- *Junctional nevi* are round, flat and less than 1cm in diameter. Usually, these are tan to brown in color and have regular borders.
- *Compound nevi* are elevated, round, dark brown lesions, which often have hair growing in them.
- *Dermal nevi* are elevated nodules with variable pigmentation, sometimes skin-colored. These do not tend to involute with age.[1,10]

Nevi carry a relatively good prognosis with a low potential for malignant transformation.[1,16,17] In fact, the annual rates of transformation of a melanocytic nevus are only one in 200,000 for younger individuals and one in 33,000 for the elderly.[18] Changes in size, color, irregular borders or bleeding are indications for histologic biopsy.[1,10]

Milia. These are small superficial white papules 1mm to 4mm in size. They represent keratin-filled pilosebaceous units. Causes include idiopathic, trauma, infection, radiotherapy or bulbous diseases. Treatment is by expression, electrodessication or excision.[1,11]

Photo: Cogan Collection, NEI/NIH

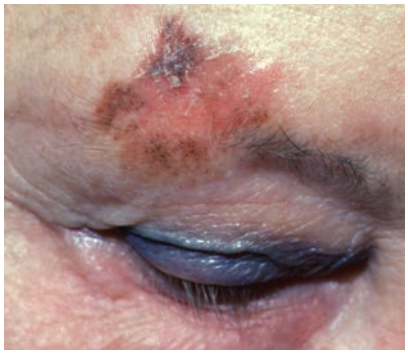


Seen here is an example of keratoacanthoma.

Hemanigiomas. These are elevated red lesions comprised of blood vessels. Three types of these vascular tumors exist, two being congenital and the other acquired:

- *Capillary hemangiomas*, often referred to as strawberry nevi, are one of the most common tumors in infancy. These are known to blanch with pressure and swell with crying.[1,10]
- *Cavernous hemangiomas*, also seen in infancy, are located deeper in dermal tissues. However, these do not blanch with pressure or swell with crying.[1,10] Both congenital forms tend to resolve spontaneously over time.
- *Cherry hemangiomas* can arise rapidly in middle age and older, but are typically associated with similar lesions on other body parts. They carry an excellent prognosis and can be excised for cosmetic reasons.[1,10]

Photo: VisualDx



Pictured above is an example of a lentigo maligna.

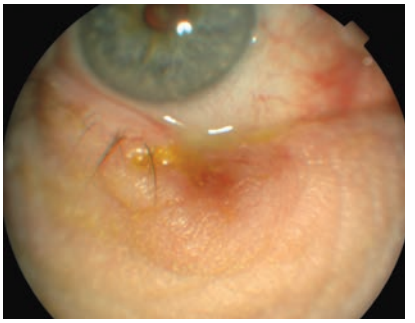
Pyogenic granuloma. In spite of its name, it is neither pyogenic nor a granuloma and presents in the form of a pinkish red mass that arises after trauma or surgery. These rapidly growing, delicate lesions are comprised of blood vessels and fibroblasts and readily bleed with minor insult. Treatment is by complete excision.[11]

Pre-Malignant Tumors

Some lesions are precursors to malignant lesions. These must be monitored closely and referred if signs of malignant transformation occur.

Keratoacanthoma. This presents as a dome-shaped nodule with a keratin-filled core on the sun-exposed skin of individuals over the age of 50.[10,11] It usually develops rapidly over weeks, only to regress spontaneously after a few months.[10] Those with fair skin, chronic sun exposure and those undergoing immunosuppressive therapy are at risk for keratoacanthoma.[1] Some argument exists as to whether these may represent some variation of squamous cell carcinoma. These tend to be more common in males, with a 2:1 predilection. Treatment is by Mohs surgery with pathologic laboratory evaluation. This lesion carries a generally good prognosis.[10] Presence of multiple neoplasms may signify underlying systemic cancer.[11]

Actinic Keratosis. Formerly known as solar keratosis, this is a slow growing precancerous cutaneous lesion. Occurring on sun-exposed areas of the skin, including the eyelids, these may be caused by ultraviolet radiation. They are common in fair-skinned individuals and are most often noted on the backs of the hands and forehead. These solitary or small-grouped, flat, scaly plaques may occasionally transform into squamous cell carcinoma, though when they do, they are typically low-grade (i.e., they have low mitotic activity).[1,10] There is some disagreement in the literature about the likelihood of malignant transformation, with research suggesting risks from 0.1% to 20%, depending on the literature.[10,11]



A basal cell carcinoma is depicted here.

Lentigo Maligna. Believed to be caused by sun exposure, these flat brown-to-black macules occur in older individuals, with a median age of occurrence at 65.[1,10] Their appearance has been described as looking like a stain on the skin.[10] Slow growth and irregular borders are typical. Nodular thickening and variations in color suggest malignant transformation. They should be excised and sent for pathologic laboratory evaluation. Prognosis is excellent so long as they are excised prior to transformation into melanoma.[1,10]

Malignant Tumors

While malignant tumors are seen much less frequently than benign neoplasms, it is imperative to quickly recognize the lesions that warrant prompt medical intervention. Here we discuss the eyelid malignancies clinicians are most likely to encounter:

Basal cell carcinoma. This is the most common type of skin cancer on the eyelid, accounting for 90% to 95% of all malignant eyelid tumors, and is the most common human malignancy overall.[1,19,20]

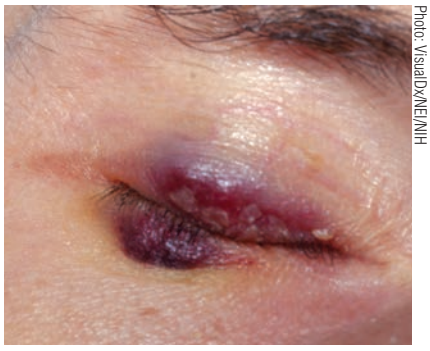


Photo: VisualDx/NEI/NIH

Kaposi's sarcoma.

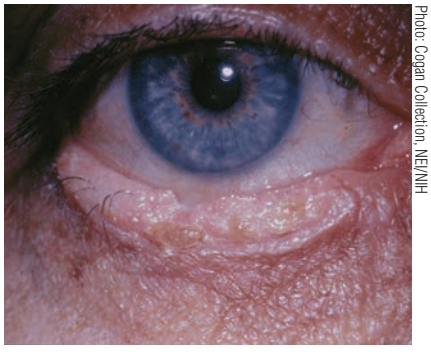


Photo: Cogan Collection, NEI/NIH

Squamous cell carcinoma.

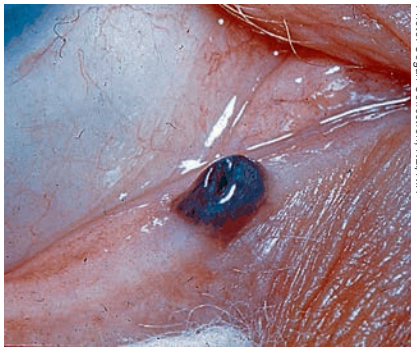


Photo: Cogan Collection, NEI/NIH

Melanoma of punctum.

Though it rarely metastasizes, BCC can be locally invasive, even invading the orbit. In order of prevalence, BCC most often occurs on the lower lid, followed by the medial canthus, upper eyelid and lateral canthus.[1,10,21] Variations in UV exposure of the different eyelid locations explains these prevalences.[22] In parallel, the highest risk for orbital and sinus invasion involves lesions of the medial canthal area.[1,10,21] Signs of orbital invasion include a firm mass that may cause displacement of the globe or restrictive strabismus.[23] These signs warrant urgent diagnostic imaging. Incidence is approximately 500 to 1000 per 100,000, and men are affected more than women. Those with fair skin and a history of chronic sun exposure are likely victims.[10]

These lesions appear as firm, round-to-oval bumps on the skin surface (i.e., nodular form) that, as they grow, develop pearly, raised borders with telangiectasia and a central ulcerated core (i.e., noduloulcerative form). A third subset, sclerosing or morpheaform BCC, is less well defined and thus more difficult to diagnose, as it tends to spread beneath the skin surface.[1,21] Prognosis is good when the lesion is completely excised, though any tumor remnants left behind tend to be agressive.[1] Mohs surgery or frozen sections should be employed to ensure complete excision. Surgical reconstruction may be required depending on the size of the lesion. Radiation treatment may be employed only in cases of poor surgical candidates, while chemical agents such as imiquimod may only be used for lesions not located on the eyelid margin.[10]

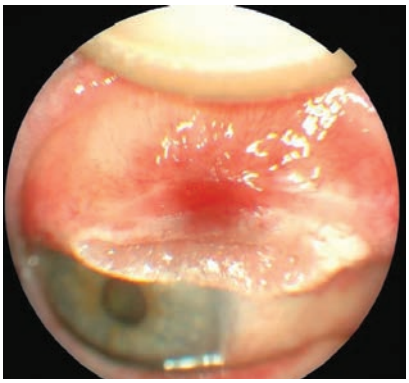
Squamous cell carcinoma. This is far less common than BCC, with an incidence of 12 per 100,000 white males.[10] It is about half as common in white females and about a tenth as common in blacks. UV light and exposure to ionizing radiation cause malignant transformation of epidermal squamous cells.[10,11] SCC most often appears on the lower eyelid, especially the eyelid margin.[1,10] In fact, while far less prevalent than BCC, SCC is more common on the upper eyelid and lateral canthus.[11]

These lesions can take on many forms. Like BCC, SCC appears in multiple presentations. These include a nodular presentation with a firm hyperkeratotic appearance, an ulcerating presentation with distinct, inflamed borders and central crater, and a buried, aggressive form with a superficial cutaneous horn.[1,10] Though less common than BCC, SCC carries more risk as it is more aggressive and spreads to regional lymph nodes in 20% of cases.[1] It has also been known to spread intracranially by growing along nerves, including the trigeminal, oculomotor and facial nerves.[1,24,25] Fortunately, the majority of lesions are not aggressive and can be treated by surgical excision, preferably by frozen section or Mohs surgery. Some may be treated with topical imiquimod cream if they are not located on the eyelid margin.[10]

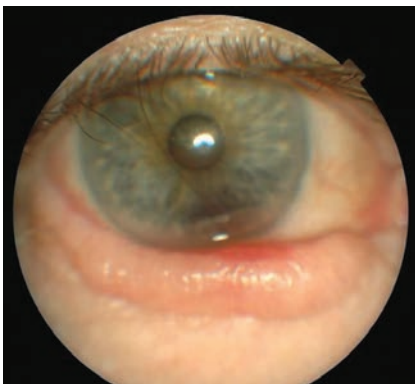
Sebaceous adenocarcinomas (SGC). Although rare, these are highly malignant and potentially lethal (5% to 10% mortality).[1] Arising from the sebaceous glands of the eyelid, they are sometimes initially mistaken for chalazia.[1] One of the few malignant eyelid tumors more common in females, this lesion usually arises from a dysplastic meibomian gland or gland of Zeiss in patients over the age of 50.[1,11] SGC has a predilection for the upper eyelid, likely due to the higher number of meibomian glands relative to the rest of the eye.[1,11] The Wills Oculoplastics Manual describes sebaceous adenocarcinoma as "the Great Masquerader." Thus, any chronic blepharitis or recalcitrant chalazion in a middle aged or elderly woman should evoke suspicion.

Nodular SGC. This presents as a hard mass in the upper eyelid, often containing yellowish lipid material, which is highly characteristic.[1]

Spreading SGC. This is less obvious, infiltrating through the dermis and causing a diffuse thickening of the lid and loss of lashes.[1] Suspicion should prompt referral for biopsy, which in and of itself poses



Pictured here is the reconstruction of an eyelid after excision and Hughes flap.



Shown above is the reconstruction of an eyelid with basal cell carcimona.

some concern, as special staining and treatment of samples must be performed, or the diagnosis could be incorrect. The surgeon must alert the pathologist as to the suspected etiology. Wide excision with controlled margins is necessary because this aggressive tumor sometimes has skip areas and could recur or spread without appropriate treatment.[9,11] Therefore, vigilant follow-up is warranted. If diagnosis of SGC is confirmed, the patient will need to be seen by their primary care doctor immediately to rule out metastases.[9,11]

Malignant melanoma. This is not common. In fact, it comprises only about 1% of eyelid malignancies. Despite the lower incidence, melanoma is the cause of over 60% of deaths from all cutaneous cancers.[11] Whites, especially those with a history of severe sunburns, are at a higher risk. Many are identified after a patient notices a change in color or increased size of a long-standing mole.[10] Four subtypes exist:

• *Lentigo malignant melanoma*, which arises from lentigo maligna, may exist for a number of years as a pigmented macule up to several centimeters in diameter with irregular borders.

• *Superficial spreading melanoma* is smaller and mildly elevated. As it begins to transform and invade deeper tissues, the lesion appearance changes, becoming multi-nodular and indurated.

• *Acral lentiginous melanoma* occurs mostly on nonocular tissues.

• *Nodular melanoma* is the most common form affecting the eyelids. It presents variably as a darkly pigmented to amelanotic nodule, which grows rapidly with notable bleeding and ulceration.[11] These dangerous lesions often spread despite aggressive excision efforts with controlled surgical margins. Sentinel lymph node (nearest the lesion) biopsy is required due to the propensity to spread via lymphatics. These malignancies have a high rate of distant metastasis, which may occur years after the initial lesion. The eight-year survival rate is 33% (greater than 3.6mm) to 93% (less than 0.76mm) depending on the tumor depth.[10] Careful follow-up care with their primary care doctor is needed long-term for these patients.

Kaposi's sarcoma of the eyelid. This is rare, but when present likely signifies an immunocompromised state. These vascular tumors appear as red-to-purple elevations on the skin surface. They can be removed by excision, cryotherapy or intralesional chemotherapeutic agents. Large lesions may require radiation. The presence of these lesions in an HIV-positive patient signifies an advanced disease state (AIDS), hence short-term mortality is high.[10]

Merkel cell carcinomas. These are rare, highly aggressive tumors affecting older individuals. They arise from sensory touch receptors within the eyelid. Characteristic appearance is a slightly purplish, well-defined nodule most commonly in the upper eyelid with no ulceration. At the time of presentation, it is estimated that 50% have metastasized. Treatment is excision followed by chemotherapy or radiation.[1]

Eyelid neoplasms are a common entity encountered in optometric practice. While the vast majority of these neoplasms are benign, it is of the utmost importance to recognize any potential malignancy. The management of these malignancies requires prompt referral to oculoplastics for biopsy and reconstruction; early intervention minimizes the amount of collateral tissue damage, resulting in easier reconstruction. This allows for retention of normal eyelid function, preservation of the globe, a functional lacrimal system and a pleasing cosmetic outcome.[2] Thankfully, a thorough case history and physical examination can easily help the primary care optometrist decide when referral is needed and avert adverse ocular and systemic outcomes related to malignant eyelid neoplasm. ■

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1. The average thickness of the human eyelid is approximately:
a. 1.0mm.
b. 2.0mm.
c. 0.3mm.
d. 0.75mm.

2. The term cancer:
a. Is a general term for any abnormal skin growth.
b. Denotes a malignant lesion.
c. Is synonymous with the term "neoplasm."
d. Describes a lesion with low potential for metastasis.

3. Signs suggestive of malignancy are:
a. Asymmetry.
b. Loss of eyelashes.
c. Lesion diameter less than 6mm.
d. Both a and b.

4. Large numbers or rapid growth of these typically benign "stuck on" lesions is suggestive of systemic malignancy:
a. Squamous papilloma.
b. Actinic keratosis.
c. Seborrheic keratosis.
d. Syringoma.

5. Which of the following is true regarding nevi?
a. Three types exist: junctional, compound and bi-directional.
b. Temporary changes in size, color and shape are common.
c. Nevi are not capable of darkening with UV exposure.
d. Nevi carry a low risk of malignant transformation.

6. Suspicious eyelid lesions should be:
a. Excised in office.
b. Photodocumented.
c. Sent for biopsy and pathologic evaluation.
d. Both b and c.

7. Signs of orbital invasion include:
a. Proptosis.
b. Strabismus.
c. Follicular conjunctivitis.
d. Both a and b.

8. Basal cell carcinoma accounts for what percentage of all malignant eyelid neoplasms?
a. 50%.
b. 75%.
c. 20%.
d. 90%.

9. Basal cell carcinoma has a highest prevalence for:
a. Lower eyelid.
b. Medial canthus.
c. Upper eyelid.
d. Lateral canthus.

10. Which basal cell carcinoma location carries the highest risk for orbital and sinus invasion?
a. Lower eyelid.
b. Medial canthus.
c. Upper eyelid.
d. Lateral canthus.

11. Squamous cell carcinoma has a highest prevalence for:
a. Upper eyelid.
b. Lateral canthus.
c. Lower eyelid.
d. Medial canthus.

12. Which of the following lesions is considered a low-grade squamous cell carcinoma?
a. Xanthelasma.
b. Squamous cell papilloma.
c. Pyogenic granuloma.
d. Keratoacanthoma.

13. Which of the following lesions, if found on a patient younger than 50, should prompt laboratory serum lipid evaluation?
a. Milia.
b. Xanthelasma.
c. Epidermal inclusion cyst.
d. Pyogenic granuloma.

14. A chronic, hard lump filled with yellow material in the upper eyelid of an older female patient should raise suspicion of which of the following neoplasms?
a. Keratoacanthoma.
b. Verruca vulgaris.

OSC QUIZ

c. Sebaceous cell carcinoma.
d. Lentigo maligna.

15. What is the treatment of choice for a cutaneous horn?
a. Warm compresses and eyelid hygiene.
b. Intralesional triamcinolone injection.
c. Application of a gentle ophthalmic antibiotic to soften the lesion.
d. Biopsy of the underlying cutaneous tissue.

16. Malignant melanoma comprises what percentage of malignant eyelid neoplasms?
a. 1%.
b. 15%.
c. 10%.
d. 5%.

17. Nodular malignant melanoma presents as:
a. A darkly pigmented lesion.
b. A lightly pigmented lesion.
c. A variably pigmented lesion.
d. Both b and c.

18. Malignant melanoma is the cause of what percentage of deaths due to cutaneous neoplasms?
a. 15%.
b. 90%.
c. 75%.
d. 60%.

19. Presence of Kaposi's sarcoma suggests which of the following systemic conditions?
a. Immunocompromised state.
b. HIV positive status with normal CD4 cell count.
c. Neurofibromatosis type I.
d. Both b and c.

20. What is the treatment of choice for Merkel cell carcinoma?
a. Electrocautery.
b. Excision followed by adjuvant chemotherapy or radiation.
c. Topical imiquimod.
d. Photodynamic therapy.

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3. Ⓐ Ⓑ Ⓒ Ⓓ
4. Ⓐ Ⓑ Ⓒ Ⓓ
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18. Ⓐ Ⓑ Ⓒ Ⓓ
19. Ⓐ Ⓑ Ⓒ Ⓓ
20. Ⓐ Ⓑ Ⓒ Ⓓ

Post-activity evaluation questions:

Rate how well the activity supported your achievement of these learning objectives:
1=Poor, 2=Fair, 3=Neutral, 4=Good, 5=Excellent

21. Improve my clinical ability to differentiate between benign, pre-malignant and malignant eyelid neoplasms ① ② ③ ④ ⑤
22. Become familiar with the key definitions related to neoplasms in general, and eyelid neoplasms specifically. ① ② ③ ④ ⑤
23. Increase skill in my examination and documentation abilities as they pertain to neoplasms of the eyelids. ① ② ③ ④ ⑤
24. Better know the best practices for performing excisional biopsy of eyelid lesions. ① ② ③ ④ ⑤
25. Increase my knowledge of the types of neoplasms within the benign, pre-malignant and malignant categories. ① ② ③ ④ ⑤
26. Improve my ability to communicate with patients about the nature of their eyelid lesions and any treatment needed. ① ② ③ ④ ⑤

Rate the quality of the material provided:
1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree

27. The content was evidence-based. ① ② ③ ④ ⑤
28. The content was balanced and free of bias. ① ② ③ ④ ⑤
29. The presentation was clear and effective. ① ② ③ ④ ⑤
30. Additional comments on this course:

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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 any fraudulent or improper means.

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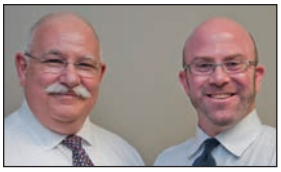

Low-Tech TBI Rehabilitation

Often, binasal occlusion with a small piece of tape can be a huge help for stroke and brain injury patients. **By Marc B. Taub, OD, MS, and Paul Harris, OD**

This is the fourth year we have been seeing patients onsite at several inpatient rehabilitation facilities. We started slowly and, with the support of Southern College of Optometry, grew the program annually. We now have a team of four doctors who see patients at several facilities, and we are busier than ever.

When we get the call to visit a patient in an inpatient rehabilitation facility, we never know what we are going to find when we walk in the room. Commonly, we encounter patients with field loss, visual inattention, diplopia or unexplained decreased vision. Our mission is to help the patient obtain clear, single binocular vision, which not only helps the patient, but also allows the doctors, therapists and even other patients to make the best use of their time while there.

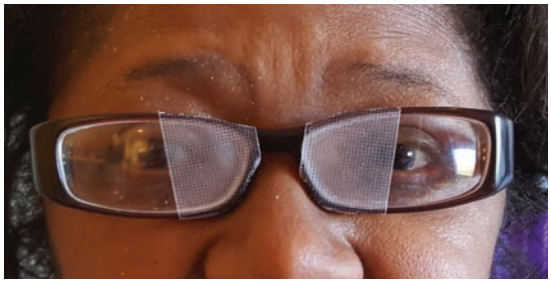

Fig. 1. Binasal occlusion helped this patient overcome a swimming sensation and get back to her rehabilitation following a stroke.

Go-to Treatment

Binasal occlusion is a staple treatment for many patients. Investigators show it can be beneficial for patients with esotropia, non-strabismic functional vision problems and amblyopia.[1] Research highlights binasal occlusion use in a patient with significant visual disturbances secondary to cerebral palsy, but little literature exists regarding its use for patients suffering a traumatic brain injury (TBI) or stroke.[1] One study demonstrates symptom and visual function improvements in a TBI patient undergoing vision therapy and using base-in prism.[3]

Binsasal occlusion is a type of sector occlusion that blocks the nasal portion of each lens to some degree. The practitioner can use virtually any kind of tape, but we prefer to use Transpore tape (3M), as it is not opaque. Some light can pass through, which stimulates the retina and helps keep the patient alert and oriented. To account for convergence when viewing at a close distance, we always tilt the occlusion so there is a smaller amount on the lower portion of the lens.

Binsasal Occlusion for TBI

Traumatic brain injury (TBI) is a major cause of death and disability worldwide.[4] The Centers for Disease Control estimates that TBIs account for 2.2 million emergency room visits, 280,000 hospitalizations and 50,000 deaths annually.[5] Changes in function following a TBI can be widespread and impact every single organ system, including the visual system. Aside from the obvious ocular injuries, after a brain injury many patients are unable to deal with the level of visual information they are receiving. They may complain of balance issues, light sensitivity, a swimming sensation and blurry or funny looking vision, to name only a few visual symptoms. Binasal occlusion reduces the amount of incoming stimulation, particularly blocking parts of the image seen by both eyes. Remember, the visual system receives information from both eyes' nasal visual field. In some TBI cases, the patient cannot process all of the data in real time, which results in the failure of the vision system to keep clear, single binocular vision. According to one study, "when the visual process is labored, the organization and integration of this portion of visual space may be the most demanding as far as maintaining comfortable and clear binocular, single vision. Modifying the input from the very core of this area may serve to relieve stress."[2] The following two cases demonstrate the benefit of binasal occlusion in the TBI population.

Case 1

A 62-year-old black female with a history of four strokes in the past several years presented, following her most recent stroke, complaining of swimming vision when she moved her head. Her occupational therapist was having trouble getting her to balance well and said the

patient preferred to be lying down or reclined in a chair. Both postures make rehabilitation problematic. The examination at the patient's bedside showed slightly decreased visual acuity with her current glasses, an intermittent alternating exotropia of about eight to 10 prism diopters at near and poor fixation, to the extent that she had trouble localizing and touching a target using her vision. She knew an issue existed and was particularly disturbed by the swimming sensation.

As this was not a case of double vision, my first inclination was to try binasal occlusion (*Figure 1*). Upon placement, the patient felt markedly better. When placing the occlusion for the first time, it's acceptable to guess the best location. We have the patient fixate on the practitioner's nose and place the tape just nasal of the pupillary margin. Then, we have the patient relax and engage with the surroundings. Some patients need more occlusion, others less. It's straightforward to remove and readjust the tape a few millimeters.

Since the patient was in the facility a few weeks, I stopped back to assess the treatment a few days later. While she was still suffering with balance issues, she was making progress, according to the therapist. I chose to leave the amount of occlusion in place for the time being and requested a follow up when she was transferred to outpatient care. She started vision therapy several weeks later and is showing wonderful progress every week. The occlusion was successfully removed at the start of the therapy process.

Case 2

A 65-year-old white male presented with a complaint of swimming vision at distance and near following a recent stroke. He was having trouble reading and watching TV. The examination showed excellent visual acuity, no restriction in eye movements and accurate localization of hand-eye coordination.

We placed the binasal occlusion and observed noticeable relaxation in the patient's body (*Figure 2*). He tried texting on his phone and looked at the TV's closed captioning and said his vision was not perfect, but more tolerable. We followed up a few days later, and the patient felt the occlusion was blocking his vision and was more annoying than helpful. We reduced the amount of occlusion, with positive feedback from the patient (*Figure 3*). He was seen several days later at the college and reported the swimming sensation was gone. The occlusion was removed and he was given several basic eye movement activities to perform several times daily. At follow up a month later, he once again reported no symptoms and performed well on a visual efficiency and processing evaluation.

Fig. 2. Although binasal occlusion improved this patient's vision, he felt it was more annoying than helpful.

Fig. 3. By reducing occlusion, we were able to eliminate the visual symptom without interrupting the patient's vision.

These cases highlight the immediate positive impact of binasal occlusion. This treatment need not be relegated to inpatient use, but can be of value to the patients in your chair. You will be surprised how often patients slip below the radar, if you ask them about concussion or stroke and the most common accompanying symptoms. You have a great opportunity to help your suffering patients—and all it takes is a little piece of tape. ■

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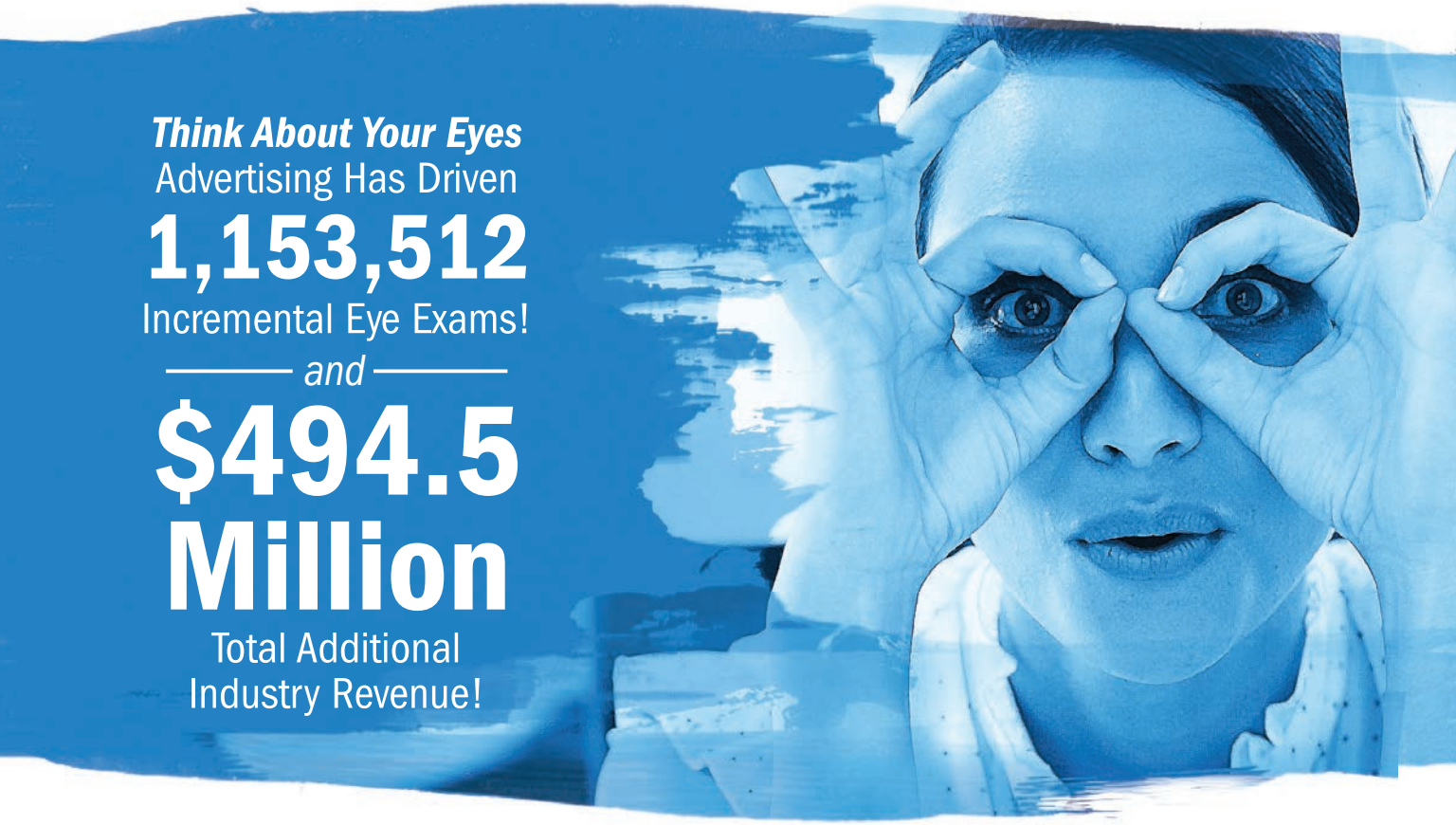

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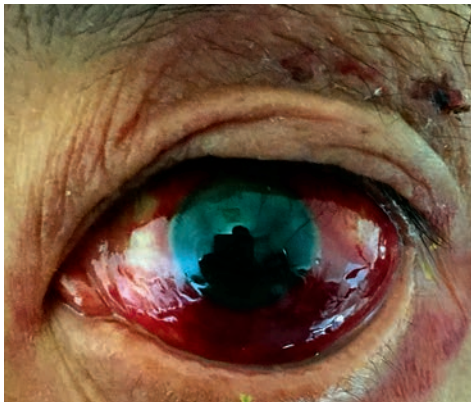
Imaging for Unilateral Proptosis

Clinical findings alone won't always be enough to make the diagnosis. Here's advice on radiologic testing and what it may reveal. **By Michael Trottini, OD, and Michael DelGiodice, OD**

Clinical evaluation of the orbit involves three critical steps: (1) taking a detailed history; (2) conducting a clinical exam of the extraocular muscles (EOMs), assessing resistance to retropulsion and performing exophthalmometry; and (3) performing imaging of the orbit and brain with computed tomography (CT) or magnetic resonance imaging (MRI). Acute symptoms of diplopia, vision loss, proptosis and hyperemia are often associated with inflammation, infection, vascular anomalies and, occasionally, tumors. Each of these conditions will be presented in a stepwise fashion based on presenting factors.



This is a subconjunctival heme from a gunshot injury.

Scenario 1: Acute painful proptosis and hemorrhage. A patient with severe subconjunctival hemorrhage and chemosis can be a diagnostic challenge. Although most cases present in the setting of trauma, post-op status and prolonged anticoagulation therapy are risk factors.

The most important condition to consider in this setting is retrobulbar hemorrhage. If a history of trauma exists, the patient should be evaluated for an open-globe injury. Evidence of rupture warrants application of a plastic shield to the affected eye and immediate transport to the closest emergency department (ED) for surgical repair. In the setting of a closed-globe injury, measure intraocular pressure and evaluate EOMs and posterior segment to determine the extent of retro-orbital involvement and risk of optic nerve compression or avulsion. Following the clinical examination, urgent emergent non-contrast orbital CT is the most appropriate modality to assess for structural damage.

Scenario 2: Acute or subacute painful proptosis, chemosis and diplopia. The three most common conditions that present similarly include orbital inflammatory syndrome (OIS), orbital cellulitis and arteriovenous malformation (AVM). Infectious causes of unilateral painful proptosis are uncommon and include cellulitis and mucormycosis.

• *OIS.* This is a disorder of the orbit characterized by a polymorphous lymphoid infiltrate with varying degrees of fibrosis.[1] In a review, the most common orbital component affected was intraconal fat, followed by lacrimal gland enlargement and EOM restriction. To determine the level of soft tissue involvement, it's best to evaluate OIS with contrast-enhanced orbital MRI.[2]

OIS is associated with autoimmune diseases such as Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis, granulomatosis with polyangiitis and sarcoidosis. The first-line therapy for OIS is systemic corticosteroids; 75% of cases show improvement within 24 to 48 hours. An initial dose of 60mg to 80mg of oral prednisone should be started after MRI is used to discount alternative etiologies such as orbital cellulitis and lymphoma.[3]

• *Orbital cellulitis.* The clinical characteristics of this condition include fever and antecedent sinusitis, periorbital swelling with proptosis, conjunctival hyperemia with chemosis and EOM restriction. Management involves emergent referral to the ED for immediate intravenous broad-spectrum antibiotics including a third-generation cephalosporin and the narrow-spectrum penicillin class antibiotic flucloxacillin, which are effective against *Staphylococcus aureus*, *Staphylococcus epidermidis*, Streptococci and *Haemophilus* species.

Next, order non-contrast CT of the brain and orbits to demonstrate an infective source in order to obtain cultures, evaluate for intracranial extension and assess the need for surgical drainage. Surgery is indicated for significant sinus disease, including orbital or subperiosteal abscess.[4]

• *Mucormycosis.* This is an aggressive opportunistic fungal

infection that enters through the paranasal sinus mucosa and travels to the orbital apex, where it can breach the intracranial space. A patient with acute symptoms should undergo emergent referral to the ED for non-contrast CT of the head, orbit and sinuses to assess the extent of the disease process followed by biopsies of involved tissues and sinus mucosal secretions. Those with less aggressive signs can be managed on an outpatient basis with contrast-enhanced MRI of the sinuses, orbit and brain. Early MRI findings include lack of enhancement within the sinus mucosa and cavernous sinus, a finding consistent with devitalized tissue. First-line medical therapy includes amphotericin B and counteracting the potential sequelae of acidemia and hyperglycemia with IV insulin and fluids.[5]

• *Arteriovenous malformations.* These are high-flow or low-flow communications between arteries and veins with no interposed capillary bed; the most common are carotid-cavernous fistulas (CCF).[6] AVM can be classified as traumatic vs. spontaneous, high-flow vs. low-flow, and direct vs. dural.

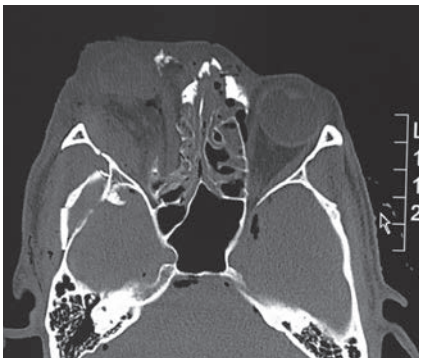
The clinical scenario of acute unilateral proptosis with severe chemosis, pain, orbital bruit, restricted ocular motilities, elevated IOP and dilated episcleral veins suggests a high-flow fistula from trauma or an aneurysmal rupture of the internal carotid artery within the cavernous sinus, necessitating emergent imaging of the brain and orbits.[7] Contrast-enhanced magnetic resonance angiography (MRA) and CT angiography are superior for evaluating venous distention, the lumen of aneurysms and increased flow to the cavernous sinus. Surgical treatment with embolization is warranted when optic nerve compression exists or when congestion from the superior ophthalmic vein and cavernous sinus places the cerebral venous circulation at risk for thrombosis.

The other CCF form is classified as low-flow. Astute clinical evaluation is essential because the signs and symptoms are relatively mild and often overlooked in favor of more benign entities such as ocular surface disease, conjunctivitis or episcleritis. Contrast-enhanced MRI or MRA of the head and orbit is the preferred imaging modality. Most lesions undergo spontaneous occlusion without visual sequelae.[8]

Scenario 3: Intermittent Pain and Proptosis. The clinical presentation of a young adult with complaints of intermittent positional pain and proptosis exaggerated during valsalva-type maneuvers should be initially evaluated with non-contrast CT, for an enlarged superior ophthalmic vein consistent with orbital varices.[9]

Varices are venous malformations that consist of low-pressure and low-flow plexi that intermingle within the orbital circulation. If the clinical history is suspicious for varices and CT imaging is normal, magnetic resonance venography (MRV) should be performed to evaluate the orbital and intracranial venule system. While surgery is reserved for varices that cause significant pain, proptosis and optic nerve compression, small lesions with minimal signs and symptoms can be observed.[10]

Scenario 4: Painless Progressive Proptosis. Suspect cavernous hemangioma in these circumstances. This is the most common orbital tumor in adults and typically presents in middle age with painless, progressive proptosis that causes hyperopia and choroidal folds. The differential diagnosis includes orbital metastasis, orbital lymphoma and hemangiopericytoma. While most orbital processes are best evaluated with MRI, progressive signs of proptosis, optic neuropathy and choroidal folds often signal a retro-orbital mass, easily identifiable with non-contrast orbital CT.[11] Lesions causing significant proptosis, optic neuropathy or visually significant choroidal folds should be surgically removed.



Here is a CT image of the gunshot injury.

Unilateral proptosis often presents a diagnostic dilemma. However, taking a detailed history, performing a comprehensive clinical exam and using appropriate neuroimaging techniques will help rule out emergent causes and increase the chance of early diagnosis for the patient. ■

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Scrambling For a Diagnosis

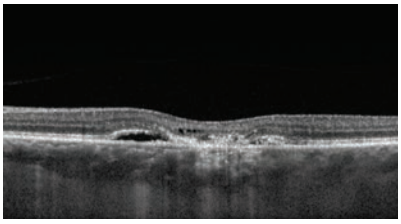
Combining old and new images may explain this patient's vision loss.

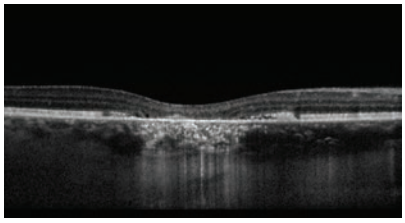
By Tea Avdic, OD, and Mark T. Dunbar, OD

A 57-year-old male presented complaining of mildly decreased vision in both eyes. He noted the change a few months prior. His medical, family and social history is noncontributory. Upon examination, his best-corrected visual acuity was 20/40 OD and 20/30 OS. Extraocular motilities showed full range of motion in both eyes. His confrontation fields were full-to-careful finger counting in the right and left eye. His pupils were unremarkable with no afferent pupillary defect. Additionally, his intraocular pressures (IOP) were 17mm Hg OD and 16mm Hg OS.

Anterior segment examination was within normal limits. The fundus showed significant retinal pigment epithelium (RPE) atrophic changes in the macula of both eyes. In the right eye, we observed some elevation of the RPE. A macular optical coherence tomography (OCT) image was obtained and is available for review (*Figures 1a and 1b*).

Further review of the patient's medical record showed fundus images that were taken three years prior (*Figures 2a and 2b*).





Figs. 1a and 1b. These two OCT images show two stages of the patient's condition. Can you make the diagnosis?

Take the Quiz

1. What is the likely diagnosis?
a. Central serous retinopathy.
b. Age-related macular degeneration.
c. Adult-onset vitelliform dystrophy.
d. Polypoidal choroidal vasculopathy.

2.What does OCT imaging show?
a. Retinal thickening with cystoid changes of the inner retina.
b. Subretinal exudates and intraretinal edema.
c. Macular edema.
d. Retinal atrophy with subretinal fluid.

3. What additional testing is warranted?
a. Fluorescein angiography.
b. Genetic testing.
c. B-scan ultrasonography.
d. No additional testing.

4. Which of the following represents the best treatment plan for this patient?
a. Observation.
b. Laser treatment.
c. Anti-VEGF.
d. b and c.

For answers, see page 98.

Diagnosis

Based on the fundus photos that were reviewed from three years prior, we determined that our patient has adult-onset vitelliform dystrophy. The fundus photos show a fairly classic "vitelliruptive" stage of the disease that, over the ensuing three years, has progressed to the "atrophic" stage.

Adult-onset vitelliform dystrophy is an autosomal dominant disorder with variable expression and incomplete penetrance that results in slow, progressive bilateral vision loss. The classic presentation resembles a sunny-side egg-yolk appearance, which can be appreciated in the images; however, it is apparent from the photos that the disease has progressed to the next stage—the "pseudohypopyon" stage.

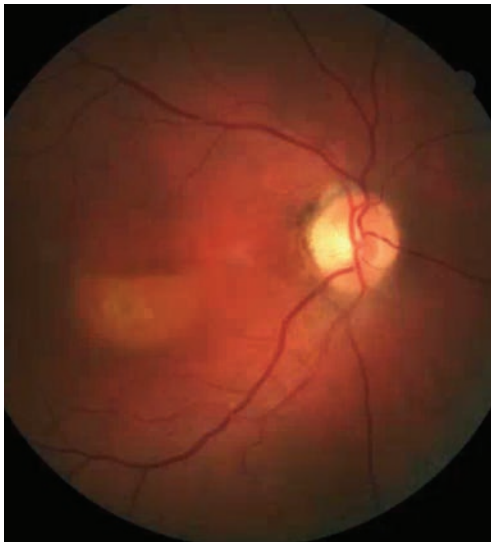
Discussion

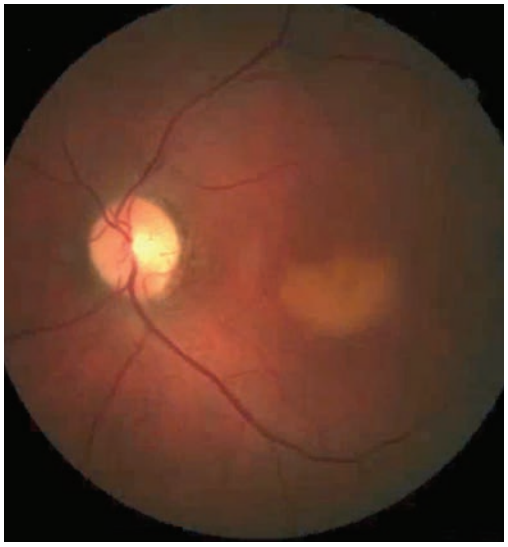
Adult-onset vitelliform dystrophy, initially referred to as "peculiar foveomacular dystrophy," is divided into five distinct stages. They are:

1. Vitelliform
2. Pseudohypopyon
3. Vitelliruptive
4. Atrophic
5. Cicatricial

The "egg-yolk" lesion that presents as a yellow subretinal

deposit and does not affect vision characterizes the vitelliform stage. In the pseudohypopyon stage, the yellow material liquefies, settling inferiorly and giving the appearance of a hypopyon. Acuity becomes affected once the disease progresses to the vitelliruptive stage, in which the central aspect of the lesion becomes atrophic and the "egg-yolk" takes on the "scrambled" appearance. When we most recently saw the patient, the disease had progressed to the atrophic stage in which the changes can be nonspecific. The OCT image shows disruption at the RPE level with loss at the inner segment/outer segment junction as well as in the right eye and area of subretinal fluid.





Figs 2a and 2b. These fundus photos show our patient from three years prior to the diagnosis. Can this presentation, combined with the current-day OCT, lead you to a diagnosis?

Researchers believe the disease develops as a result of genetic mutations in the photoreceptor protein-encoding genes, which leads to breakdown of the RPE-photoreceptor complex causing toxic accumulation of cellular debris at the RPE level, resulting in the classic presentation of bilateral yellow subfoveal deposits.[1,2] The deposits intensify over time, ultimately resulting in RPE atrophy and vision loss.[2]

The age of onset remains variable with many patients remaining asymptomatic until the fifth or sixth decade of life.

Monitoring

Diagnostic testing often includes OCT, fluorescein angiography (FA) and, in some cases, electrophysiological studies. Despite variability in visual outcomes and acuity, full-field and multifocal electroretinograms in patients with adult-onset vitelliform dystrophy reveal that the disease significantly disrupts macular function.[3] Furthermore, the electro-oculograms may be slightly reduced or normal.[4] Early in the disease, the FA will expectedly reveal a pattern of patchy hypofluorescence at the macula with surrounding hyperfluorescence.[5,6] OCT can be used to identify the anatomical location of the lesion and will reveal a linear RPE layer separated from the photoreceptor layer by cellular debris, likely to be lipofuscin.[7] Note that the fluorescein pattern and OCT findings will change as the lesions progress.

As the disease evolves, vision loss becomes more severe. In the later disease stage, as visual impairment and loss of central acuity become a greater concern, patients should be issued an Amsler grid to monitor for visual changes at home. Referrals to vision rehabilitation should be made to enhance quality of life. Although rare, complications such as full thickness macular holes, choroidal neovascular membranes and retinal detachment can occur; therefore, annual dilated exams and close observation are warranted.[8] ■

Dr. Avdic is a resident at Bascom Palmer Eye Institute in Miami.

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The Compliance Conundrum

Sustained-release delivery aims to keep patients adherent.

By Joseph W. Sowka, OD, and Alan G. Kabat, OD

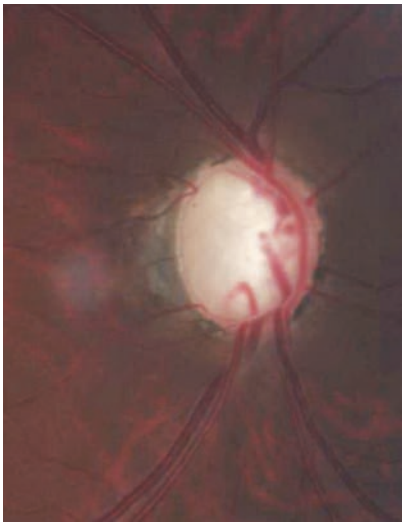
A 48-year-old man was referred to our office for urgent glaucoma management. He reported that his sight had been getting worse "over some time" and knew that he had poor vision in his right eye. Indeed, his corrected visual acuity was hand motion in the right eye and 20/30 OS.

He reported no systemic health issues, but said he "didn't really go to the doctor much." He had no biomicroscopic abnormalities, and his intraocular pressures (IOP) were 46mm Hg OD and 38mm Hg OS. He had advanced glaucomatous damage to both optic discs.

After a discussion of the diagnosis and treatment options (he adamantly refused surgery), he was prescribed latanoprost in each eye and scheduled for a follow-up; however, it took several months of no-shows before he returned. He reported that he used the medication "a bit," but didn't really feel a difference, never refilled the prescription and discontinued after a month. His IOP hadn't changed. He again refused surgery, was again educated about his prognosis and re-prescribed latanoprost. He has since been lost to follow up.

The Compliance Challenge

The greatest challenge in managing glaucoma has got to be medication adherence. Great IOP lowering medications don't work if patients don't use them. Sustained-release medications haven't been used with any great effect since the 1970s when Ocusert wafers were used to deliver pilocarpine in a more-or-less continuous fashion. It was not readily adapted due to discomfort and the overall poor tolerability of pilocarpine.



Researchers are investigating whether glaucoma patients, such as the one shown in this photo, may be better treated using sustained-release medications.

Today, many innovators are reviving sustained-release options in an attempt to solve the compliance issue. For instance, bimatoprost SR (Allergan), is an intracameral depot implant placed in the anterior chamber. Bimatoprost SR is a biodegradable polymer matrix that releases a steady amount of bimatoprost 0.03%.[1] One study shows the overall mean IOP reduction from baseline through week 16 using bimatoprost SR was 7.2mm Hg, 7.4mm Hg, 8.1mm Hg and 9.5mm Hg with the 6-µg, 10-µg, 15-µg, and 20-µg dose strengths of implant, respectively, vs. 8.4mm Hg in topical bimatoprost-treated fellow eyes.[1] The implant lowered IOP in 92% of patients at four months and 71% at six months.[1] No serious adverse ocular events were noted, and the most common adverse events were related to the injection procedure.[1]

Similarly used as an intracameral implant is ENV515 (Envisia), an extended release form of travoprost. A Phase 2a open-label, 28-day dose-ranging study of 21 patients yielded 28% IOP lowering at day 25 in one group, which was comparable with once-daily Travatan Z (travoprost, Alcon).[2] Interim Phase 2 results showed a favorable safety profile and sustained IOP reduction up to three months.[2] Envisia is planning to advance to a 12-month study to evaluate the long-term IOP lowering of ENV515.[2]

Sustained-release Devices

Additionally, researchers have considerable work to do on sustained-release platforms delivered externally. One such device is a bimatoprost-laden ring being developed by Allergan. This thin silicone ring suffused with bimatoprost that slowly releases medication over time is fit under the upper and lower eyelids by a doctor, so that it rests in the

conjunctival sulcus. It is designed to be replaced every six months. In a Phase 2 randomized, double-masked controlled study, the bimatoprost-delivery device was compared with timolol 0.5% BID. The bimatoprost ring lowered IOP, but less than did topical timolol 0.5% dosed twice daily. Retention was 90% at six months and was generally well tolerated by the study patients.[3] There exists a possibility to develop the device to contain a fixed combination of bimatoprost and timolol.

Beyond an externally applied medication-eluting conjunctival ring, punctal plugs may serve as a promising method of delivering sustained-release medications via punctual plugs.[4] Ocular Therapeutix is developing the OTX-TP, a travoprost-eluting intracanalicular punctal plug designed to slowly deliver the medication. It can be placed in either the superior or inferior canaliculus. Because it is intracanalicular, it can only be visualized in place by a fluorescent light, thus retention cannot be determined by the patient. In clinical trials, retention of the OTX-TP device was 91% at 60 days but only 48% at 90 days.[5] One study noted that IOP with OTX-TP was reduced 23% to 28% at day 10.[3] However, at 30 days, plug retention had declined to 42%, and the overall IOP reduction had decreased to 16%.[5]

Mati Therapeutics is working on its own drug-eluting punctal plug, the latanoprost-punctal plug delivery system, which releases latanoprost and is grossly visible. As a superficial punctal plug, it can be verified present and pulled out relatively easily.[6]

Pitfalls

The concept of sustained-release devices for glaucoma medications is exciting and promises to reduce adherence and persistence issues. However, they carry potential drawbacks.

In regards to injectable implants, a medication cannot be easily discontinued if there is an adverse reaction, whereas a patient can simply stop using a topical drop. Anterior chamber implants can, theoretically, block parts of the angle or even a trabeculectomy site. Invasive options carry the risk of infection and even endophthalmitis. Also, a great many patients are cared for by optometrists. Should the direction of glaucoma care shift towards invasive options, access to care will decrease as these options may be beyond the scope of optometric licensure. Also, it is not clear if insurance will pay for these medications and procedures simply to increase adherence. Further, glaucoma patients who perceive no vision loss may not be as accepting of an injection into the eye as those, say, with severely deteriorating vision from macular degeneration. Intravitreal therapy for macular degeneration has shown great advances in vision recovery and preservation, but those patients who have dropped out of regimented therapy are mostly doing poorly.

Still a Ways Away

As for externally delivered sustained-release options, patients will have to verify if a punctal plug or ring is still in place. Retention of external devices may pose a problem for patients who are scheduled for replacement at three- or six-month intervals. It may be that patients are not receiving therapy for a significant period of time between visits. There will be limitations on the number of drugs that can be placed within the anterior chamber or into a medication-eluting ring. Patients also, obviously, have a limited number of puncta, and additional topical therapy may still be needed.

Some drugs may work better in pulsatile form and not so well in constant delivery systems. We know that prostaglandin analogs are less effective at BID dosing, likely due to receptor supersaturation and desensitization.[7] Likely, the once-a-day dosing of these medications provides needed downtime between drops to prevent receptor desensitization. In clinical trials, it appears that these sustained-release prostaglandins are not as effective at lowering IOP as they are in topical form.[3]

Sustained delivery of glaucoma therapy is still several years away. Some options will be invasive, which may limit access to care. Many options will be noninvasive. All offer some benefits combined with limitations. We anxiously await the results from clinical trials and the introduction of these devices to the ophthalmic marketplace. However, we believe that drops, laser and surgery will not become obsolete any time soon. ■

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Edited By Derek N. Cunningham, OD, and Walter O. Whitley, OD, MBA

Extend Your Patient's Vision

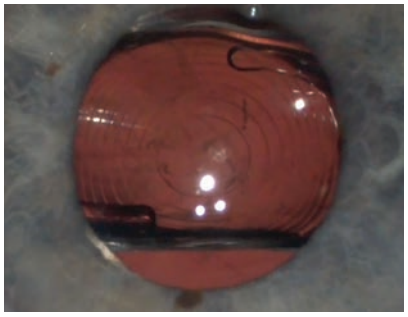
Can the Symfony intraocular lens provide significant benefits for presbyopic patients in need of cataract surgery? Here's what its proponents anticipate. **By Jillian Janes, OD**

When patients first start to develop cataracts, many look to us to walk them through the surgical options. Because an intraocular lens (IOL) choice is a once-in-a-lifetime decision, patients must be confident in that choice—and the more educated our patients are, the more confident they'll be, resulting in better outcomes.

A New Read on Presbyopia

Currently, our options for correcting presbyopia at the time of cataract surgery are traditional multifocal IOLs, accommodating IOLs, monovision with monofocal IOLs and now the new Tecnis Symfony IOL (Abbott Medical Optics). Traditional multifocal lens implants use diffraction, which allocates light to multiple focal points by creating zones on the anterior surface of the lens. This allows for simultaneous viewing of images at distance and near. Accommodating IOLs hinge forward by their haptics as the natural ciliary muscle contracts and relaxes to provide near vision focus.

Independent research on the new Symfony lens is limited at this time, but its manufacturer says it was designed with what's called an extended range of vision to provide clear vision though a limited depth of focus without splitting light or changing position.[1] The lens has refractive echelettes, which appear as concentric rings and have a similar appearance to traditional multifocal lenses at the slit lamp.[1] These echelettes do not split the light into different foci; rather, they introduce a pattern of light diffraction that elongates the focus of the eye, providing an extended range of vision.



The Symfony's refractive echelettes look similar to concentric rings found on traditional multifocal IOLs.

AMO also says the lens design corrects for spherical and chromatic aberrations, and that the aspheric anterior surface and posterior achromatic diffracting surface provide great retinal image quality and contrast sensitivity.[1] The Symfony also has a toric version for astigmats.

The manufacturer says contrast sensitivity with Symfony is similar to that of monofocal IOLs, which may be better than that obtained with a multifocal IOL due to the latter's splitting of light. Instead, AMO says, Symfony images are not out of focus, causing fewer halos.[1]

Sacrificing Near Vision

Despite its advantages, this new lens may not provide the same near vision obtained with traditional multifocal lenses, and clinicians must keep this in mind with patients whose work or hobbies require precise near vision. Some cataract surgeons may compensate for this by using bilateral Symfony lenses and leaving the non-dominant eye slightly myopic, in the -0.75D to -1.00D range.

Procedure Basics

Preoperatively, we have to keep in mind other ocular pathologies (e.g., severe ocular surface disease, corneal dystrophy, retinal pathology) that would limit patients' quality of vision after cataract removal and make them less than ideal candidates for this lens.

Clinicians must check distance, intermediate and near vision at all post-op visits. To ensure patient satisfaction, we need to ask patients how their "new eyes" are functioning during activities of daily living. While most achieve positive outcomes, it's important to reassure those with less than ideal outcomes that you will work closely with them and their surgeon to address any concerns. Luckily, these conversations, in our experience, are few and far between.

Staying up to date on the latest IOLs allows us to better educate patients on this important decision. Often, patients are unaware they could possibly regain some of the range of vision they used to have. ■

To see a video of this procedure, visit www.reviewofoptometry.com, or scan the QR code.

1. Abbott Medical Optics. Tecnis Symfony IOL. 2017. Available at www.vision.abbott/us/iols/extended-depth-of-focus/tecnis-symfony.html. Accessed March 8, 2017.

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Product **Review**

Lens Technology

HLM-1 Huvitz Lensmaster

Practitioners can now upgrade to Coburn's new HLM-1 Lensmaster, which comes with the same wavefront analysis as in older models but with more measurement points, according to Coburn. Other features include multifocal measurement, with on-screen prompts; enhanced camera performance; high processing speed and frames per second; and newly designed nose cone and lens support for measuring smaller frame styles.

Visit www.coburntechnologies.com.

FastGrind Photochromic FT28 Lens

Patients can look forward to a new photochromic lens from FastGrind. The FT28 lens quickly changes opacity while blocking harmful UV rays. You can produce lenses in-office for immediate dispensing, FastGrind says.

Visit www.superoptical.com/fast-grind.

New Edging System

Essilor's Pro-E 600 gives high-volume labs something to look forward to. The company says it's designed with faster processes and suited for specialty edging and mountings—from bevel and mini-bevel, to asymmetric and step bevel, groove, mix, drill, chamfer and polish. The edging system is roughly 50% faster than other tabletop edgers, quickly integrates, is intuitive (no vacuum or compressed air) and interfaces effortlessly with laboratory management software, according to Essilor.

Visit www.essilorinstrumentsusa.com.

Diagnostic Technology

Topcon SL-D301 Slit Lamp

Optometrists in need of a new slit lamp can consider Topcon's SL-D301, which comes with a Galilean-type observation system and 10x, 16x and 25x magnifications. Topcon says it can be easily upgraded to full digital with an optional camera attachment, and can be used with R-900 and 870 model applanation tonometers.

Visit www.topcon.com.

Icare Home Tonometer

This device lets patients self-monitor IOP and gives their doctors access to the data to better track diurnal fluctuations, according to Icare. The unit is easy to use, performs automatic OD/OS recognition and uses red and green signals to help correctly position the tonometer, the company says. An automated measuring sequence can take a single measurement or a series of six.

Visit www.icare-usa.com.

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Diagnostic **Quiz**

Bullseye

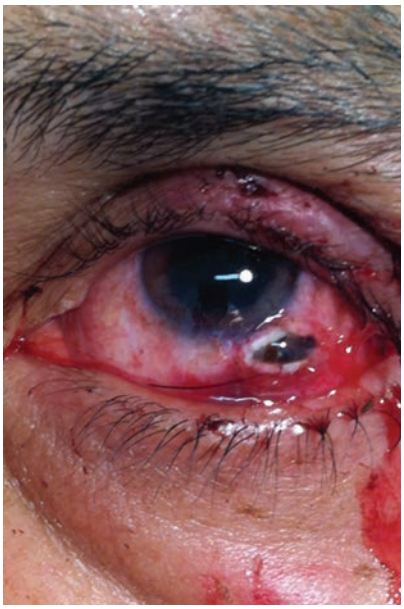
By Andrew S. Gurwood, OD

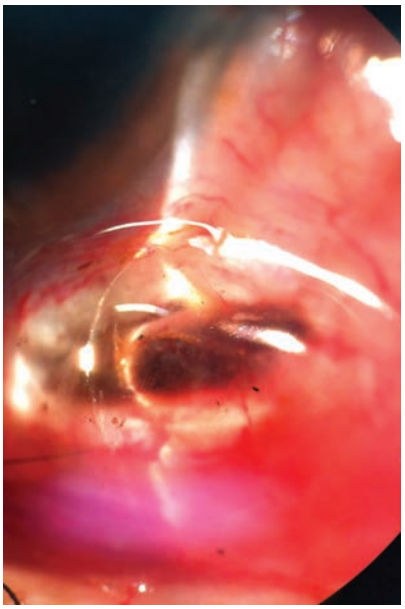
History

A 57-year-old Caucasian male reported to the office emergently following blunt trauma to his left eye caused by a falling 2x4. He was clearly in distress, suffering from pain, photophobia, lacrimation, hemolacria (bloody tears) and blurry vision. He had no previous ocular history and his systemic history was remarkable for hypertension, for which he was properly controlled with lisinopril. He denied allergies of any kind.

Diagnostic Data

His best-corrected entering visual acuities were 20/20 OD and 20/100 OS at distance and near with no improvement upon pinhole. His external examination is demonstrated in the gross photograph. His pupils were normal with no evidence of afferent pupil defect. The biomicroscopic examination of the anterior segment is demonstrated in the magnified photograph. No other testing or manipulation was done.





This 57-year-old patient's left eye shows the result of a blunt trauma. Can you diagnose him?

Your Diagnosis

Does this case require additional tests? How would you manage this patient? What is the likely prognosis?

To find out, please visit www.reviewofoptometry.com. ■

Retina Quiz Answers *(from page 86):* 1) b; 2) d; 3) a; 4) a.

Next Month in the Mag

In May, *Review of Optometry* will present its annual dry eye report.

Topics include:

- *Omega Fatty Acids for Dry Eye: How They Differ and Why it Matters*
- *Managing Severe Dry Eye*
- *A Comprehensive Look at Dry Eye Therapy: Tears, Meds, Wipes, Plugs and More* (earn 2 CE credits)

Also in this issue:

- *The Online Refraction Threat: Are You Prepared?*
- *Collagen Crosslinking: What do Real-World Results Show?*
- *Is Dropless Cataract Surgery Improving Outcomes?*
- *Spectacles: How Would You Handle These Tricky Refraction Challenges?*

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REFERENCES: 1. Results from a 7-investigator, multi-site 2-week study of Bausch + Lomb ULTRA® for Astigmatism contact lenses on 157 current soft contact lens wearer. **2.** Data on file. Bausch & Lomb Incorporated. Rochester, NY; 2013.

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References: 1. Nash W, Gabriel M, Mowrey-Mckee M. A comparison of various silicone hydrogel lenses; lipid and protein deposition as a result of daily wear. *Optom Vis Sci.* 2010;87:E-abstract 105110. **2.** Nash WL, Gabriel MM. Ex vivo analysis of cholesterol deposition for commercially available silicone hydrogel contact lenses using a fluorometric enzymatic assay. *Eye Contact Lens.* 2014;40(5):277-282. **3.** *In vitro* study over 16 hours to measure wetting substantivity; Alcon data on file, 2015. **4.** *In vitro* wetting analysis: out-of-pack and wetting substantivity; Alcon data on file, 2014.

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